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(73) **Assignee: Bristol-Myers Squibb Company**(57) **ABSTRACT**

The present disclosure relates to compounds, compositions and methods for the treatment of hepatitis C virus (HCV) infection. Also disclosed are pharmaceutical compositions containing such compounds and methods for using these compounds in the treatment of HCV infection.

HEPATITIS C VIRUS INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. non-provisional application Ser. No. 11/835,462, filed Aug. 8, 2007, and claims the benefit of U.S. provisional application No. 60/836,996, filed Aug. 11, 2006.

[0002] The present disclosure is generally directed to antiviral compounds, and more specifically directed to compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), compositions comprising such compounds, and methods for inhibiting the function of the NS5A protein.

[0003] HCV is a major human pathogen, infecting an estimated 170 million persons worldwide—roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

[0004] Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection.

[0005] HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

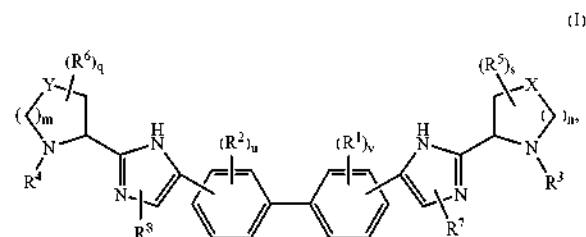
[0006] Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

[0007] The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polypeptide of about 3000 amino acids. In infected cells, this polypeptide is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to herein as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the mem-

brane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to herein as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

[0008] Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in Tan, S.-L., Katzel, M. G. *Virology* 2001, 284, 1-12; and in Park, K.-J.; Choi, S.-H, *J. Biological Chemistry* 2003.

[0009] In a first aspect the present disclosure provides a compound of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

[0010] m and n are independently 0, 1, or 2;

[0011] q and s are independently 0, 1, 2, 3, or 4;

[0012] u and v are independently 0, 1, 2, or 3;

[0013] X is selected from O, S, S(O), SO₂, CH₂, CHR⁵, and C(R⁵)₂;

provided that when n is 0, X is selected from CH₂, CHR⁵, and C(R⁵)₂;

[0014] Y is selected from O, S, S(O), SO₂, CH₂, CHR⁶, and C(R⁶)₂;

provided that when m is 0, Y is selected from CH₂, CHR⁶, and C(R⁶)₂;

[0015] each R¹ and R² is independently selected from alkoxy, alkoxyalkyl, alkoxyalkenyl, alkyl, arylalkoxyalkenyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, —NR^aR^b, (R^aR^b)alkyl, and (NR^aR^b)carbonyl;

[0016] R³ and R⁴ are each independently selected from hydrogen, R⁹—C(O)—, and R⁹—C(S)—;

[0017] each R⁵ and R⁶ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and —NR^aR^b, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

[0018] R⁷ and R⁸ are each independently selected from hydrogen, alkoxyalkenyl, alkyl, arylalkoxyalkenyl, carboxy, haloalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl; and

[0019] each R⁹ is independently selected from alkoxy, alkoxyalkyl, alkoxyalkenyl, alkoxyalkenylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocy-

cylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocycloxyalkyl, hydroxyalkyl, $\text{—NR}^{\text{c}}\text{R}^{\text{d}}$, $\text{R}^{\text{c}}\text{R}^{\text{d}}$ alkenyl, $(\text{R}^{\text{c}}\text{R}^{\text{d}})$ alkyl, and $(\text{NR}^{\text{c}}\text{R}^{\text{d}})$ carbonyl.

[0020] In a first embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1.

[0021] In a second embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

[0022] u and v are each independently 0, 1, or 2; and

[0023] each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxyalkyl, $(\text{NR}^{\text{a}}\text{R}^{\text{b}})$ alkyl, and $(\text{NR}^{\text{a}}\text{R}^{\text{b}})$ carbonyl.

[0024] In a third embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

[0025] u and v are each independently 0 or 1; and

[0026] when present, R^1 and/or R^2 are halo.

[0027] In a fourth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

[0028] u and v are each independently 0 or 1; and

[0029] when present, R^1 and/or R^2 are halo, wherein the halo is fluoro.

[0030] In a fifth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of X and Y is S.

[0031] In a sixth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X and Y are each S.

[0032] In a seventh embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X is selected from CHR^5 , and $\text{C}(\text{R}^5)_2$; and Y is selected from CH_2 , CHR^6 , and $\text{C}(\text{R}^6)_2$.

[0033] In an eighth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are independently selected from hydrogen, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and $(\text{NR}^{\text{a}}\text{R}^{\text{b}})$ carbonyl.

[0034] In a ninth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are each hydrogen.

[0035] In a tenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

[0036] q and s are independently 0, 1, or 2; and

[0037] each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups.

[0038] In an eleventh embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

[0039] q and s are independently 0 or 1; and

[0040] when present, R^5 and/or R^6 are each halo.

[0041] In a twelfth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

[0042] q and s are independently 0 or 1; and

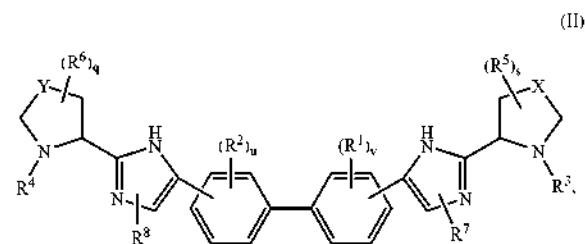
[0043] when present, R^5 and/or R^6 are each halo, wherein the halo is fluoro.

[0044] In a thirteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of R^3 and R^4 is hydrogen.

[0045] In a fourteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each $\text{R}^9\text{—C}(\text{O})\text{—}$.

[0046] In a fifteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkoxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, $\text{—NR}^{\text{c}}\text{R}^{\text{d}}$, $(\text{NR}^{\text{c}}\text{R}^{\text{d}})$ alkenyl, $(\text{NR}^{\text{c}}\text{R}^{\text{d}})$ alkyl, and $(\text{NR}^{\text{c}}\text{R}^{\text{d}})$ carbonyl.

[0047] In a second aspect the present disclosure provides a compound of Formula (II)



or a pharmaceutically acceptable salt thereof, wherein

[0048] q and s are independently 0, 1, or 2;

[0049] u and v are independently 0, 1, or 2;

[0050] X is selected from S, CH_2 , CHR^5 , and $\text{C}(\text{R}^5)_2$;

[0051] Y is selected from S, CH_2 , CHR^6 , and $\text{C}(\text{R}^6)_2$;

[0052] each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxyalkyl, $(\text{NR}^{\text{a}}\text{R}^{\text{b}})$ alkyl, and $(\text{NR}^{\text{a}}\text{R}^{\text{b}})$ carbonyl;

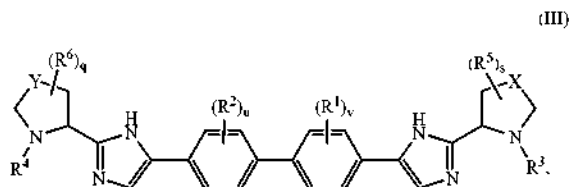
[0053] R^3 and R^4 are each independently selected from hydrogen and $\text{R}^9\text{—C}(\text{O})\text{—}$;

[0054] each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

[0055] R^7 and R^8 are each independently selected from hydrogen, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and $(\text{NR}^{\text{a}}\text{R}^{\text{b}})$ carbonyl; and

[0056] each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkoxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, $\text{—NR}^{\text{c}}\text{R}^{\text{d}}$, $(\text{NR}^{\text{c}}\text{R}^{\text{d}})$ alkenyl, $(\text{NR}^{\text{c}}\text{R}^{\text{d}})$ alkyl, and $(\text{NR}^{\text{c}}\text{R}^{\text{d}})$ carbonyl.

[0057] In a third aspect the present disclosure provides a compound of Formula (III)



or a pharmaceutically acceptable salt thereof, wherein

[0058] q and s are independently 0, 1, or 2;

[0059] u and v are independently 0 or 1;

[0060] X is selected from CH₂, CHR⁵, and C(R⁵)₂;

[0061] Y is selected from CH₂, CHR⁶, and C(R⁶)₂;

[0062] when present, R¹ and/or R² are halo, wherein the halo is fluoro;

[0063] R³ and R⁴ are each R⁹—C(O)—;

[0064] when present, R⁵ and/or R⁶ are halo, wherein the halo is fluoro; and

[0065] each R⁹ is independently selected from alkoxy, alkoxyalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkyl carbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, —NR⁹R^d, (NR⁹R^d)alkenyl, (NR⁹R^d)alkyl, and (NR⁹R^d)carbonyl.

[0066] In a fourth aspect the present disclosure provides a compound selected from

[0067] methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

[0068] (1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

[0069] methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

[0070] methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

[0071] methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

[0072] methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

[0073] methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

[0074] methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-

imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

[0075] dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

[0076] (1R)—N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

[0077] methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate; and

[0078] methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;

or a pharmaceutically acceptable salt thereof.

[0079] In a first embodiment of the fifth aspect the pharmaceutically acceptable salt is a dihydrochloride salt.

[0080] In a sixth aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0081] In a first embodiment of the sixth aspect the composition further comprises one or two additional compounds having anti-HCV activity. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

[0082] In a fourth embodiment of the sixth aspect the composition further comprises one or two additional compounds having anti-HCV activity wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

[0083] In a fifth embodiment of the sixth aspect the composition further comprises one or two additional compounds having anti-HCV activity wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

[0084] In a seventh aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (J), or a pharmaceutically acceptable salt thereof.

[0085] In a first embodiment of the seventh aspect the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

[0086] In a fourth embodiment the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

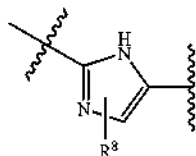
[0087] In a fifth embodiment the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

[0088] Other embodiments of the present disclosure may comprise suitable combinations of two or more of embodiments and/or aspects disclosed herein.

[0089] Yet other embodiments and aspects of the disclosure will be apparent according to the description provided below.

[0090] The compounds of the present disclosure also exist as tautomers; therefore the present disclosure also encompasses all tautomeric forms.

[0091] The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order accommodate a substituent at any given location. For example, in the structure shown below



R^8 may be attached to either the carbon atom in the imidazole ring or, alternatively, R^8 may take the place of the hydrogen atom on the nitrogen ring to form an N-substituted imidazole.

[0092] It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

[0093] It is intended that the definition of any substituent or variable (e.g., R^1 , R^2 , R^5 , R^6 , etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when u is 2, each of the two R^1 groups may be the same or different.

[0094] All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

[0095] As used in the present specification, the following terms have the meanings indicated:

[0096] As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

[0097] Unless stated otherwise, all aryl, cycloalkyl, and heterocyclyl groups of the present disclosure may be substituted as described in each of their respective definitions. For example, the aryl part of an arylalkyl group may be substituted as described in the definition of the term "aryl".

[0098] The term "alkenyl," as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond.

[0099] The term "alkenyloxy," as used herein, refers to an alkenyl group attached to the parent molecular moiety through an oxygen atom.

[0100] The term "alkenyloxycarbonyl," as used herein, refers to an alkenyloxy group attached to the parent molecular moiety through a carbonyl group.

[0101] The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

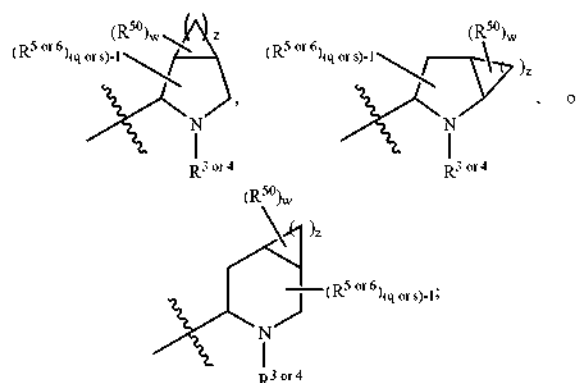
[0102] The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

[0103] The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

[0104] The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

[0105] The term "alkoxycarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxycarbonyl groups.

[0106] The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms. In the compounds of the present disclosure, when m and/or n is 1 or 2; X and/or Y is CHR^5 and/or CHR^6 , respectively, and R^5 and/or R^6 is alkyl, each alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom to provide one of the structures shown below:



where z is 1, 2, 3, or 4, w is 0, 1, or 2, and R^{50} is alkyl. When w is 2, the two R^{50} alkyl groups may be the same or different.

[0107] The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

[0108] The term "alkylcarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkylcarbonyl groups.

[0109] The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group attached to the parent molecular moiety through an oxygen atom.

[0110] The term "alkylsulfanyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfur atom.

[0111] The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

[0112] The term "aryl," as used herein, refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring. The aryl groups of the present disclosure can be attached to the parent molecular moiety through any substitutable carbon atom in the group. Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-\text{NR}^{\text{R}}\text{R}^{\text{R}}$, $(\text{NR}^{\text{R}}\text{R}^{\text{R}})$ alkyl, oxo, and $-\text{P}(\text{O})(\text{OR})_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

[0113] The term "arylalkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three aryl groups.

[0114] The term "arylalkoxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[0115] The term "arylalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three arylalkoxy groups.

[0116] The term "arylalkoxyalkylcarbonyl," as used herein, refers to an arylalkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

[0117] The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group attached to the parent molecular moiety through a carbonyl group.

[0118] The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups. The alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, and $-\text{NR}^{\text{R}}\text{R}^{\text{R}}$, wherein the heterocyclyl is further optionally substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-\text{NR}^{\text{R}}\text{R}^{\text{R}}$.

[0119] The term "arylalkylcarbonyl," as used herein, refers to an arylalkyl group attached to the parent molecular moiety through a carbonyl group.

[0120] The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

[0121] The term "aryloxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

[0122] The term "aryloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryloxy groups.

[0123] The term "aryloxycarbonyl," as used herein, refers to an aryloxy group attached to the parent molecular moiety through a carbonyl group.

[0124] The term "arylsulfonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

[0125] The terms "Cap" and "cap" as used herein, refer to the group which is placed on the nitrogen atom of the terminal nitrogen-containing ring, i.e., the pyrrolidine rings of compound 1e. It should be understood that "Cap" or "cap" can refer to the reagent used to append the group to the terminal nitrogen-containing ring or to the fragment in the final product, i.e., "Cap-51" or "The Cap-51 fragment found in LS-19".

[0126] The term "carbonyl," as used herein, refers to $-\text{C}(\text{O})-$.

[0127] The term "carboxy," as used herein, refers to $-\text{CO}_2\text{H}$.

[0128] The term "cyano," as used herein, refers to $-\text{CN}$.

[0129] The term "cycloalkyl," as used herein, refers to a saturated monocyclic hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, nitro, and $-\text{NR}^{\text{R}}\text{R}^{\text{R}}$, wherein the aryl and the heterocyclyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

[0130] The term "(cycloalkyl)alkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three cycloalkyl groups.

[0131] The term "(cycloalkyl)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups. The alkyl part of the (cycloalkyl)alkyl is further optionally substituted with one or two groups independently selected from hydroxy and $-\text{NR}^{\text{R}}\text{R}^{\text{R}}$.

[0132] The term "cycloalkyloxy," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0133] The term "cycloalkyloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyloxy groups.

[0134] The term "cycloalkylsulfonyl," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through a sulfonyl group.

[0135] The term "formyl," as used herein, refers to $-\text{CHO}$.

[0136] The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, or I.

[0137] The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0138] The term "haloalkoxycarbonyl," as used herein, refers to a haloalkoxy group attached to the parent molecular moiety through a carbonyl group.

[0139] The term “haloalkyl,” as used herein, refers to an alkyl group substituted by one, two, three, or four halogen atoms.

[0140] The term “heterocyclyl,” as used herein, refers to a four-, five-, six-, or seven-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur. The four-membered ring has zero double bonds, the five-membered ring has zero to two double bonds, and the six- and seven-membered rings have zero to three double bonds. The term “heterocyclyl” also includes bicyclic groups in which the heterocyclyl ring is fused to another monocyclic heterocyclyl group, or a four- to six-membered aromatic or non-aromatic carbocyclic ring; as well as bridged bicyclic groups such as 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-yl, and 2-azabicyclo[2.2.2]oc-3-yl. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through any carbon atom or nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, thiazolyl, thienyl, thiomorpholinyl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-yl, and 2-azabicyclo[2.2.2]oc-3-yl. The heterocyclyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $\text{—NR}^a\text{R}^b$, $(\text{NR}^a\text{R}^b)\text{alkyl}$, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

[0141] The term “heterocyclylalkenyl,” as used herein, refers to an alkenyl group substituted with one, two, or three heterocyclyl groups.

[0142] The term “heterocyclylalkoxy,” as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an alkoxy group.

[0143] The term “heterocyclylalkoxycarbonyl,” as used herein, refers to a heterocyclylalkoxy group attached to the parent molecular moiety through a carbonyl group.

[0144] The term “heterocyclylalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups. The alkyl part of the heterocyclylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, aryl, halo, haloalkoxy, haloalkyl, hydroxy, and $\text{—NR}^a\text{R}^b$, wherein the aryl is further optionally substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $\text{—NR}^a\text{R}^b$.

[0145] The term “heterocyclylalkylcarbonyl,” as used herein, refers to a heterocyclylalkyl group attached to the parent molecular moiety through a carbonyl group.

[0146] The term “heterocyclylcarbonyl,” as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a carbonyl group.

[0147] The term “heterocycliloxy,” as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an oxygen atom.

[0148] The term “heterocycliloxyalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three heterocycliloxy groups.

[0149] The term “heterocycliloxyalkylcarbonyl,” as used herein, refers to a heterocycliloxy group attached to the parent molecular moiety through a carbonyl group.

[0150] The term “hydroxy,” as used herein, refers to —OH .

[0151] The term “hydroxyalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

[0152] The term “hydroxyalkylcarbonyl,” as used herein, refers to a hydroxyalkyl group attached to the parent molecular moiety through a carbonyl group.

[0153] The term “nitro,” as used herein, refers to —NO_2 .

[0154] The term “ $\text{—NR}^a\text{R}^b$,” as used herein, refers to two groups, R^a and R^b , which are attached to the parent molecular moiety through a nitrogen atom. R^a and R^b are independently selected from hydrogen, alkenyl, and alkyl.

[0155] The term “ $(\text{NR}^a\text{R}^b)\text{alkyl}$,” as used herein, refers to an alkyl group substituted with one, two, or three $\text{—NR}^a\text{R}^b$ groups.

[0156] The term “ $(\text{NR}^a\text{R}^b)\text{carbonyl}$,” as used herein, refers to an $\text{—NR}^a\text{R}^b$ group attached to the parent molecular moiety through a carbonyl group.

[0157] The term “ $\text{—NR}^a\text{R}^d$,” as used herein, refers to two groups, R^a and R^d , which are attached to the parent molecular moiety through a nitrogen atom. R^a and R^d are independently selected from hydrogen, alkenyloxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxy, aryloxyalkyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocycliloxy, carbonyl, hydroxyalkylcarbonyl, $(\text{NR}^a\text{R}^d)\text{alkyl}$, $(\text{NR}^a\text{R}^d)\text{alkylcarbonyl}$, $(\text{NR}^a\text{R}^d)\text{carbonyl}$, $(\text{NR}^a\text{R}^d)\text{sulfonyl}$, $\text{—C}(\text{NCN})\text{OR}^d$, and $\text{—C}(\text{NCN})\text{NR}^a\text{R}^d$, wherein R^d is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $\text{—NR}^a\text{R}^d$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxy, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocycliloxy, carbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

[0158] The term “ $(\text{NR}^a\text{R}^d)\text{alkenyl}$,” as used herein, refers to an alkenyl group substituted with one, two, or three $\text{—NR}^a\text{R}^d$ groups.

[0159] The term “ $(\text{NR}^a\text{R}^d)\text{alkyl}$,” as used herein, refers to an alkyl group substituted with one, two, or three $\text{—NR}^a\text{R}^d$ groups. The alkyl part of the $(\text{NR}^a\text{R}^d)\text{alkyl}$ is further optionally substituted with one or two additional groups selected from alkoxy, alkoxyalkylcarbonyl, alkoxycarbonyl, alkylsul-

fanyl, arylalkoxyalkylcarbonyl, carboxy, heterocyclyl, heterocyclcarbonyl, hydroxy, and (NR^eR^f)carbonyl; wherein the heterocyclyl is further optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

[0160] The term "(NR^eR^f)carbonyl," as used herein, refers to an —NR^eR^f group attached to the parent molecular moiety through a carbonyl group.

[0161] The term "—NR^eR^f," as used herein, refers to two groups, R^e and R^f which are attached to the parent molecular moiety through a nitrogen atom. R^e and R^f are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cycloalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclalkyl, (NR^eR^f)alkyl, and (NR^eR^f)carbonyl.

[0162] The term "(NR^eR^f)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three —NR^eR^f groups.

[0163] The term "(NR^eR^f)alkylcarbonyl," as used herein, refers to an (NR^eR^f)alkyl group attached to the parent molecular moiety through a carbonyl group.

[0164] The term "(NR^eR^f)carbonyl," as used herein, refers to an —NR^eR^f group attached to the parent molecular moiety through a carbonyl group.

[0165] The term "(NR^eR^f)sulfonyl," as used herein, refers to an —NR^eR^f group attached to the parent molecular moiety through a sulfonyl group.

[0166] The term "—NR^xR^y," as used herein, refers to two groups, R^x and R^y, which are attached to the parent molecular moiety through a nitrogen atom. R^x and R^y are independently selected from hydrogen, alkoxy, carbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxy, carbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and (NR^xR^y)carbonyl, wherein R^x and R^y are independently selected from hydrogen and alkyl.

[0167] The term "(NR^xR^y)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three —NR^xR^y groups.

[0168] The term "oxo," as used herein, refers to =O.

[0169] The term "sulfonyl," as used herein, refers to —SO₂—. The term "trialkylsilyl," as used herein, refers to —SiR₃, wherein R is alkyl. The R groups may be the same or different.

[0170] The term "trialkylsilylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilyl groups.

[0171] The term "trialkylsilylalkoxy," as used herein, refers to a trialkylsilylalkyl group attached to the parent molecular moiety through an oxygen atom.

[0172] The term "trialkylsilylalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilylalkoxy groups.

[0173] Asymmetric centers exist in the compounds of the present disclosure. These centers are designated by the symbols "R" or "S", depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to inhibit NS5A. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by

separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

[0174] Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

[0175] The term "compounds of the present disclosure", and equivalent expressions, are meant to embrace compounds of Formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates are meant to embrace their salts where the context so permits.

[0176] The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, dihydrobromide, dihydrochloride, dihydroiodide, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylsulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

[0177] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0178] When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0179] Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Treatment may be initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

[0180] When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

[0181] Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration or administration by injection are preferred.

[0182] Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

[0183] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

[0184] Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

[0185] Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an algininate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as bentonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch

paste, acacia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

[0186] Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

[0187] Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax, or the like.

[0188] The compounds of formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[0189] The compounds of formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidophenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

[0190] Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research* 1986, 3(6), 318.

[0191] Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

[0192] Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

[0193] Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

[0194] Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

[0195] Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

[0196] Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

[0197] It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0198] The term "patient" includes both human and other mammals.

[0199] The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder, and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder, or condition, i.e., arresting its development; and (iii) relieving the disease, disorder, or condition, i.e., causing regression of the disease, disorder, and/or condition.

[0200] The compounds of the present disclosure can also be administered with a cyclosporin, for example, cyclosporin A. Cyclosporin A has been shown to be active against HCV in clinical trials (*Hepatology* 2003, 38, 1282; *Biochem. Biophys. Res. Commun.* 2004, 313, 42; *J. Gastroenterol.* 2003, 38, 567).

[0201] Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity compounds in combination therapy, either jointly or separately, or by combining the compounds into a composition.

TABLE 1

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
NIM811		Cyclophilin Inhibitor	Novartis
Zadaxin		Immunomodulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Bstabulin (T67)	Anticancer	β -tubulin inhibitor	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	antisense	ISIS Pharmaceuticals Inc., Carlsbad, CA/Elan Pharmaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion/Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Israel
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B Replicase Inhibitor	Wyeth/Viropharma
NM-283	Antiviral	NS5B Replicase Inhibitor	Idenix/Novartis
GL-59728	Antiviral	NS5B Replicase Inhibitor	Gene Labs/Novartis
GL-60667	Antiviral	NS5B Replicase Inhibitor	Gene Labs/Novartis
2'C MeA	Antiviral	NS5B Replicase Inhibitor	Gilead
PSI 6130	Antiviral	NS5B Replicase Inhibitor	Roche
R1626	Antiviral	NS5B Replicase Inhibitor	Roche
2'C Methyl adenosine	Antiviral	NS5B Replicase Inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA

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TABLE 1-continued

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	serine protease inhibitor	Schering Plough
Zadaxim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Immunosuppressant	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albupheron-α	Interferon	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN-ω	Intarcia Therapeutics
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Rebif	Interferon	IFN-β1s	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx Biopharmaceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc., San Mateo, CA

TABLE 1-continued

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
Rebetron	Interferon	IFN- α 2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferon	INF- γ	InterMune Inc., Brisbane, CA
Interferon- β	Interferon	Interferon- β -1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen/Valentis
Wellferon	Interferon	lymphoblastoid IFN- α n1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN- α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN- α 2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN- α 2a/immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys and Ribavirin	Interferon	PEGylated IFN- α 2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN- α 2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron/Ribavirin	Interferon	PEGylated IFN- α 2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys

[0202] The compounds of the present disclosure may also be used as laboratory reagents. Compounds may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms. Further, the compounds of the present disclosure are useful in establishing or determining the binding site of other antiviral compounds, for example, by competitive inhibition.

[0203] The compounds of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments,

laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

[0204] This disclosure is intended to encompass compounds having formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (in vivo) or processes occurring in vitro.

[0205] The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; Boc or BOC for tert-butoxycarbonyl; NBS for N-bromosuccinimide; tBu or t-Bu for tert-butyl;

SEM for -(trimethylsilyl)ethoxymethyl; DMSO for dimethylsulfoxide; MeOH for methanol; TFA for trifluoroacetic acid; RT for room temperature or retention time (context will dictate); t_R for retention time; EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP for 4-dimethylaminopyridine; THF for tetrahydrofuran; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; t-Bu; DEA for diethylamine; HMDS for hexamethyldisilazide; DMF for N,N-dimethylformamide; Bzl for benzyl; EtOH for ethanol; iPrOH or i-PrOH for isopropanol; Me₂S for dimethylsulfide; Et₃N or TEA for triethylamine; Ph for phenyl; OAc for acetate; EtOAc for ethyl acetate; dppf for 1,1'-bis(diphenylphosphino)ferrocene; iPr₂EtN or DIPEA for diisopropylethylamine; Cbz for carbobenzyloxy; n-BuLi for n-butyllithium; ACN for acetonitrile; h or hr for hours; m or min for minutes; s for seconds; LiHMDS for lithium hexamethyldisilazide; DIBAL for diisobutyl aluminum hydride; TBDMSCl for tert-butyldimethylsilyl chloride; Me for methyl; ca. for about; OAc for acetate; iPr for isopropyl; Et for ethyl; Bn for benzyl; and HOAT for 1-hydroxy-7-azabenzotriazole.

[0206] The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows:

[0207] The compounds and processes of the present disclosure will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the present disclosure may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art. It will be readily apparent to one of ordinary skill in the art that the compounds defined above can be synthesized by substitution of the appropriate reactants and agents in the syntheses shown below. It will also

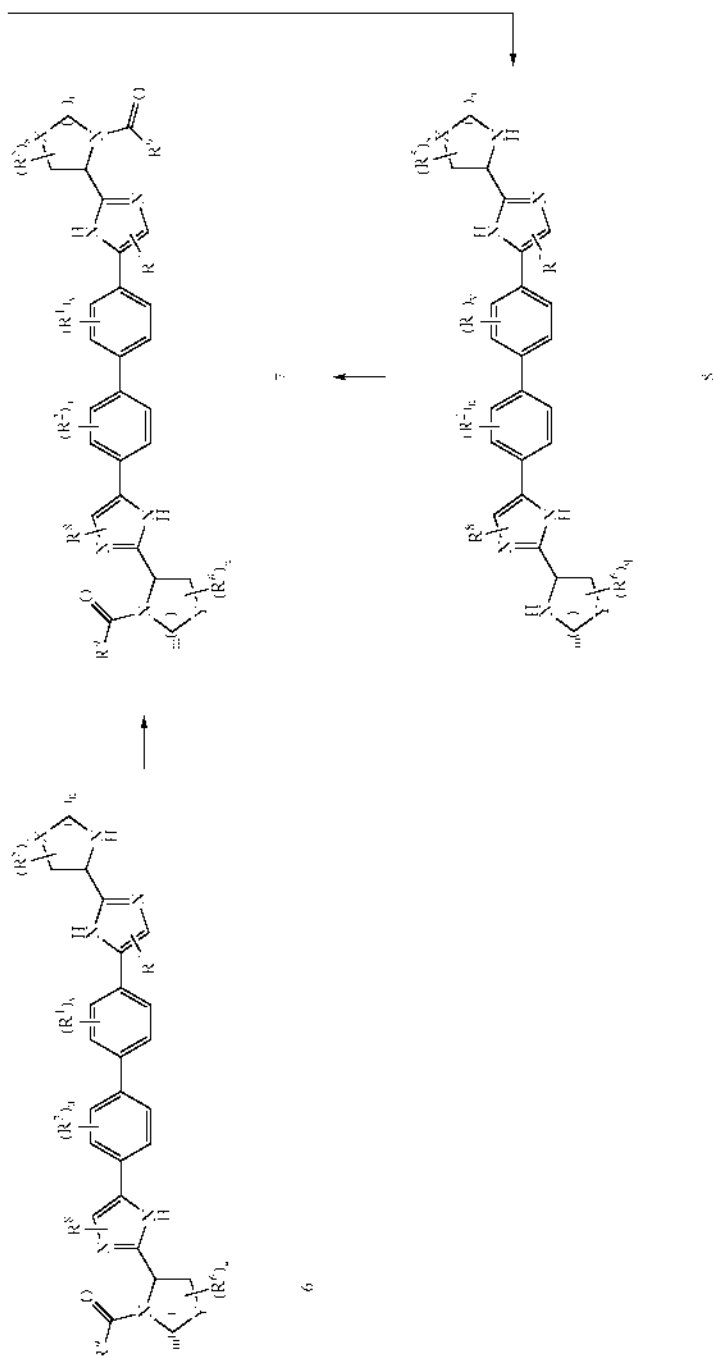
be readily apparent to one skilled in the art that the selective protection and deprotection steps, as well as the order of the steps themselves, can be carried out in varying order, depending on the nature of the variables to successfully complete the syntheses below. The variables are as defined above unless otherwise noted below.

Scheme 1

Symmetric or Asymmetric Biphenyls

[0208] Aryl halide 1 and boronic ester 2 can be coupled to produce biaryl 3 using standard Suzuki-Miyaura coupling conditions (*Angew. Chem. Int. Ed. Engl.* 2001, 40, 4544). It should be noted that the boronic acid analog of 2 may be used in place of the ester. Mono-deprotection of the pyrrolidine moiety may be accomplished when R¹² and R¹³ are different. When R¹²=benzyl, and R¹³=t-butyl treatment to hydrolytic conditions produces 4. For example, Pd/C catalyst in the presence of a base such as potassium carbonate can be used. Acylation of 4 can be accomplished under standard acylation conditions. A coupling reagent such as HATU in combination with an amine base such as Hunig's base can be used in this regard. Alternatively, 4 may be reacted with an isocyanate or carbamoyl chloride to provide compounds of formula 5 where R⁹ is an amine. Further deprotection of 5 can be accomplished by treatment with strong acid such as HCl or trifluoroacetic acid. Standard conditions analogous to those used to convert 4 to 5 can be used to prepare 7 from 6. In another embodiment where R¹²=R¹³=t-Bu, direct conversion to 8 can be accomplished by treatment of 3 with strong acid such as HCl or trifluoroacetic acid. Conversion of 8 to 7 is accomplished in analogous fashion to the methods used to prepare 5 from 4 or 7 from 6. In this instance however, the caps in 7 will be identical.

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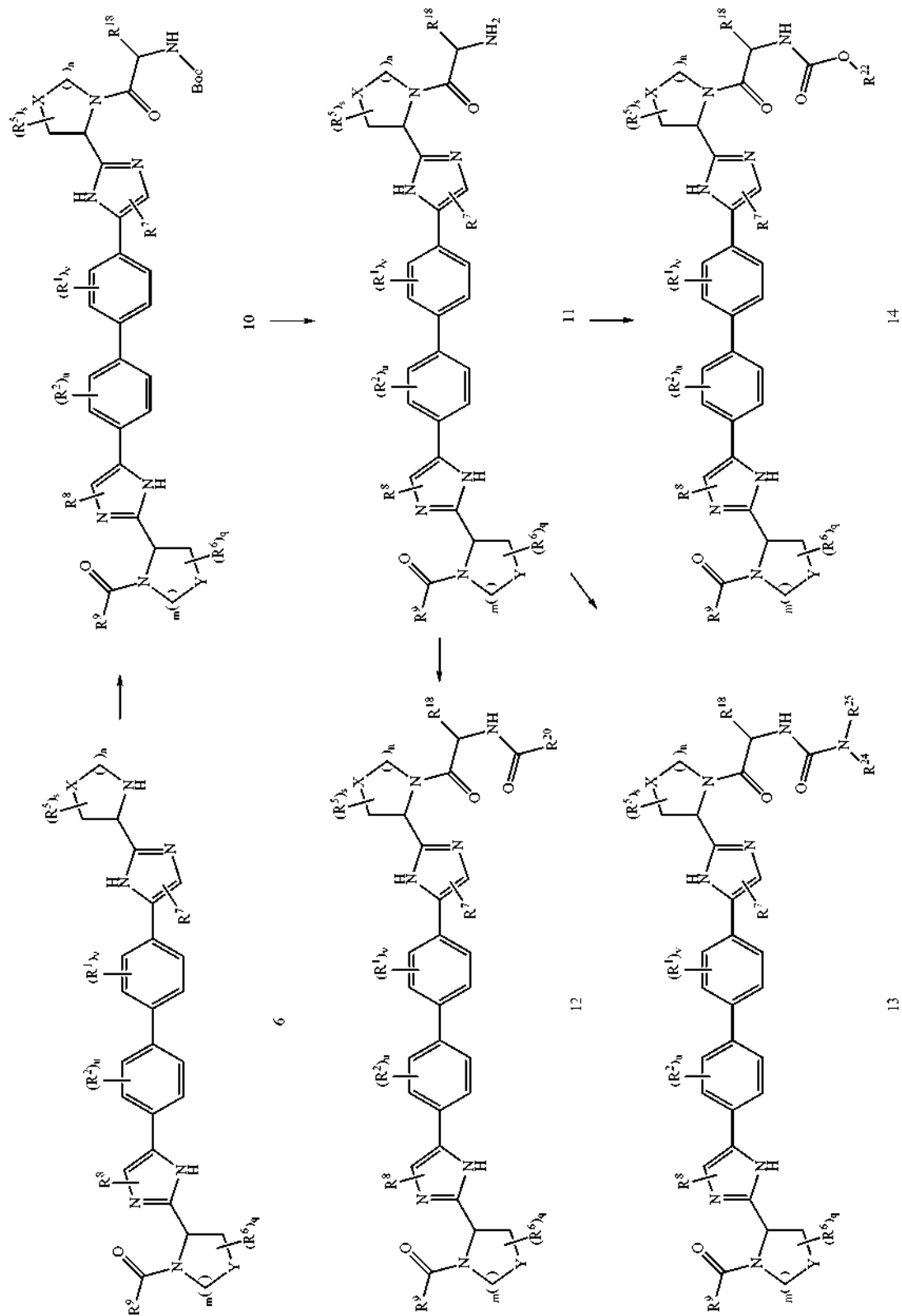


Scheme 2

Asymmetrically Capped Biphenyls

[0209] Conversion of 6 (from Scheme 1) to 10 can be done using standard amide coupling conditions such as HATU with

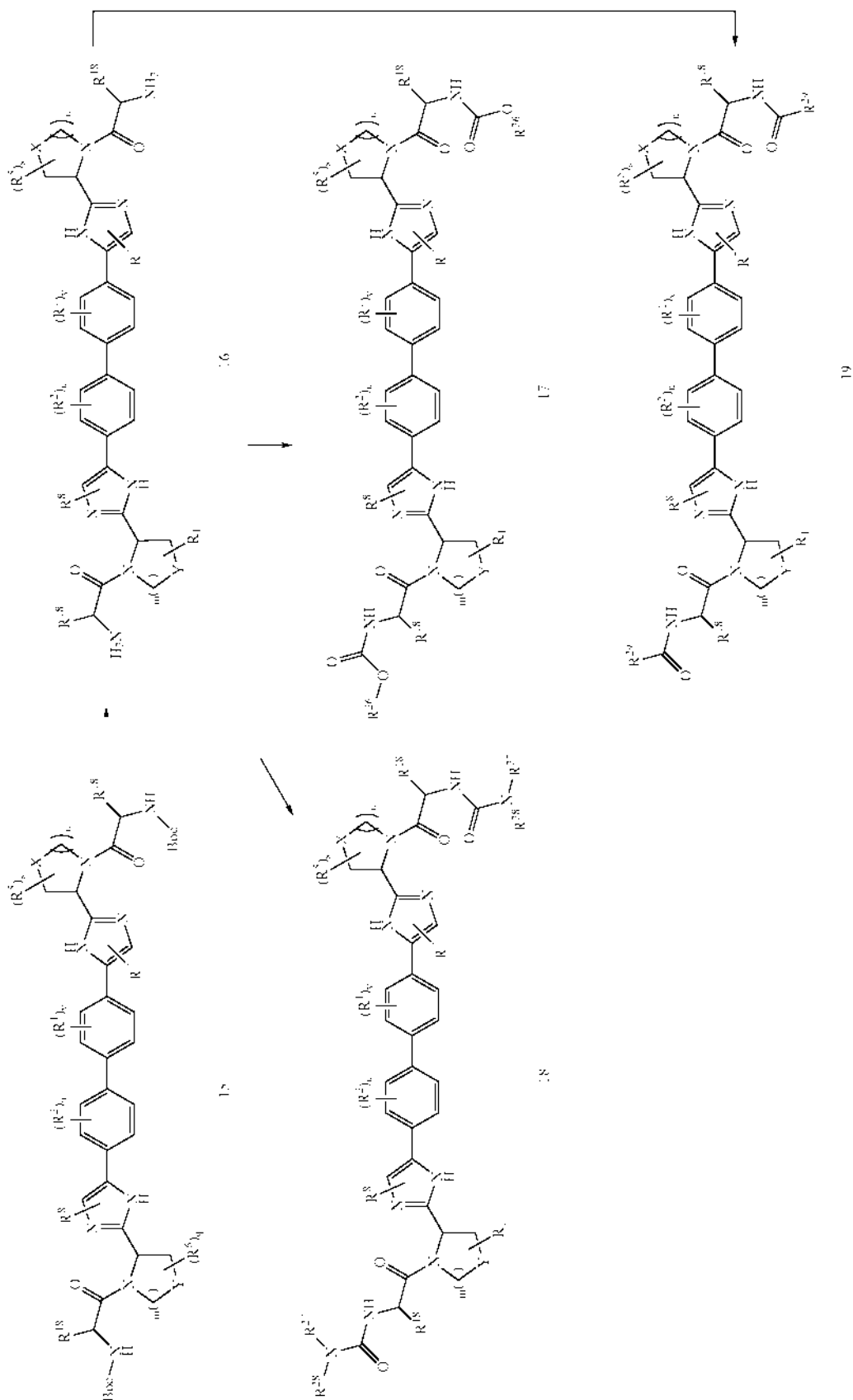
an amine base, such as Hunig's base. Deprotection can be accomplished with strong acid such as HCl or trifluoroacetic acid affording 11. Compound 11 can then be converted to 12, 13, or 14 using an acid chloride, an isocyanate or carbamoyl chloride, or a chloroformate respectively.



Scheme 3

Symmetric Cap Elaborated Biphenyls

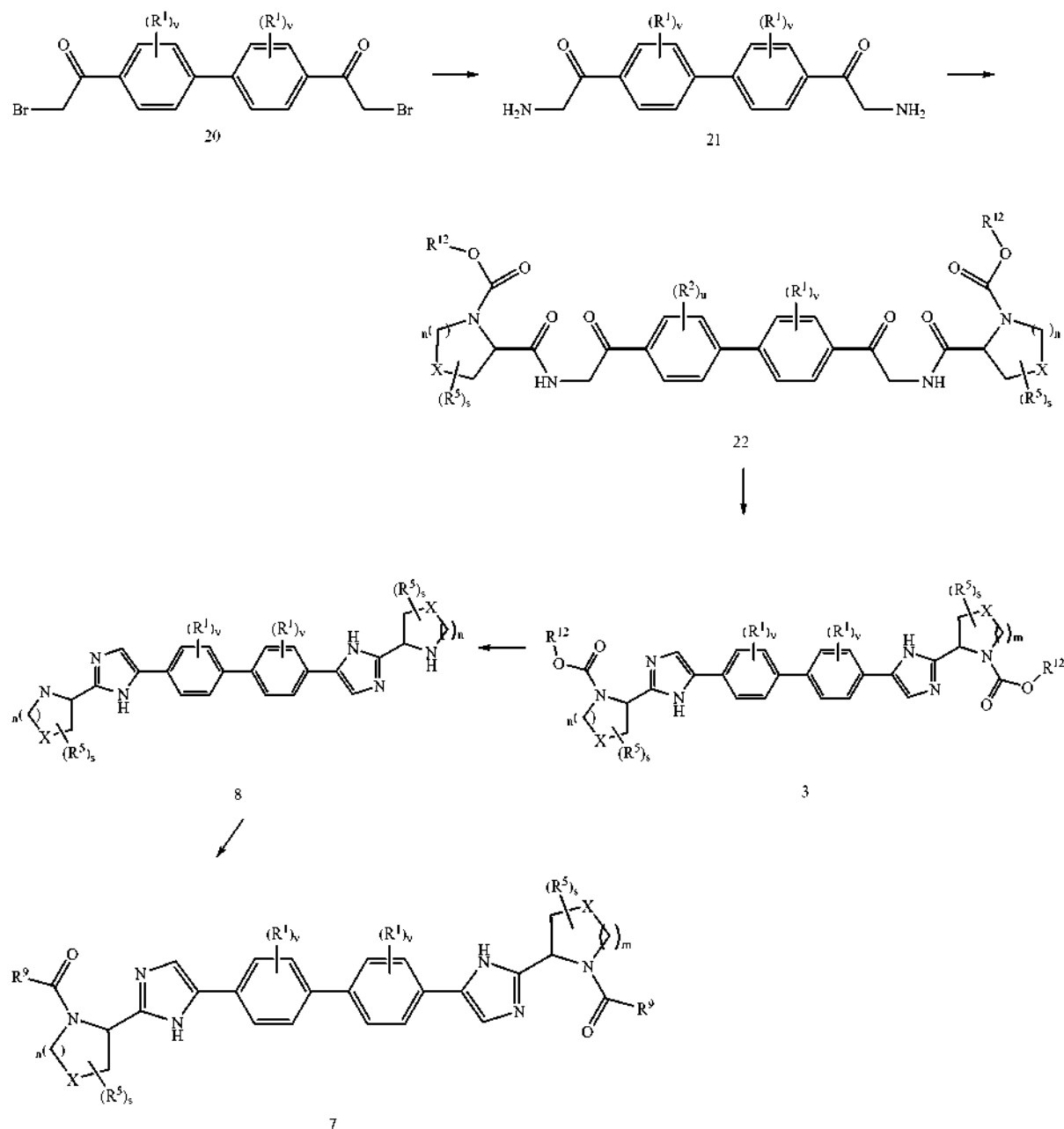
[0210] Compound 15 (15=7 (Scheme 1) wherein each R^9 is $-\text{CH}(\text{NHBoc})R^{18}$) can be converted to 16 via treatment with strong acid such as HCl or trifluoroacetic acid. Compounds 17, 18, and 19 can be prepared from 16 by treating 16 with an appropriate chloroformate, isocyanate or carbamoyl chloride, or an acid chloride respectively.



Scheme 4
Symmetric Biphenyls

[0211] Symmetrical biphenyl analogs (compounds of formula 7 where both halves of the molecule are equivalent) can be synthesized starting from bromoketone 20. Amination by displacement with a nucleophile such as azide, phthalimide or preferably sodium diformylamide (Yinglin and Hongwen, *Synthesis* 1990, 122) followed by deprotection affords 21. Condensation under standard amination conditions such as HATU and Hunig's base with an appropriately protected

amino acid provides 22. Heating with ammonium acetate under thermal or microwave conditions results in the formation of 3 which can be deprotected with strong acid such as HCl or trifluoroacetic acid ($R^{12}=R^{13}=t\text{-Bu}$) or by hydrogenolysis with hydrogen gas and a transition metal catalyst such as Pd/C ($R^{12}=R^{13}=\text{benzyl}$). Acylation can be affected with a carboxylic acid ($R^9\text{CO}_2\text{H}$) in a manner similar to the conversion of 21 to 22. Urea formation can be accomplished by treatment with an appropriate isocyanate ($R^9=R^{24}R^{25}\text{N}$; $R^{25}=\text{H}$) or carbamoyl chloride ($R^9=R^{24}R^{25}\text{N}$; R^{25} is other than hydrogen).

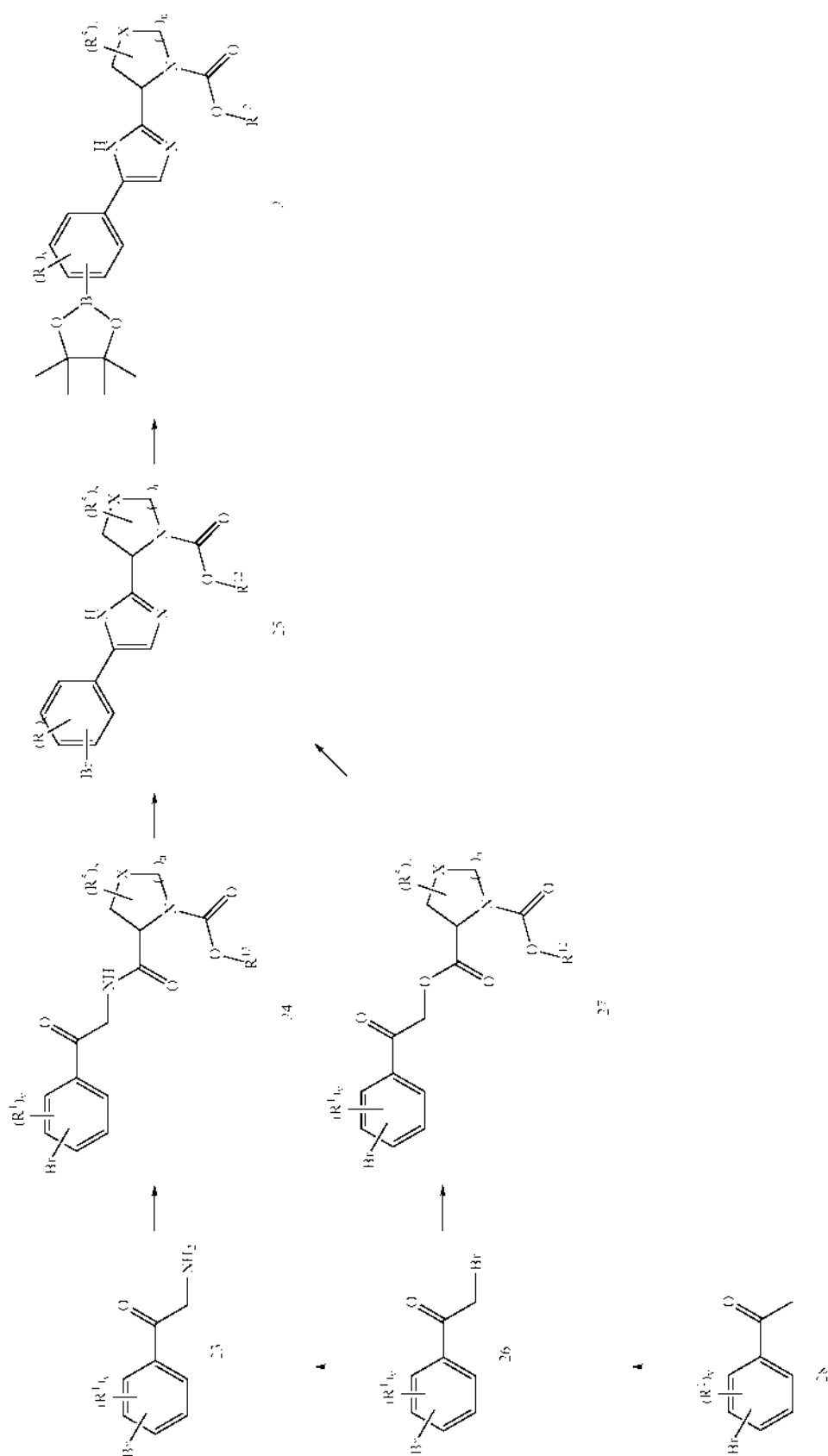


Scheme 5

Starting Materials 25 and 2

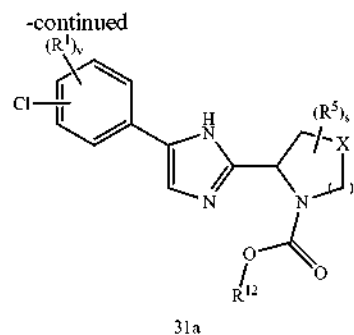
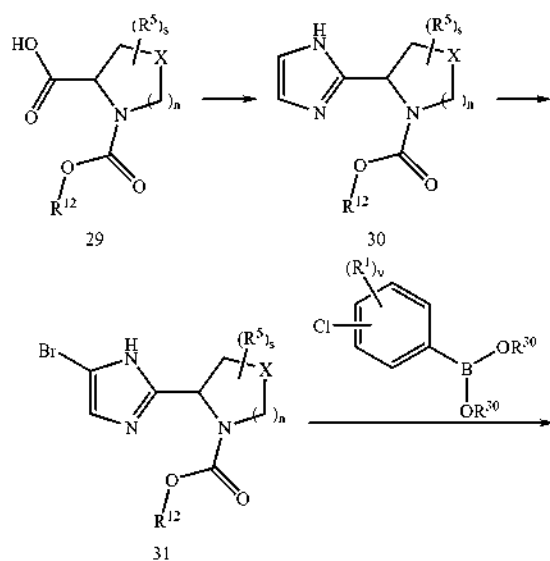
[0212] Scheme 5 describes the preparation of some of the starting materials required for the synthetic sequences depicted in Schemes 1-4. Key intermediate 25 (analogous to 1 in Scheme 1) is prepared from keto-amide 24 or keto-ester 27 via heating with ammonium acetate under thermal or microwave conditions. Keto-amide 24 can be prepared from 23 via condensation with an appropriate cyclic or acyclic amino acid under standard amide formation conditions. Bro-

mide 26 can give rise to 23 by treatment with a nucleophile such as azide, phthalimide or sodium diformylamide (*Synthesis* 1990, 122) followed by deprotection. Bromide 26 can also be converted to 27 by reacting with an appropriate cyclic or acyclic N-protected amino acid in the presence of base such as potassium carbonate or sodium bicarbonate. Bromination of 28 with a source of bromonium ion such as bromine, NBS, or CBr₄ results in the formation of 26. Bromide 25 can be converted to boronic ester 2 via treatment with bis-pinacolatodiboron under palladium catalysis according to the method described in *Journal of Organic Chemistry* 1995, 60, 7508, or variations thereof.



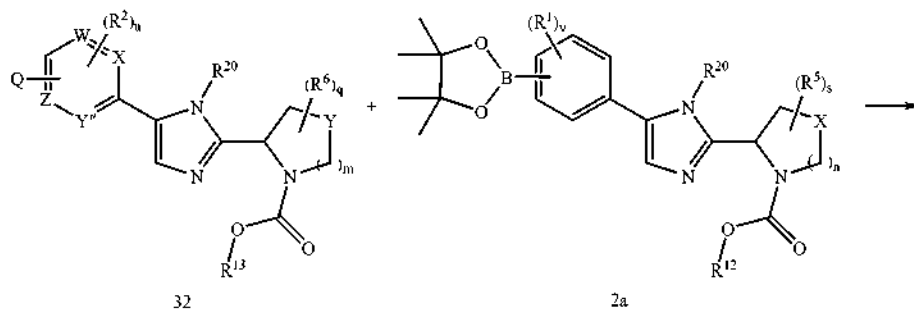
Scheme 6
Starting Material 31a

[0213] In another embodiment, starting materials such as 31a (analogous to 25 in Scheme 5 and 1 in Scheme 1) may be prepared by reacting bromoimidazole derivatives 31 under Suzuki-type coupling conditions with a variety of chloro-substituted aryl boronic acids which can either be prepared by standard methodologies (see, for example, *Organic Letters* 2006, 8, 305 and references cited therein) or purchased from commercial suppliers. Bromoimidazole 31 can be obtained by brominating imidazole 30 with a source of bromonium ion such as bromine, CBr_4 , or N-bromosuccinimide. Imidazole 30 can be prepared from N-protected amino acids which are appropriately substituted by reacting with glyoxal in a methanolic solution of ammonium hydroxide.



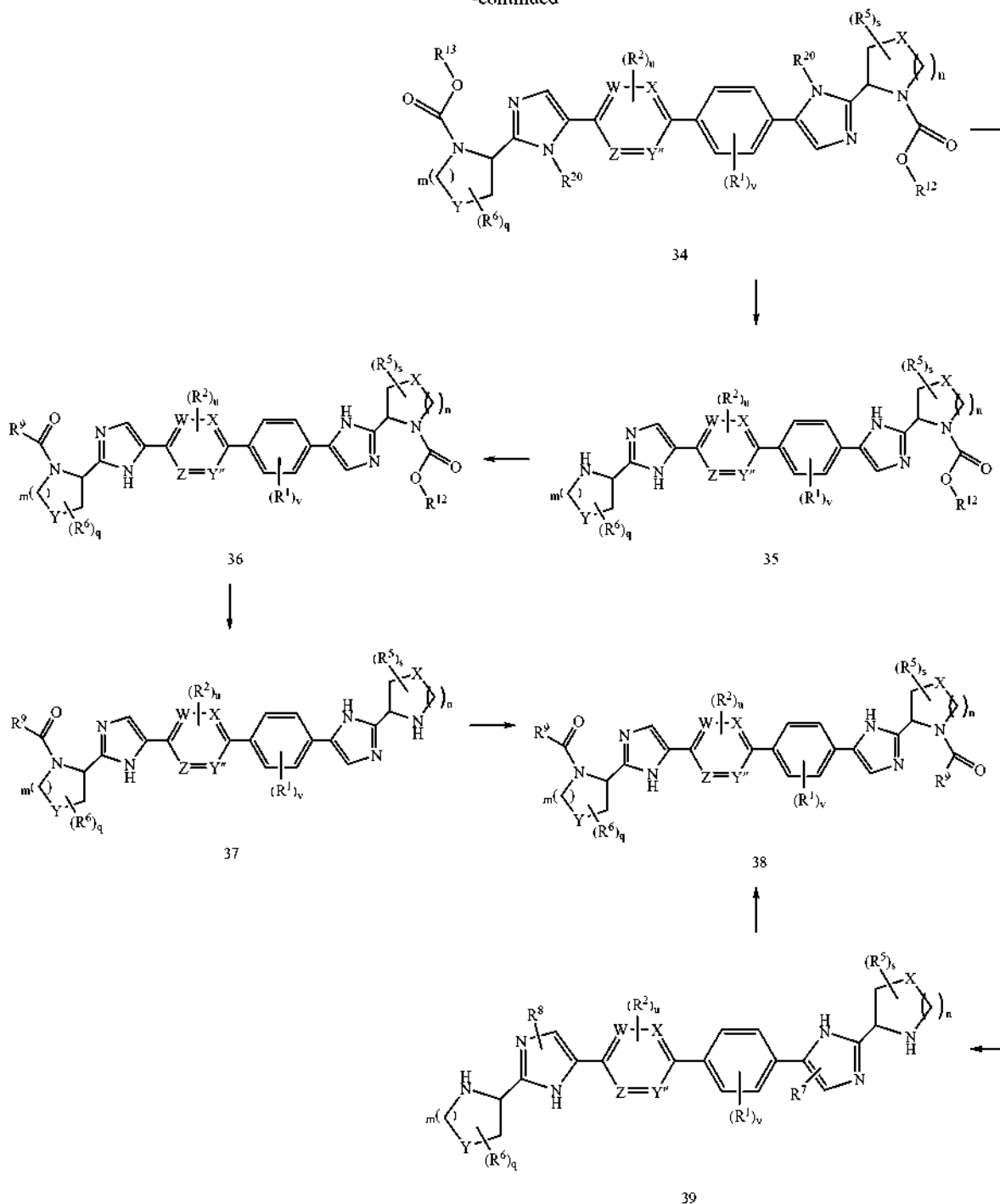
Scheme 7
Heteroaryls

[0214] In yet another embodiment of the current disclosure, aryl halide 32 can be coupled under Suzuki-Miyaura palladium catalyzed conditions to form the heteroaryl derivative 34. Compound 34 can be elaborated to 35 by treatment to hydrogenolytic conditions with hydrogen and a transition metal catalyst such as palladium on carbon ($\text{R}^{13}=\text{benzyl}$). Acylation of 35 can be accomplished with an appropriate acid chloride (R^9COCl) in the presence of a base such as triethylamine, with an appropriately substituted carboxylic acid ($\text{R}^9\text{CO}_2\text{H}$) in the presence of a standard coupling reagent such as HATU, or with an isocyanate (R^{27}NCO wherein $\text{R}^9=\text{R}^{27}\text{R}^{28}\text{N}-$; $\text{R}^{28}=\text{H}$) or carbamoyl chloride ($\text{R}^9\text{R}^{28}\text{NCOC}$ wherein $\text{R}^9=\text{R}^{27}\text{R}^{28}\text{N}-$). Compound 37 can be prepared from 36 ($\text{R}^{12}=\text{t-Bu}$) via treatment with strong acid such as HCl or trifluoroacetic acid. Acylation of the resulting amine in 37 to give 38 can be accomplished as in the transformation of 35 to 36. In cases where $\text{R}^{12}=\text{R}^{13}$, 34 can be directly transformed into 39 by treatment with strong acid such as HCl or trifluoroacetic acid ($\text{R}^{12}=\text{R}^{13}=\text{t-Bu}$) or by employing hydrogenolytic conditions with hydrogen and a transition metal catalyst such as palladium on carbon ($\text{R}^{12}=\text{R}^{13}=\text{benzyl}$). Acylation of 39 can be accomplished in analogous fashion to that described for the transformation of 35 to 36.



R^{12} and R^{13} are independently alkoxymethyl or H
 $\text{Q} = \text{Cl}$ or Br

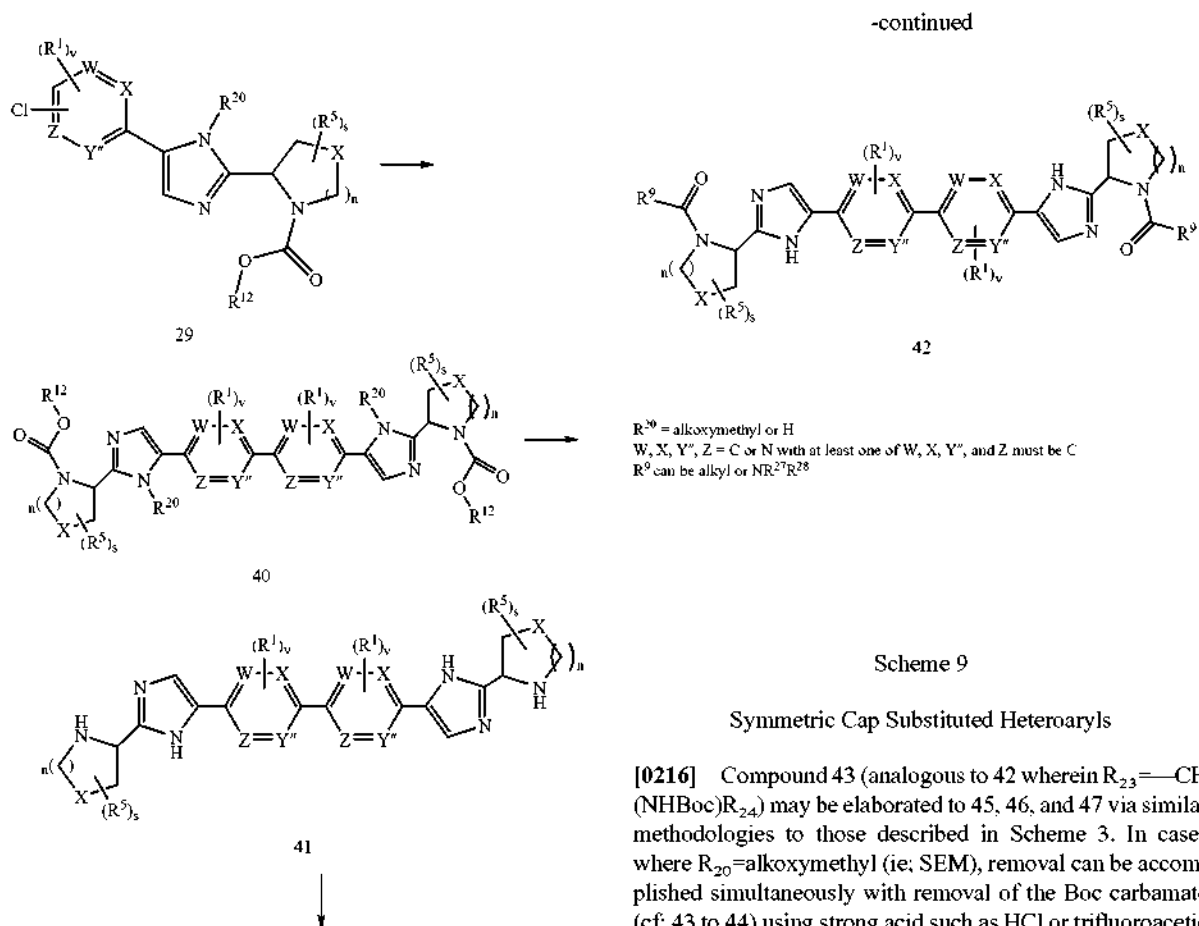
-continued



Scheme 8

[0215] Heteroaryl chloride 29 can be converted to symmetrical analog 40 via treatment with a source of palladium such as dichlorobis(benzonitrile) palladium in the presence of tetrakis(dimethylamino)ethylene at elevated temperature.

Removal of the SEM ether and Boc carbamates found in 40 can be accomplished in one step by treatment with a strong acid such as HCl or trifluoroacetic acid providing 41. Conversion to 42 can be accomplished in similar fashion to the conditions used to convert 38 to 39 in Scheme 7.

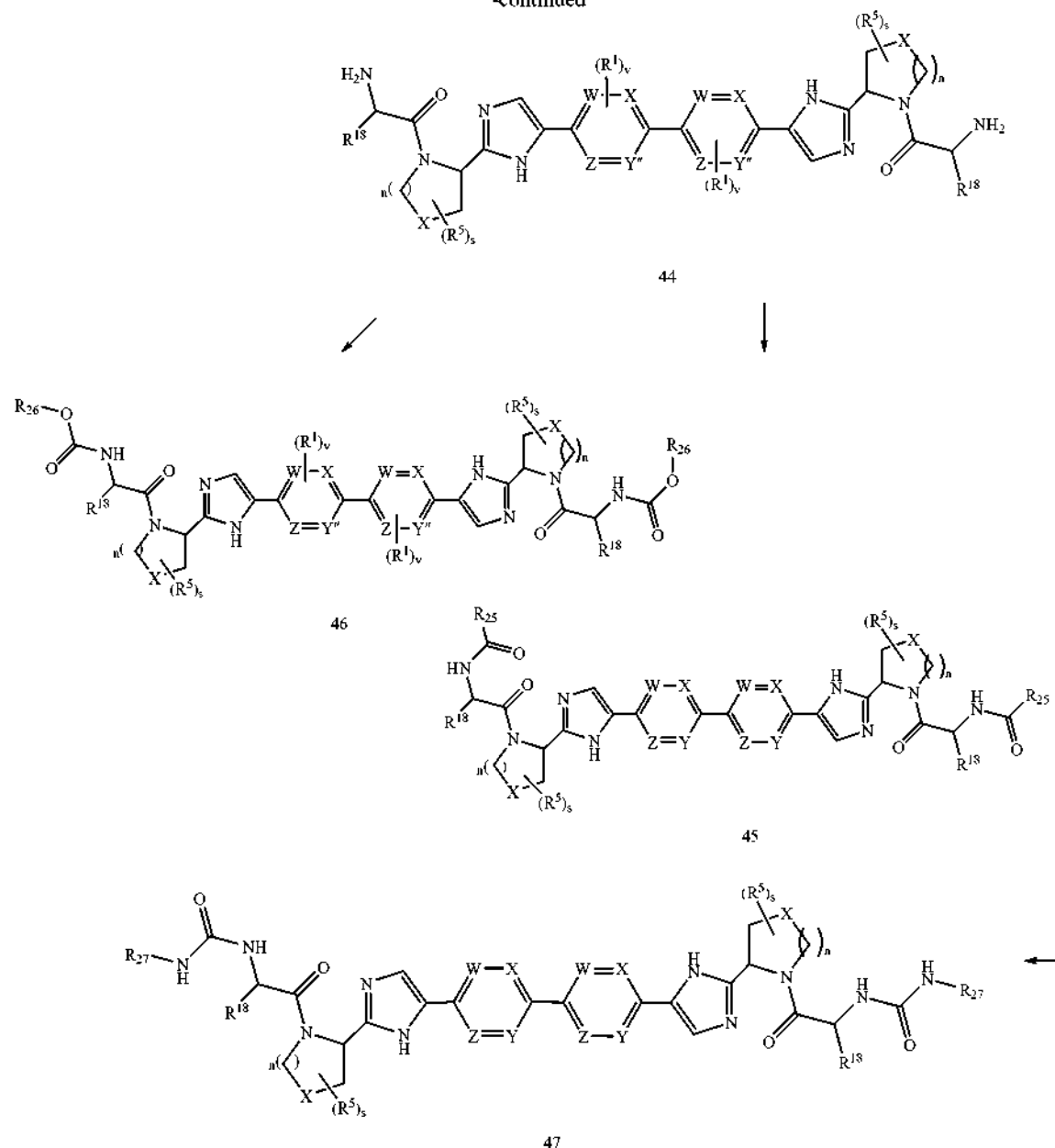


Scheme 9

Symmetric Cap Substituted Heteroaryls

[0216] Compound 43 (analogous to 42 wherein R_{23} = —CH(NHBoc) R_{24}) may be elaborated to 45, 46, and 47 via similar methodologies to those described in Scheme 3. In cases where R_{20} = alkoxymethyl (ie; SEM), removal can be accomplished simultaneously with removal of the Boc carbamate (cf; 43 to 44) using strong acid such as HCl or trifluoroacetic acid.

-continued

R₂₀ = alkoxyethyl or H

W, X, Y, Z = C or N with at least one of W, X, Y, and Z must be C; at least one of W, X, Y, and Z must be N

Scheme 10

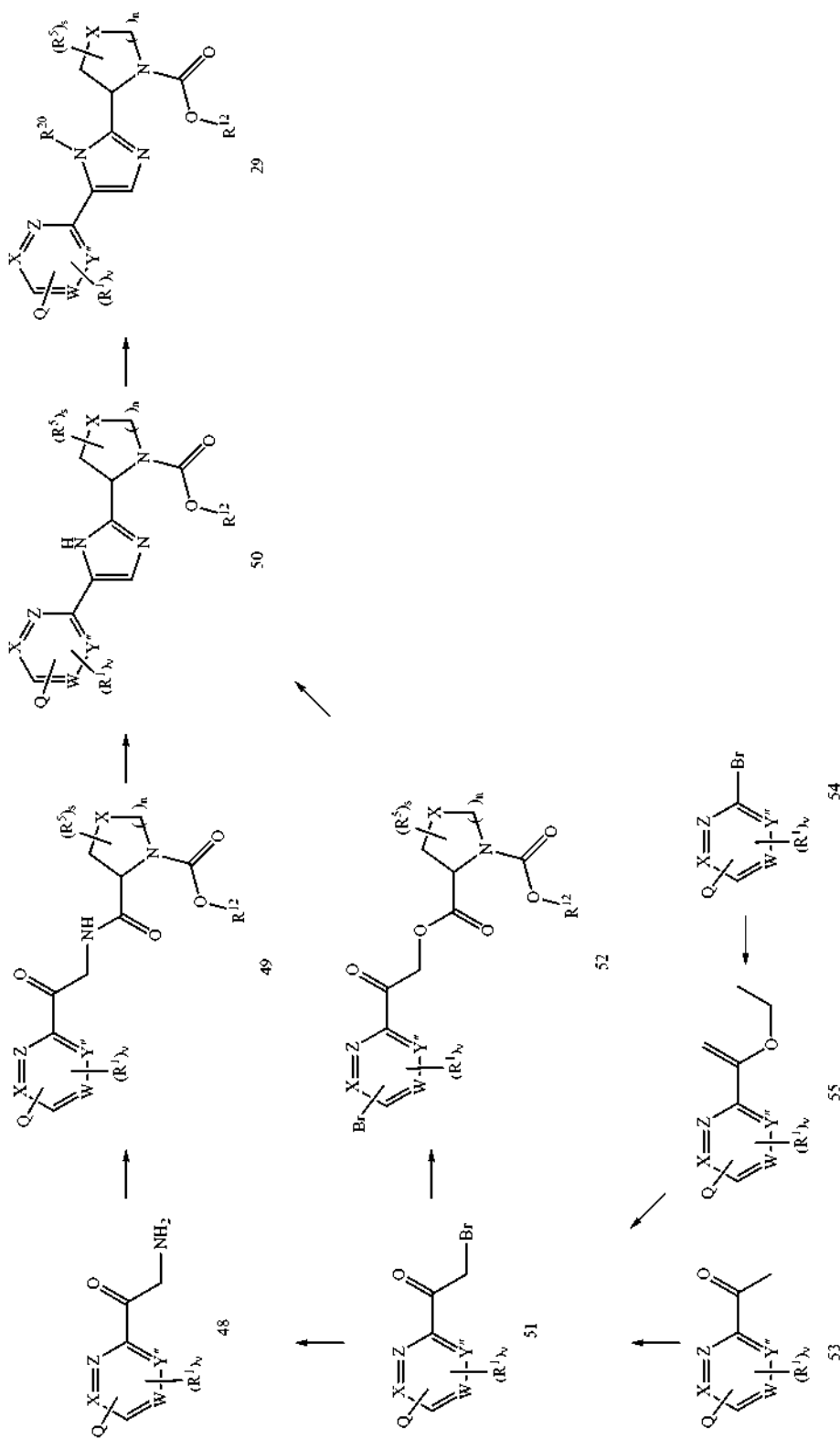
Starting Material 29

[0217] Heteroaryl bromides 54 may be reacted with a vinyl stannane such as tributyl(1-ethoxyvinyl)tin in the presence of a source of palladium such as dichlorobis(triphenylphosphine)palladium (II) to provide 55 which can be subsequently transformed into bromoketone 51 via treatment with a source of bromonium ion such as N-bromosuccinimide, CBr₄, or bromine. Alternatively, keto-substituted heteroaryl bromides

53 may be directly converted to 51 via treatment with a source of bromonium ion such as bromine, CBr₄, or N-bromosuccinimide. Bromide 51 can be converted to aminoketone 48 via addition of sodium azide, potassium phthalimide or sodium diformylamide (*Synthesis* 1990 122) followed by deprotection. Aminoketone 48 can then be coupled with an appropriately substituted amino acid under standard amide formation conditions (i.e.; a coupling reagent such as HATU in the presence of a mild base such as Hunig's base) to provide 49. Compound 49 can then be further transformed into imidazole 50 via reacting with ammonium acetate under thermal or

microwave conditions. Alternatively, 51 can be directly reacted with an appropriately substituted amino acid in the presence of a base such as sodium bicarbonate or potassium carbonate providing 52 which can in turn be reacted with ammonium acetate under thermal or microwave conditions to

provide 50. Imidazole 50 can be protected with an alkoxymethyl group by treatment with the appropriate alkoxymethyl halide such as 2-(trimethylsilyl)ethoxymethyl chloride after first being deprotonated with a strong base such as sodium hydride.



Q = Cl or Br
W, X, Y, Z = C or N; at least one of W, X, Y, and Z must be C; at least one of W, X, Y, and Z must be N

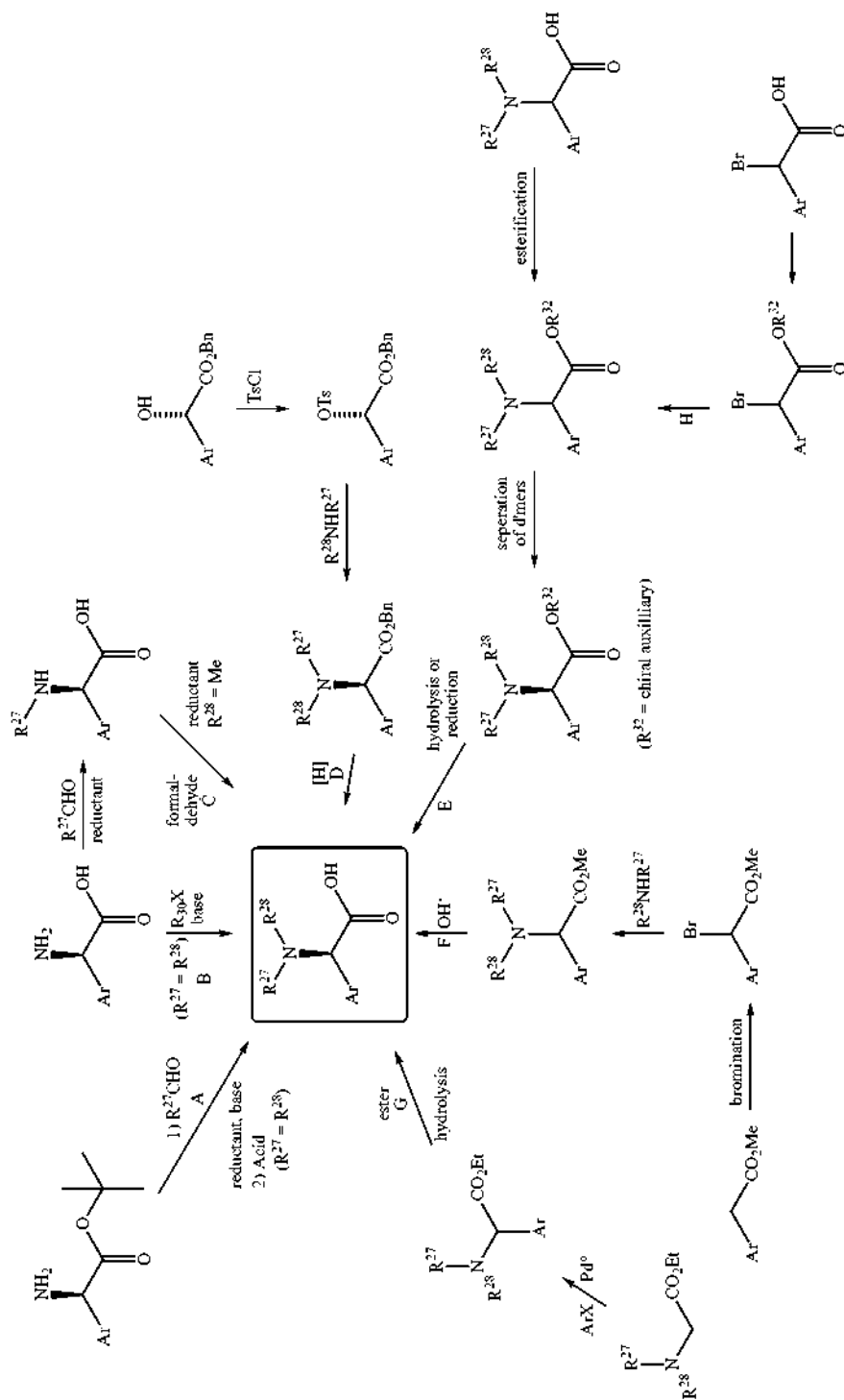
Scheme 11

Substituted Phenylglycine Derivatives

[0218] Substituted phenylglycine derivatives can be prepared by a number of methods shown below. Phenylglycine t-butyl ester can be reductively alkylated (pathway A) with an appropriate aldehyde and a reductant such as sodium cyanoborohydride in acidic medium. Hydrolysis of the t-butyl ester can be accomplished with strong acid such as HCl or trifluoroacetic acid. Alternatively, phenylglycine can be alkylated with an alkyl halide such as ethyl iodide and a base such as sodium bicarbonate or potassium carbonate (pathway B). Pathway C illustrates reductive alkylation of phenylglycine as in pathway A followed by a second reductive alkylation with an alternate aldehyde such as formaldehyde in the presence of a reducing agent and acid. Pathway D illustrates the synthesis of substituted phenylglycines via the corresponding mandelic acid analogs. Conversion of the secondary alcohol to a competent leaving group can be accomplished with p-toluenesulfonyl chloride. Displacement of the tosylate group with an appropriate amine followed by reductive removal of the benzyl ester can provide substituted phenylglycine derivatives. In pathway E a racemic substituted phenylglycine derivative is resolved by esterification with an enantiomerically pure chiral auxiliary such as but not limited to (+)-1-phenylethanol, (-)-1-phenylethanol, an Evan's

oxazolidinone, or enantiomerically pure pantolactone. Separation of the diastereomers is accomplished via chromatography (silica gel, HPLC, crystallization, etc) followed by removal of the chiral auxiliary providing enantiomerically pure phenylglycine derivatives. Pathway H illustrates a synthetic sequence which intersects with pathway E wherein the aforementioned chiral auxiliary is installed prior to amine addition. Alternatively, an ester of an arylacetic acid can be brominated with a source of bromonium ion such as bromine, N-bromosuccinimide, or CBr_4 . The resultant benzylic bromide can be displaced with a variety of mono- or disubstituted amines in the presence of a tertiary amine base such as triethylamine or Hunig's base. Hydrolysis of the methyl ester via treatment with lithium hydroxide at low temperature or 6N HCl at elevated temperature provides the substituted phenylglycine derivatives. Another method is shown in pathway G. Glycine analogs can be derivatized with a variety of aryl halides in the presence of a source of palladium (0) such as palladium bis(tributylphosphine) and base such as potassium phosphate. The resultant ester can then be hydrolyzed by treatment with base or acid. It should be understood that other well known methods to prepare phenylglycine derivatives exist in the art and can be amended to provide the desired compounds in this description. It should also be understood that the final phenylglycine derivatives can be purified to enantiomeric purity greater than 98% ee via preparative HPLC.

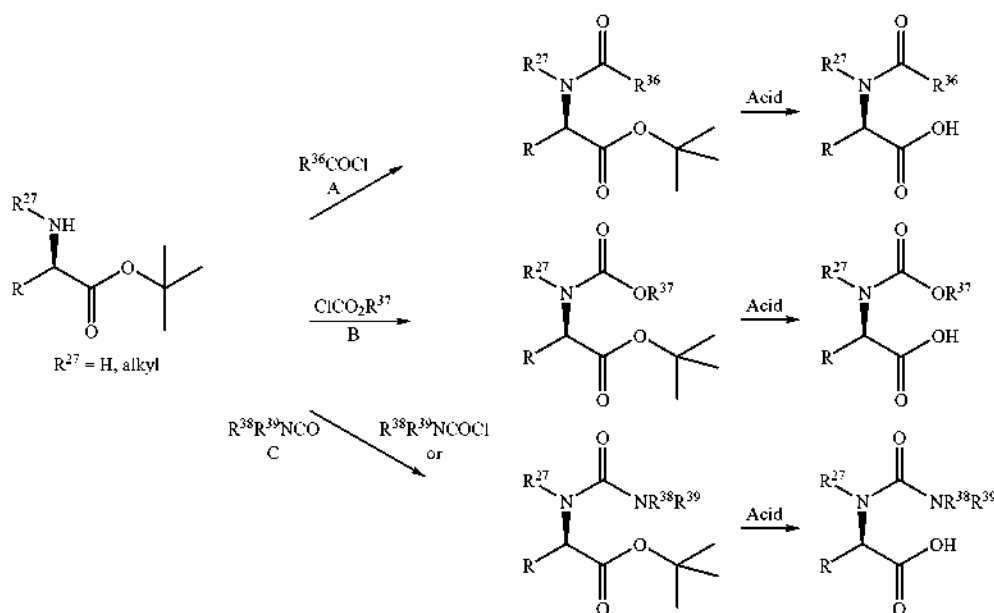
Mar. 12, 2009



Scheme 12

Acylated Amino Acid Derivatives

[0219] In another embodiment of the present disclosure, acylated phenylglycine derivatives may be prepared as illustrated below. Phenylglycine derivatives wherein the carboxylic acid is protected as an easily removed ester, may be acylated with an acid chloride in the presence of a base such as triethylamine to provide the corresponding amides (pathway A). Pathway B illustrates the acylation of the starting phenylglycine derivative with an appropriate chloroformate while pathway C shows reaction with an appropriate isocyanate or carbamoyl chloride. Each of the three intermediates shown in pathways A-C may be deprotected by methods known by those skilled in the art (ie; treatment of the t-butyl ester with strong base such as HCl or trifluoroacetic acid).



Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Condition 1

Column=Phenomenex-Luna 3.0×50 mm S10

Start % B=0

Final % B=100

[0222] Gradient time=2 min

Stop time=3 min

Flow Rate=4 mL/min

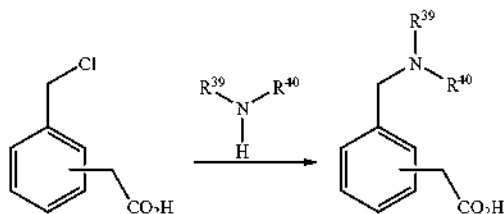
Wavelength=220 nm

[0223] Solvent A=0.1% TFA in 10% methanol/90% H₂O

Solvent B=0.1% TFA in 90% methanol/10% H₂O

Scheme 13

[0220] Amino-substituted phenylacetic acids may be prepared by treatment of a chloromethylphenylacetic acid with an excess of an amine.



Condition 2

Column=Phenomenex-Luna 4.6×50 mm S10

Start % B=0

Final % B=100

[0224] Gradient time=2 min

Stop time=3 min

Flow Rate=5 mL/min

Wavelength=220 nm

[0225] Solvent A=0.1% TFA in 10% methanol/90% H₂O

Solvent B=0.1% TFA in 90% methanol/10% H₂O

Condition 3

Column=HPLC XTERRA C18 3.0×50 mm S7

Start % B=0

Final % B=100

Compound Analysis Conditions

[0221] Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with

[0226] Gradient time=3 min
Stop time=4 min
Flow Rate=4 mL/min

Wavelength=220 nm

[0227] Solvent A=0.1% TFA in 10% methanol/90% H₂O
Solvent B=0.1% TFA in 90% methanol/10% H₂O

Condition M1

Column: Luna 4.6x50 mm S10

Start % B=0

Final % B=100

[0228] Gradient time=3 min

Stop time=4 min

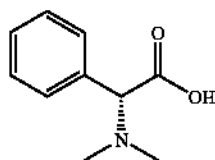
Flow rate=4 mL/min

Solvent A:=95% H₂O: 5% CH₃CN; 10 mm Ammonium acetate

Solvent B:=5% H₂O: 95% CH₃CN; 10 mm Ammonium acetate

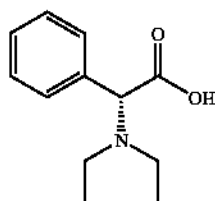
Synthesis of Common Caps

[0229]



Cap-1

[0230] A suspension of 10% Pd/C (2.0 g) in methanol (10 mL) was added to a mixture of (R)-2-phenylglycine (10 g, 66.2 mmol), formaldehyde (33 mL of 37% wt. in water), 1N HCl (30 mL) and methanol (30 mL), and exposed to H₂ (60 psi) for 3 hours. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated in vacuo. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of Cap-1 as a white needle (4.0 g). Optical rotation: -117.1° [$c=9.95$ mg/mL in H₂O; $\lambda=589$ nm]. ¹H NMR (DMSO-d₆, $\delta=2.5$ ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H); LC (Cond. 1): RT=0.25; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₀H₁₄NO₂ 180.10; found 180.17; HRMS: Anal. Calcd. for [M+H]⁺ C₁₀H₁₄NO₂ 180.1025; found 180.1017.

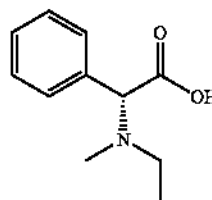


Cap-2

[0231] NaBH₃CN (6.22 g, 94 mmol) was added in portions over a few minutes to a cooled (ice/water) mixture of (R)-2-Phenylglycine (6.02 g, 39.8 mmol) and MeOH (100 mL), and stirred for 5 min. Acetaldehyde (10 mL) was added drop-wise

over 10 min and stirring was continued at the same cooled temperature for 45 min and at ambient temperature for ~6.5 hr. The reaction mixture was cooled back with ice-water bath, treated with water (3 mL) and then quenched with a drop-wise addition of concentrated HCl over ~45 min until the pH of the mixture is ~1.5-2.0. The cooling bath was removed and the stirring was continued while adding concentrated HCl in order to maintain the pH of the mixture around 1.5-2.0. The reaction mixture was stirred over night, filtered to remove the white suspension, and the filtrate was concentrated in vacuo. The crude material was recrystallized from ethanol to afford the HCl salt of Cap-2 as a shining white solid in two crops (crop-1: 4.16 g; crop-2: 2.19 g). ¹H NMR (DMSO-d₆, $\delta=2.5$ ppm, 400 MHz): 10.44 (1.00, br s, 1H), 7.66 (m, 2H), 7.51 (m, 3H), 5.30 (s, 1H), 3.15 (br m, 2H), 2.98 (br m, 2H), 1.20 (app br s, 6H). Crop-1: $[\alpha]^{25}_{D}-102.21^\circ$ ($c=0.357$, H₂O); crop-2: $[\alpha]^{25}_{D}-99.7^\circ$ ($c=0.357$, H₂O). LC (Cond. 1): RT=0.43 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₂H₁₈NO₂: 208.13; found 208.26

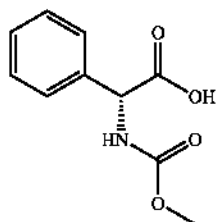
Cap-3



[0232] Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H₂O (4 mL/1 mL) was sequentially added to a cooled (~15° C.) mixture of (R)-2-phenylglycine (3.096 g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under a balloon of H₂ for 17 hours. An additional acetaldehyde (10 mL, 178.2 mmol) was added and stirring continued under H₂ atmosphere for 24 hours [Note: the supply of H₂ was replenished as needed throughout the reaction]. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated in vacuo. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of (R)-2-(ethylamino)-2-phenylacetic acid as a shining white solid (2.846 g). ¹H NMR (DMSO-d₆, $\delta=2.5$ ppm, 400 MHz): δ 14.15 (br s, 1H), 9.55 (br s, 2H), 7.55-7.48 (m, 5H), 2.88 (br m, 1H), 2.73 (br m, 1H), 1.20 (app t, J=7.2, 3H). LC (Cond. 1): RT=0.39 min; >95% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₀H₁₄NO₂: 180.10; found 180.18.

[0233] A suspension of 10% Pd/C (536 mg) in methanol/H₂O (3 mL/1 mL) was added to a mixture of (R)-2-(ethylamino)-2-phenylacetic acid/HCl (1.492 g, 6.918 mmol), formaldehyde (20 mL of 37% wt. in water), 1N HCl (20 mL) and methanol (23 mL). The reaction mixture was stirred under a balloon of H₂ for ~72 hours, where the H₂ supply was replenished as needed. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated in vacuo. The resulting crude material was recrystallized from isopropanol (50 mL) to provide the HCl salt of Cap-3 as a white solid (985 mg). ¹H NMR (DMSO-d₆, $\delta=2.5$ ppm, 400 MHz): δ 10.48 (br s, 1H), 7.59-7.51 (m, 5H), 5.26 (s, 1H), 3.08 (app br s, 2H), 2.65 (br s, 3H), 1.24 (br m, 3H). LC (Cond. 1): RT=0.39 min; >95% homogeneity index;

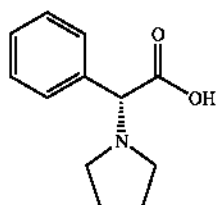
LC/MS: Anal. Calcd. for $[M+H]^+ C_{11}H_{16}NO_2$: 194.12; found 194.18; HRMS: Anal. Calcd. for $[M+H]^+ C_{11}H_{16}NO_2$: 194.1180; found 194.1181.



Cap-4

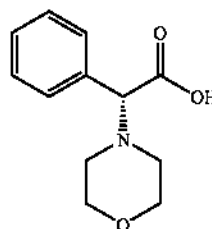
[0234] $ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-tert-butyl 2-amino-2-phenylacetate/HCl (9.877 g, 40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component was removed in vacuo, and the residue was partitioned between water (100 mL) and ethyl acetate (200 mL). The organic layer was washed with 1N HCl (25 mL) and saturated $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resultant colorless oil was triturated from hexanes, filtered and washed with hexanes (100 mL) to provide (R)-tert-butyl 2-(methoxycarbonylamino)-2-phenylacetate as a white solid (7.7 g). 1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): 7.98 (d, J=8.0, 1H), 7.37-7.29 (m, 5H), 5.09 (d, J=8, 1H), 3.56 (s, 3H), 1.33 (s, 9H). LC (Cond. 1): RT=1.53 min; ~90% homogeneity index; LC/MS: Anal. Calcd. for $[M+Na]^+ C_{14}H_{19}NNaO_4$: 288.12; found 288.15.

[0235] TFA (16 mL) was added dropwise to a cooled (ice/water) CH_2Cl_2 (160 mL) solution of the above product over 7 minutes, and the cooling bath was removed and the reaction mixture was stirred for 20 hours. Since the deprotection was still not complete, an additional TFA (1.0 mL) was added and stirring continued for an additional 2 hours. The volatile component was removed in vacuo, and the resulting oil residue was treated with diethyl ether (15 mL) and hexanes (12 mL) to provide a precipitate. The precipitate was filtered and washed with diethyl ether/hexanes (~1:3 ratio; 30 mL) and dried in vacuo to provide Cap-4 as a fluffy white solid (5.57 g). Optical rotation: -176.9° [c =3.7 mg/mL in H_2O ; λ =589 nm]. 1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): δ 12.84 (br s, 1H), 7.96 (d, J=8.3, 1H), 7.41-7.29 (m, 5H), 5.14 (d, J=8.3, 1H), 3.55 (s, 3H). LC (Cond. 1): RT=1.01 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+ C_{10}H_{12}NO_4$: 210.08; found 210.17; HRMS: Anal. Calcd. for $[M+H]^+ C_{10}H_{12}NO_4$: 210.0766; found 210.0756.



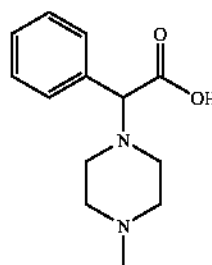
Cap-5

[0236] A mixture of (R)-2-phenylglycine (1.0 g, 6.62 mmol), 1,4-dibromobutane (1.57 g, 7.27 mmol) and Na_2CO_3 (2.10 g, 19.8 mmol) in ethanol (40 mL) was heated at 100° C. for 21 hours. The reaction mixture was cooled to ambient temperature and filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in ethanol and acidified with 1N HCl to pH 3-4, and the volatile component was removed in vacuo. The resulting crude material was purified by a reverse phase HPLC (water/methanol/TFA) to provide the TFA salt of Cap-5 as a semi-viscous white foam (1.0 g). 1H NMR (DMSO- d_6 , δ =2.5, 500 MHz) δ 10.68 (br s, 1H), 7.51 (m, 5H), 5.23 (s, 1H), 3.34 (app br s, 2H), 3.05 (app br s, 2H), 1.95 (app br s, 4H); RT=0.30 min (Cond. 1); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+ C_{12}H_{16}NO_2$: 206.12; found 206.25.



Cap-6

[0237] The TFA salt of Cap-6 was synthesized from (R)-2-phenylglycine and 1-bromo-2-(2-bromoethoxy)ethane by using the method of preparation of Cap-5. 1H NMR (DMSO- d_6 , δ =2.5, 500 MHz) δ 12.20 (br s, 1H), 7.50 (m, 5H), 4.92 (s, 1H), 3.78 (app br s, 4H), 3.08 (app br s, 2H), 2.81 (app br s, 2H); RT=0.32 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+ C_{12}H_{16}NO_3$: 222.11; found 222.20; HRMS: Anal. Calcd. for $[M+H]^+ C_{12}H_{16}NO_3$: 222.1130; found 222.1121.



Cap-7

Cap-7a: enantiomer-1
Cap-7b: enantiomer-2

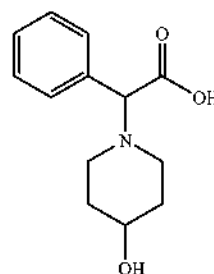
[0238] A CH_2Cl_2 (200 mL) solution of p-toluenesulfonyl chloride (8.65 g, 45.4 mmol) was added dropwise to a cooled ($-5^\circ C$.) CH_2Cl_2 (200 mL) solution of (S)-benzyl 2-hydroxy-2-phenylacetate (10.0 g, 41.3 mmol), triethylamine (5.75 mL, 41.3 mmol) and 4-dimethylaminopyridine (0.504 g, 4.13 mmol), while maintaining the temperature between $-5^\circ C$. and $0^\circ C$. The reaction was stirred at $0^\circ C$. for 9 hours, and then stored in a freezer ($-25^\circ C$.) for 14 hours. It was allowed to thaw to ambient temperature and washed with water (200 mL), 1N HCl (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to provide benzyl 2-phenyl-2-(tosyloxy)acetate as a viscous oil which solidified upon

standing (16.5 g). The chiral integrity of the product was not checked and that product was used for the next step without further purification. ^1H NMR (DMSO- d_6 , δ =2.5, 500 MHz) δ 7.78 (d, J =8.6, 2H), 7.43-7.29 (m, 10H), 7.20 (m, 2H), 6.12 (s, 1H), 5.16 (d, J =12.5, 1H), 5.10 (d, J =12.5, 1H), 2.39 (s, 3H). RT=3.00 (Cond. 3); >90% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{22}\text{H}_{20}\text{NaO}_5$: 419.09; found 419.04.

[0239] A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and *N,N*-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65°C. for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed in vacuo. The residue was partitioned between ethylacetate and water, and the organic layer was washed with water and brine, dried (MgSO_4), filtered, and concentrated in vacuo. The resulting crude material was purified by flash chromatography (silica gel, ethyl acetate) to provide benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate as an orangish-brown viscous oil (4.56 g). Chiral HPLC analysis (Chiralcel OD-H) indicated that the sample is a mixture of enantiomers in a 38.2 to 58.7 ratio. The separation of the enantiomers were effected as follow: the product was dissolved in 120 mL of ethanol/heptane (1:1) and injected (5 mL/injection) on chiral HPLC column (Chiracel OJ, 5 cm ID \times 50 cm L, 20 μm) eluting with 85:15 Heptane/ethanol at 75 mL/min, and monitored at 220 nm. Enantiomer-1 (1.474 g) and enantiomer-2 (2.2149 g) were retrieved as viscous oil. ^1H NMR (CDCl_3 , δ =7.26, 500 MHz) 7.44-7.40 (m, 2H), 7.33-7.24 (m, 6H), 7.21-7.16 (m, 2H), 5.13 (d, J =12.5, 1H), 5.08 (d, J =12.5, 1H), 4.02 (s, 1H), 2.65-2.38 (app br s, 8H), 2.25 (s, 3H). RT=2.10 (Cond. 3); >98% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2$: 325.19; found 325.20.

[0240] A methanol (10 mL) solution of either enantiomer of benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate (1.0 g, 3.1 mmol) was added to a suspension of 10% Pd/C (120 mg) in methanol (5.0 mL). The reaction mixture was exposed to a balloon of hydrogen, under a careful monitoring, for <50 min. Immediately after the completion of the reaction, the catalyst was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated in vacuo to provide Cap-7, contaminated with phenylacetic acid as a tan foam (867.6 mg; mass is above the theoretical yield). The product was used for the next step without further purification. ^1H NMR (DMSO- d_6 , δ =2.5, 500 MHz) δ 7.44-7.37 (m, 2H), 7.37-7.24 (m, 3H), 3.92 (s, 1H), 2.63-2.48 (app. bs, 2H), 2.48-2.32 (m, 6H), 2.19 (s, 3H); RT=0.31 (Cond. 2); >90% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2$: 235.14; found 235.15; HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2$: 235.1447; found 235.1440.

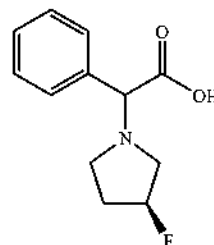
[0241] The synthesis of Cap-8 and Cap-9 was conducted according to the synthesis of Cap-7 by using appropriate amines for the $\text{S}_\text{N}2$ displacement step (i.e., 4-hydroxypiperidine for Cap-8 and (S)-3-fluoropyrrolidine for Cap-9) and modified conditions for the separation of the respective stereoisomeric intermediates, as described below.



Cap-8

8a: enantiomer-1
8b: enantiomer-2

[0242] The enantiomeric separation of the intermediate benzyl 2-(4-hydroxypiperidin-1-yl)-2-phenyl acetate was effected by employing the following conditions: the compound (500 mg) was dissolved in ethanol/heptane (5 mL/45 mL). The resulting solution was injected (5 mL/injection) on a chiral HPLC column (Chiracel OJ, 2 cm ID \times 25 cm L, 10 μm) eluting with 80:20 heptane/ethanol at 10 mL/min, monitored at 220 nm, to provide 186.3 mg of enantiomer-1 and 209.1 mg of enantiomer-2 as light-yellow viscous oils. These benzyl ester was hydrogenolysed according to the preparation of Cap-7 to provide Cap-8: ^1H NMR (DMSO- d_6 , δ =2.5, 500 MHz) 7.40 (d, J =7, 2H), 7.28-7.20 (m, 3H), 3.78 (s 1H), 3.46 (m, 1H), 2.93 (m, 1H), 2.62 (m, 1H), 2.20 (m, 2H), 1.70 (m, 2H), 1.42 (m, 2H). RT=0.28 (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{13}\text{H}_{18}\text{NO}_3$: 236.13; found 236.07; HRMS: Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{13}\text{H}_{18}\text{NO}_3$: 236.1287; found 236.1283.



Cap-9

9a: diastereomer-1
9b: diastereomer-2

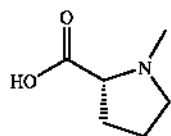
[0243] The diastereomeric separation of the intermediate benzyl 2-((S)-3-fluoropyrrolidin-1-yl)-2-phenylacetate was effected by employing the following conditions: the ester (220 mg) was separated on a chiral HPLC column (Chiracel OJ-H, 0.46 cm ID \times 25 cm L, 5 μm) eluting with 95% CO_2 /5% methanol with 0.1% TFA, at 10 bar pressure, 70 mL/min flow rate, and a temperature of 35°C. The HPLC elute for the respective stereoisomers was concentrated, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with an aqueous medium (10 mL water+1 mL saturated NaHCO_3 solution). The organic phase was dried (MgSO_4), filtered, and concentrated in vacuo to provide 92.5 mg of fraction-1 and 59.6 mg of fraction-2. These benzyl esters were hydrogenolysed according to the preparation of Cap-7 to prepare Caps 9a and 9b. Cap-9a (diastereomer-1; the sample is a TFA salt as a

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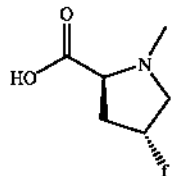
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result of purification on a reverse phase HPLC using H₂O/methanol/TFA solvent): ¹H NMR (DMSO-d₆, δ=2.5, 400 MHz) 7.55-7.48 (m, 5H), 5.38 (d of m, J=53.7, 1H), 5.09 (br s, 1H), 3.84-2.82 (br m, 4H), 2.31-2.09 (m, 2H). RT=0.42 (Cond. 1); >95% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₂H₁₅FNO₂: 224.11; found 224.14; Cap-9b (diastereomer-2): ¹H NMR (DMSO-d₆, δ=2.5, 400 MHz) 7.43-7.21 (m, 5H), 5.19 (d of m, J=55.9, 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). RT=0.44 (Cond. 1); LC/MS: Anal. Calcd. for [M+H]⁺ C₁₂H₁₅FNO₂: 224.11; found 224.14.



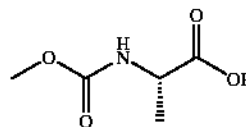
Cap-10

[0244] To a solution of D-proline (2.0 g, 17 mmol) and formaldehyde (2.0 mL of 37% wt. in H₂O) in methanol (15 mL) was added a suspension of 10% Pd/C (500 mg) in methanol (5 mL). The mixture was stirred under a balloon of hydrogen for 23 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated in vacuo to provide Cap-10 as an off-white solid (2.15 g). ¹H NMR (DMSO-d₆, δ=2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, J=9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). RT=0.28 (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₆H₁₂NO₂: 130.09; found 129.96.



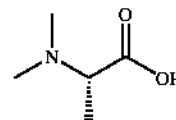
Cap-11

[0245] A mixture of (2S,4R)-4-fluoropyrrolidine-2-carboxylic acid (0.50 g, 3.8 mmol), formaldehyde (0.5 mL of 37% wt. in H₂O), 12 N HCl (0.25 mL) and 10% Pd/C (50 mg) in methanol (20 mL) was stirred under a balloon of hydrogen for 19 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated in vacuo. The residue was recrystallized from isopropanol to provide the HCl salt of Cap-11 as a white solid (337.7 mg). ¹H NMR (DMSO-d₆, δ=2.5, 500 MHz) 5.39 (d m, J=53.7, 1H), 4.30 (m, 1H), 3.90 (ddd, J=31.5, 13.5, 4.5, 1H), 3.33 (dd, J=25.6, 13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2.26 (m, 1H). RT=0.28 (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₆H₁₁FNO₂: 148.08; found 148.06.



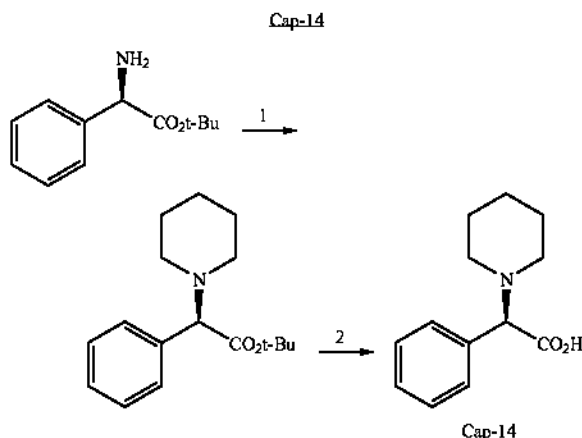
Cap-12

[0246] L-Alanine (2.0 g, 22.5 mmol) was dissolved in 10% aqueous sodium carbonate solution (50 mL), and a THF (50 mL) solution of methyl chloroformate (4.0 mL) was added to it. The reaction mixture was stirred under ambient conditions for 4.5 hours and concentrated in vacuo. The resulting white solid was dissolved in water and acidified with 1N HCl to a pH=2-3. The resulting solutions was extracted with ethyl acetate (3x100 mL), and the combined organic phase was dried (Na₂SO₄), filtered, and concentrated in vacuo to provide a colorless oil (2.58 g). 500 mg of this material was purified by a reverse phase HPLC (H₂O/methanol/TFA) to provide 150 mg of Cap-12 as a colorless oil. ¹H NMR (DMSO-d₆, δ=2.5, 500 MHz) 7.44 (d, J=7.3, 0.8H), 7.10 (brs, 0.2H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J=7.3, 3H).



Cap-13

[0247] A mixture of L-alanine (2.5 g, 28 mmol), formaldehyde (8.4 g, 37 wt. %), 1N HCl (30 mL) and 10% Pd/C (500 mg) in methanol (30 mL) was stirred under a hydrogen atmosphere (50 psi) for 5 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated in vacuo to provide the HCl salt of Cap-13 as an oil which solidified upon standing under vacuum (4.4 g; the mass is above theoretical yield). The product was used without further purification. ¹H NMR (DMSO-d₆, δ=2.5, 500 MHz) δ 12.1 (br s, 1H), 4.06 (q, J=7.4, 1H), 2.76 (s, 6H), 1.46 (d, J=7.3, 3H).



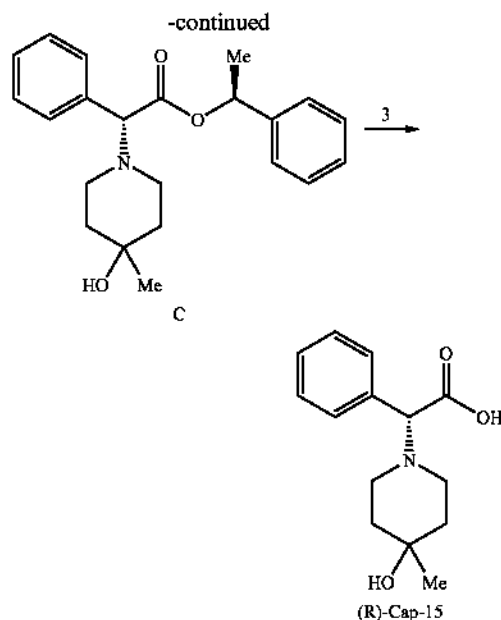
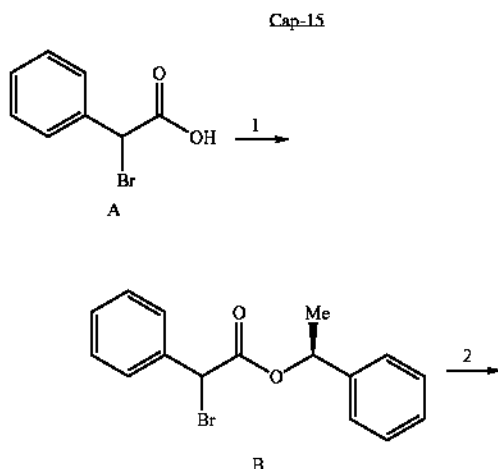
Cap-14

Cap-14

[0248] Step 1: A mixture of (R)-(-)-D-phenylglycine tert-butyl ester (3.00 g, 12.3 mmol), NaBH₃CN (0.773 g, 12.3

mmol), KOH (0.690 g, 12.3 mmol) and acetic acid (0.352 mL, 6.15 mmol) were stirred in methanol at 0° C. To this mixture was added glutaric dialdehyde (2.23 mL, 12.3 mmol) dropwise over 5 minutes. The reaction mixture was stirred as it was allowed to warm to ambient temperature and stirring was continued at the same temperature for 16 hours. The solvent was subsequently removed and the residue was partitioned with 10% aqueous NaOH and ethyl acetate. The organic phase was separated, dried (MgSO₄), filtered and concentrated to dryness to provide a clear oil. This material was purified by reverse-phase preparative HPLC (Primesphere C-18, 30×100 mm; CH₃CN—H₂O-0.1% TFA) to give the intermediate ester (2.70 g, 56%) as a clear oil. ¹HNMR (400 MHz, CDCl₃) δ 7.53-7.44 (m, 3H), 7.40-7.37 (m, 2H), 3.87 (d, J=10.9 Hz, 1H), 3.59 (d, J=10.9 Hz, 1H), 2.99 (t, J=11.2 Hz, 1H), 2.59 (t, J=11.4 Hz, 1H), 2.07-2.02 (m, 2H), 1.82 (d, J=1.82 Hz, 3H), 1.40 (s, 9H). LC/MS: Anal. Calcd. for C₁₇H₂₅NO₂: 275; found: 276 (M+H)⁺.

[0249] Step 2: To a stirred solution of the intermediate ester (1.12 g, 2.88 mmol) in dichloromethane (10 mL) was added TFA (3 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then it was concentrated to dryness to give a light yellow oil. The oil was purified using reverse-phase preparative HPLC (Primesphere C-18, 30×100 mm; CH₃CN—H₂O-0.1% TFA). The appropriate fractions were combined and concentrated to dryness in vacuo. The residue was then dissolved in a minimum amount of methanol and applied to MCX LP extraction cartridges (2×6 g). The cartridges were rinsed with methanol (40 mL) and then the desired compound was eluted using 2M ammonia in methanol (50 mL). Product-containing fractions were combined and concentrated and the residue was taken up in water. Lyophilization of this solution provided the title compound (0.492 g, 78%) as a light yellow solid. ¹HNMR (DMSO-d₆) δ 7.50 (s, 5H), 5.13 (s, 1H), 3.09 (br s, 2H), 2.92-2.89 (m, 2H), 1.74 (m, 4H), 1.48 (br s, 2H). LC/MS: Anal. Calcd. for C₁₃H₁₇NO₂: 219; found: 220 (M+H)⁺.

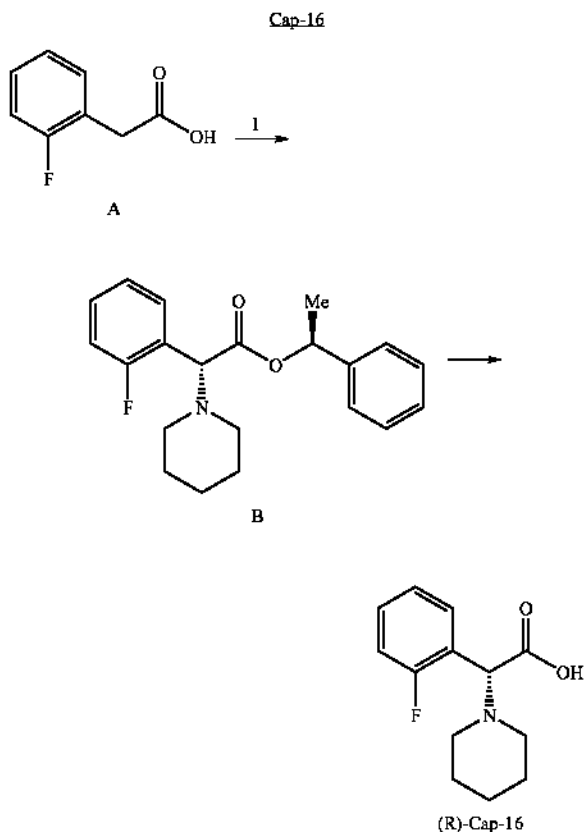


[0250] Step 1; (S)-1-Phenylethyl 2-bromo-2-phenylacetate: To a mixture of α-bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution was stirred at room temperature under Ar for 18 hours and then it was diluted with ethyl acetate, washed (H₂O×2, brine), dried (Na₂SO₄), filtered, and concentrated to give a pale yellow oil. Flash chromatography (SiO₂/hexane-ethyl acetate, 4:1) of this oil provided the title compound (11.64 g, 73%) as a white solid. ¹HNMR (400 MHz, CDCl₃) δ 7.53-7.17 (m, 10H), 5.95 (q, J=6.6 Hz, 0.5H), 5.94 (q, J=6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, J=6.6 Hz, 1.5H), 1.51 (d, J=6.6 Hz, 1.5H).

[0251] Step 2; (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (0.464 g, 1.45 mmol) in THF (8 mL) was added triethylamine (0.61 mL, 4.35 mmol), followed by tetrabutylammonium iodide (0.215 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-methyl-4-hydroxypiperidine (0.251 g, 2.18 mmol) in THF (2 mL) was added. The mixture was stirred for 1 hour at room temperature and then it was heated at 55-60° C. (oil bath temperature) for 4 hours. The cooled reaction mixture was then diluted with ethyl acetate (30 mL), washed (H₂O×2, brine), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography (0-60% ethyl acetate-hexane) to provide first the (S,R)-isomer of the title compound (0.306 g, 60%) as a white solid and then the corresponding (S,S)-isomer (0.120 g, 23%), also as a white solid. (S,R)-isomer: ¹HNMR (CD₃OD) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q, J=6.6 Hz, 1H), 4.05 (s, 1H), 2.56-2.45 (m, 2H), 2.41-2.29 (m, 2H), 1.71-1.49 (m, 4H), 1.38 (d, J=6.6 Hz, 3H), 1.18 (s, 3H). LCMS: Anal. Calcd. for C₂₂H₂₇NO₃: 353; found: 354 (M+H)⁺. (S,S)-isomer: ¹HNMR (CD₃OD) δ 7.41-7.30 (m, 5H), 7.20-7.14 (m, 3H), 7.06-7.00 (m, 2H), 5.85 (q, J=6.6 Hz, 1H), 4.06 (s, 1H), 2.70-2.60 (m, 1H), 2.51 (dt,

$J=6.6, 3.3$ Hz, 1H), 2.44-2.31 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.54 (m, 3H), 1.50 (d, $J=6.8$ Hz, 3H), 1.20 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 (M+H)⁺.

[0252] Step 3; (R)-2-(4-Hydroxy-4-methylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate (0.185 g, 0.52 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed in vacuo and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20×100 mm; $CH_3CN-H_2O-0.1\%$ TFA) to give the title compound (as TFA salt) as a pale bluish solid (0.128 g, 98%). LCMS: Anal. Calcd. for $C_{14}H_{19}NO_3$: 249; found: 250 (M+H)⁺.

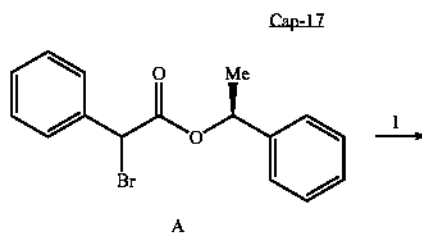


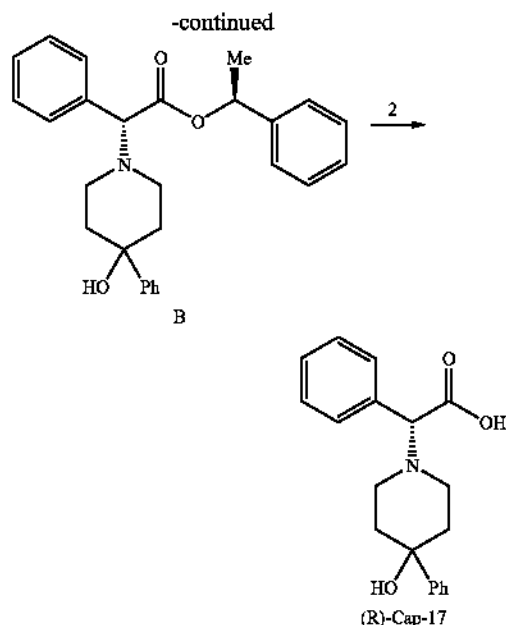
[0253] Step 1; (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated and the residue partitioned with H_2O -ethyl acetate. The phases were separated and the aqueous layer back-extracted with ethyl acetate (2×). The combined organic phases were washed (H_2O , brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (Biotage/0-20% ethyl acetate-hexane) to provide the title compound as a colorless oil (8.38 g, 92%). ¹HNMR (400 MHz, CD_3OD) δ

7.32-7.23 (m, 7H), 7.10-7.04 (m, 2), 5.85 (q, $J=6.5$ Hz, 1H), 3.71 (s, 2H), 1.48 (d, $J=6.5$ Hz, 3H).

[0254] Step 2; (R)-((S)-1-Phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate: To a solution of (S)-1-phenylethyl 2-(2-fluorophenyl)acetate (5.00 g, 19.4 mmol) in THF (1200 mL) at 0° C. was added DBU (6.19 g, 40.7 mmol) and the solution was allowed to warm to room temperature while stirring for 30 minutes. The solution was then cooled to -78° C. and a solution of CBr_4 (13.5 g, 40.7 mmol) in THF (100 mL) was added and the mixture was allowed to warm to -10° C. and stirred at this temperature for 2 hours. The reaction mixture was quenched with saturated aq. NH_4Cl and the layers were separated. The aqueous layer was back-extracted with ethyl acetate (2×) and the combined organic phases were washed (H_2O , brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. To the residue was added piperidine (5.73 mL, 58.1 mmol) and the solution was stirred at room temperature for 24 hours. The volatiles were then concentrated in vacuo and the residue was purified by silica gel chromatography (Biotage/0-30% diethyl ether-hexane) to provide a pure mixture of diastereomers (2:1 ratio by ¹HNMR) as a yellow oil (2.07 g, 31%), along with unreacted starting material (2.53 g, 51%). Further chromatography of the diastereomeric mixture (Biotage/0-10% diethyl ether-toluene) provided the title compound as a colorless oil (0.737 g, 11%). ¹HNMR (400 MHz, CD_3OD) δ 7.52 (ddd, $J=9.4, 7.6, 1.8$ Hz, 1H), 7.33-7.40 (m, 1), 7.23-7.23 (m, 4H), 7.02-7.23 (m, 4H), 5.86 (q, $J=6.6$ Hz, 1H), 4.45 (s, 1H), 2.39-2.45 (m, 4H), 1.52-1.58 (m, 4H), 1.40-1.42 (m, 1H), 1.38 (d, $J=6.6$ Hz, 3H). LCMS: Anal. Calcd. for $C_{21}H_{24}FNO_2$: 341; found: 342 (M+H)⁺.

[0255] Step 3; (R)-2-(2-fluorophenyl)-2-(piperidin-1-yl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate (0.737 g, 2.16 mmol) and 20% $Pd(OH)_2/C$ (0.070 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 2 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated in vacuo. This provided the title compound as a colorless solid (0.503 g, 98%). ¹HNMR (400 MHz, CD_3OD) δ 7.65 (ddd, $J=9.1, 7.6, 1.5$ Hz, 1H), 7.47-7.53 (m, 1H), 7.21-7.30 (m, 2H), 3.07-3.13 (m, 4H), 1.84 (br s, 4H), 1.62 (br s, 2H). LCMS: Anal. Calcd. for $C_{13}H_{16}FNO_2$: 237; found: 238 (M+H)⁺.

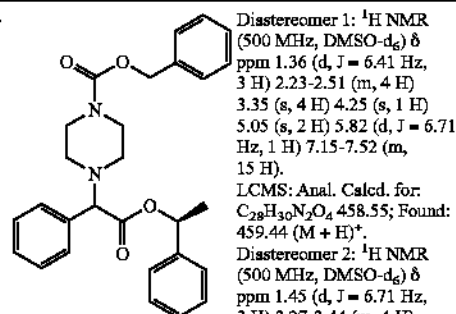




[0256] Step 1; (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (1.50 g, 4.70 mmol) in THF (25 mL) was added triethylamine (1.31 mL, 9.42 mmol), followed by tetrabutylammonium iodide (0.347 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-phenyl-4-hydroxypiperidine (1.00 g, 5.64 mmol) in THF (5 mL) was added. The mixture was stirred for 16 hours and then it was diluted with ethyl acetate (100 mL), washed (H₂O 2, brine), dried (MgSO₄), filtered and concentrated. The residue was purified on a silica gel column (0-60% ethyl acetate-hexane) to provide an approximately 2:1 mixture of diastereomers, as judged by ¹HNMR. Separation of these isomers was performed using supercritical fluid chromatography (Chiralcel OJ-H, 30×250 mm; 20% ethanol in CO₂ at 35° C.), to give first the (R)-isomer of the title compound (0.534 g, 27%) as a yellow oil and then the corresponding (S)-isomer (0.271 g, 14%), also as a yellow oil. (S,R)-isomer: ¹HNMR (400 MHz, CD₃OD) δ 7.55-7.47 (m, 4H), 7.44-7.25 (m, 10H), 7.25-7.17 (m, 1H), 5.88 (q, J=6.6 Hz, 1H), 4.12 (s, 1H), 2.82-2.72 (m, 1H), 2.64 (dt, J=11.1, 2.5 Hz, 1H), 2.58-2.52 (m, 1H), 2.40 (dt, J=11.1, 2.5 Hz, 1H), 2.20 (dt, J=12.1, 4.6 Hz, 1H), 2.10 (dt, J=12.1, 4.6 Hz, 1H), 1.72-1.57 (m, 2H), 1.53 (d, J=6.5 Hz, 3H). LCMS: Anal. Calcd. for C₂₇H₂₉NO₃: 415; found: 416 (M+H)⁺; (S,S)-isomer: ¹HNMR (400 MHz, CD₃OD) δ 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.13 (m, 4H), 7.08-7.00 (m, 2H), 5.88 (q, J=6.6 Hz, 1H), 4.12 (s, 1H), 2.95-2.85 (m, 1H), 2.68 (dt, J=11.1, 2.5 Hz, 1H), 2.57-2.52 (m, 1H), 2.42 (dt, J=11.1, 2.5 Hz, 1H), 2.25 (dt, J=12.1, 4.6 Hz, 1H), 2.12 (dt, J=12.1, 4.6 Hz, 1H), 1.73 (dd, J=13.6, 3.0 Hz, 1H), 1.64 (dd, J=13.6, 3.0 Hz, 1H), 1.40 (d, J=6.6 Hz, 3H). LCMS: Anal. Calcd. for C₂₇H₂₉NO₃: 415; found: 416 (M+H)⁺.

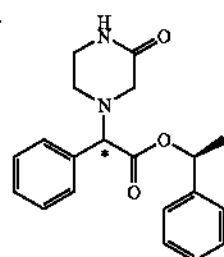
[0257] The following esters were prepared in similar fashion employing step 1 in the synthesis of Cap-17.

Intermediate-17a



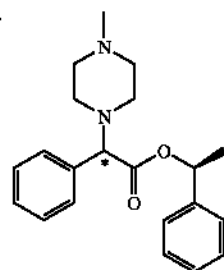
Diastereomer 1: ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.36 (d, J = 6.41 Hz, 3 H) 2.23-2.51 (m, 4 H) 3.35 (s, 4 H) 4.25 (s, 1 H) 5.05 (s, 2 H) 5.82 (d, J = 6.71 Hz, 1 H) 7.15-7.52 (m, 15 H).
LCMS: Anal. Calcd. for: C₂₈H₃₀N₂O₄ 458.55; Found: 459.44 (M + H)⁺.
Diastereomer 2: ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.45 (d, J = 6.71 Hz, 3 H) 2.27-2.44 (m, 4 H) 3.39 (s, 4 H) 4.23 (s, 1 H) 5.06 (s, 2 H) 5.83 (d, J = 6.71 Hz, 1 H) 7.12 (dd, J = 6.41, 3.05 Hz, 2 H) 7.19-7.27 (m, 3 H) 7.27-7.44 (m, 10 H).
LCMS: Anal. Calcd. for: C₂₈H₃₀N₂O₄ 458.55; Found: 459.44 (M + H)⁺.

Intermediate-17b



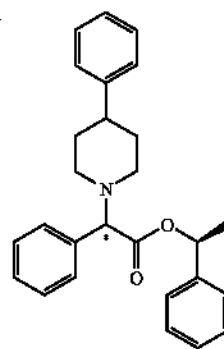
Diastereomer 1: RT = 11.76 min (Cond'n II); LCMS: Anal. Calcd. for: C₂₀H₂₂N₂O₃ 338.4 Found: 339.39 (M + H)⁺; Diastereomer 2: RT = 10.05 min (Cond'n II); LCMS: Anal. Calcd. for: C₂₀H₂₂N₂O₃ 338.4; Found: 339.39 (M + H)⁺.

Intermediate-17c



Diastereomer 1: T_R = 4.55 min (Cond'n I); LCMS: Anal. Calcd. for: C₂₁H₂₆N₂O₂ 338.44 Found: 339.45 (M + H)⁺; Diastereomer 2: T_R = 6.00 min (Cond'n I); LCMS: Anal. Calcd. for: C₂₁H₂₆N₂O₂ 338.44 Found: 339.45 (M + H)⁺.

Intermediate-17d



Diastereomer 1: RT = 7.19 min (Cond'n I); LCMS: Anal. Calcd. for: C₂₇H₂₉NO₂ 399.52 Found: 400.48 (M + H)⁺; Diastereomer 2: RT = 9.76 min (Cond'n I); LCMS: Anal. Calcd. for: C₂₇H₂₉NO₂ 399.52 Found: 400.48 (M + H)⁺.

Chiral SFC Conditions for Determining Retention Time for Intermediates 17b-17d

US 2009/0068140 A1

Mar. 12, 2009

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Condition 1

Column: Chiralpak AD-H Column, 4.6×250 mm, 5 μm

[0258] Solvents: 90% CO₂—10% methanol with 0.1% DEA

Temp: 35° C.

Pressure: 150 bar

[0259] Flow rate: 2.0 mL/min.

UV monitored@220 nm

Injection: 1.0 mg/3 mL methanol

Condition 2

Column: Chiralcel OD-H Column, 4.6×250 mm, 5 μm

[0260] Solvents: 90% CO₂—10% methanol with 0.1% DEA

Temp: 35° C.

Pressure: 150 bar

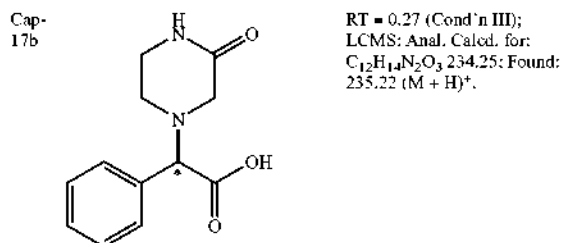
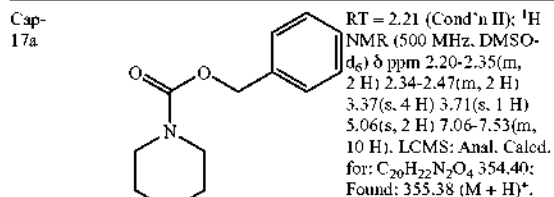
[0261] Flow rate: 2.0 mL/min.

UV monitored@220 nm

Injection: 1.0 mg/mL methanol

[0262] Cap-17, Step 2: (R)-2-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetate (0.350 g, 0.84 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed in vacuo and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20×100 mm; CH₃CN—H₂O-0.1% TFA) to give the title compound (as TFA salt) as a white solid (0.230 g, 88%). LCMS: Anal. Calcd. for C₁₉H₂₁NO₃: 311; found: 312 (M+H)⁺.

[0263] The following carboxylic acids were prepared in a similar fashion:



-continued



LCMS Conditions for Determining Retention Time for Caps 17a-17d

Condition 1

Column: Phenomenex-Luna 4.6×50 mm S10

Start % B=0

Final % B=100

Gradient Time=4 min

[0264] Flow Rate=4 mL/min

Wavelength=220

[0265] Solvent A=10% methanol—90% H₂O—0.1% TFA
Solvent B=90% methanol—10% H₂O—0.1% TFA

Condition 2

Column: Waters-Sunfire 4.6×50 mm S5

Start % B=0

Final % B=100

Gradient Time=2 min

[0266] Flow Rate=4 mL/min

Wavelength=220

[0267] Solvent A=10% methanol—90% H₂O—0.1% TFA
Solvent B=90% methanol—10% H₂O—0.1% TFA

Condition 3

Column: Phenomenex 10μ 3.0×50 mm

Start % B=0

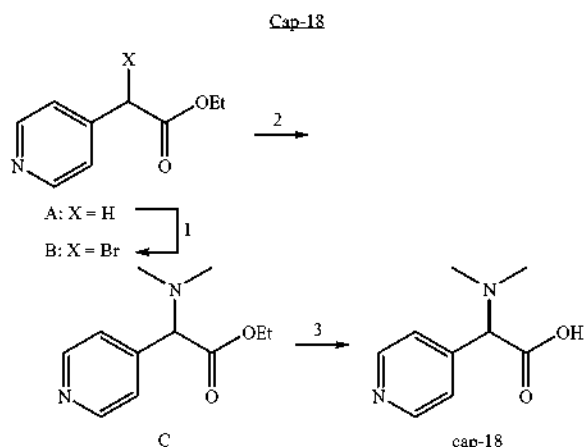
Final % B=100

Gradient Time=2 min

[0268] Flow Rate=4 mL/min

Wavelength=220

[0269] Solvent A=10% methanol—90% H₂O—0.1% TFA
Solvent B=90% methanol—10% H₂O—0.1% TFA



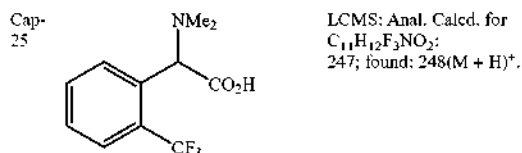
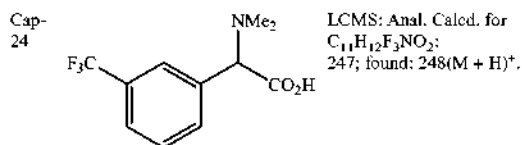
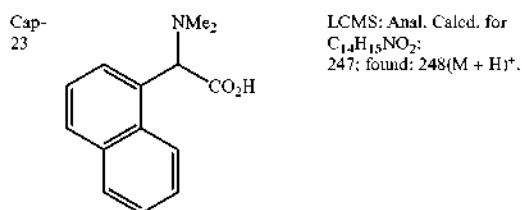
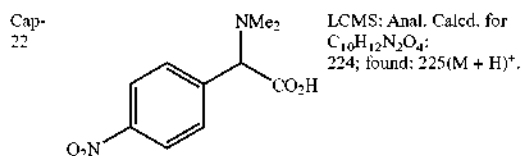
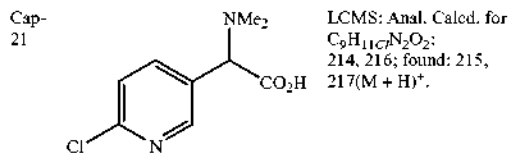
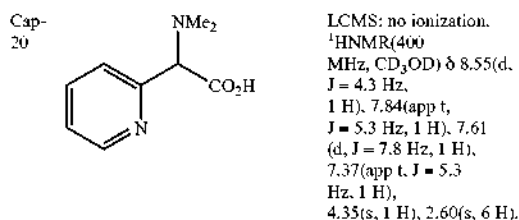
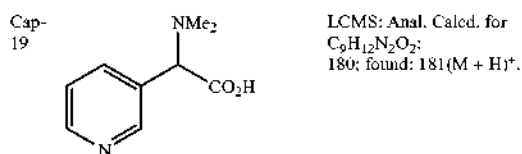
[0270] Step 1; (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0° C. under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78° C. To this mixture was added CBr₄ (2.21 g, 6.66 mmol) and stirring was continued at -78° C. for 2 hours. The reaction mixture was then quenched with sat. aq. NH₄Cl and the phases were separated. The organic phase was washed (brine), dried (Na₂SO₄), filtered, and concentrated in vacuo. The resulting yellow oil was immediately purified by flash chromatography (SiO₂/hexane-ethyl acetate, 1:1) to provide the title compound (1.40 g, 95%) as a somewhat unstable yellow oil. ¹HNMR (400 MHz, CDCl₃) δ 8.62 (dd, J=4.6, 1.8 Hz, 2H), 7.45 (dd, J=4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H), 1.28 (t, J=7.1 Hz, 3H). LCMS: Anal. Calcd. for C₉H₁₀BrNO₂: 242, 244; found: 243, 245 (M+H)⁺.

[0271] Step 2; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by tlc) the volatiles were removed in vacuo and the residue was purified by flash chromatography (Biotage, 40+M SiO₂ column; 50%-100% ethyl acetate-hexane) to provide the title compound (0.539 g, 31%) as a light yellow oil. ¹HNMR (400 MHz, CDCl₃) δ 8.58 (d, J=6.0 Hz, 2H), 7.36 (d, J=6.0 Hz, 2H), 4.17 (m, 2H), 3.92 (s, 1H), 2.27 (s, 6H), 1.22 (t, J=7.0 Hz, 3H). LCMS: Anal. Calcd. for C₁₁H₁₆N₂O₂: 208; found: 209 (M+H)⁺.

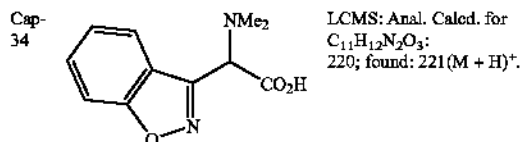
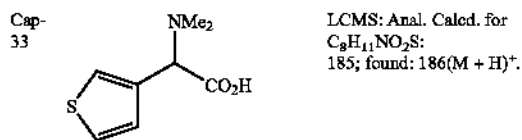
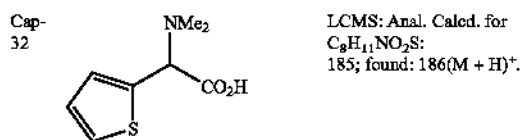
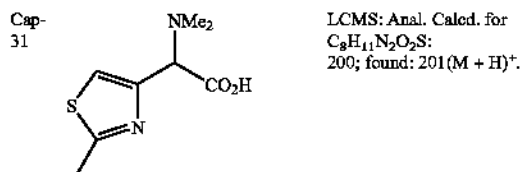
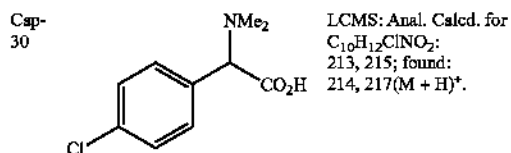
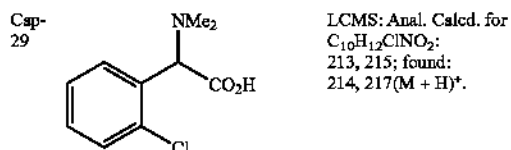
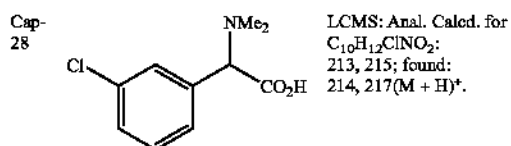
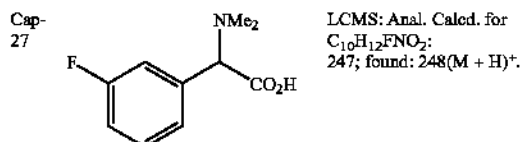
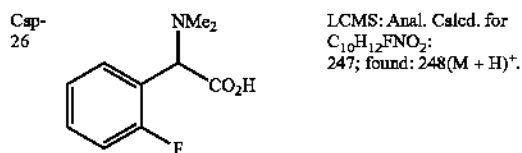
[0272] Step 3; (R,S)-2-(4-Pyridyl)-2-(N,N-dimethylamino)acetic acid: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate (0.200 g, 0.960 mmol) in a mixture of THF-methanol-H₂O (1:1:1, 6 mL) was added powdered LiOH (0.120 g, 4.99 mmol) at room temperature. The solution was stirred for 3 hours and then it was acidified to pH 6 using 1N HCl. The aqueous phase was washed with

ethyl acetate and then it was lyophilized to give the dihydrochloride of the title compound as a yellow solid (containing LiCl). The product was used as such in subsequent steps. ¹HNMR (400 MHz, DMSO-d₆) δ 8.49 (d, J=5.7 Hz, 2H), 7.34 (d, J=5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

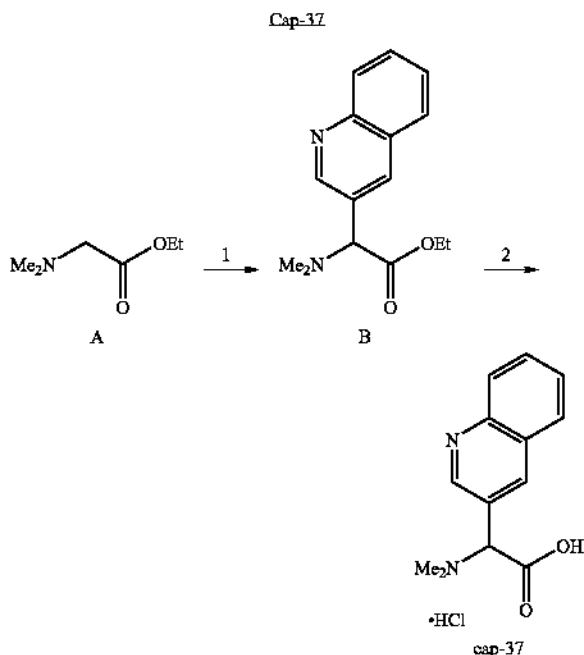
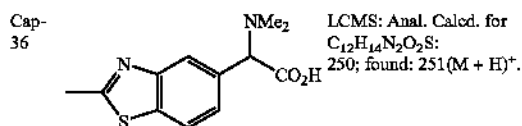
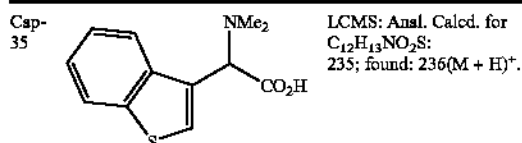
[0273] The following examples were prepared in similar fashion using the method described in Example 4;



-continued



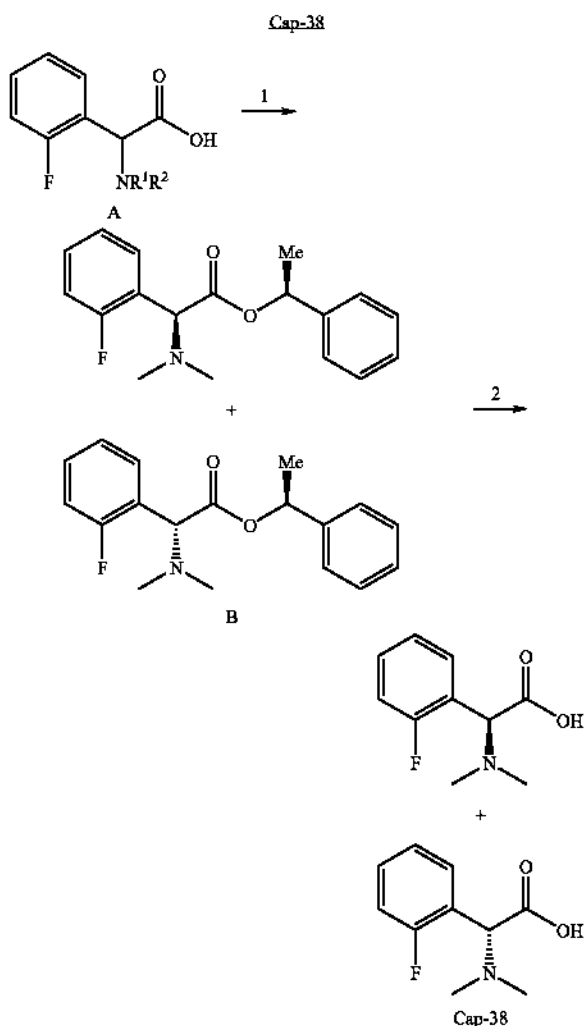
-continued



[0274] Step 1; (R,S)-Ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)acetate: A mixture of ethyl N,N-dimethylaminoacetate (0.462 g, 3.54 mmol), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t-Bu_3P)_2$ (0.090 g, 0.176 mmol) and toluene (10 mL) was degassed with a stream of Ar bubbles for 15 minutes. The reaction mixture was then heated at 100° C. for 12 hours, after which it was cooled to room temperature and poured into H_2O . The mixture was extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O , brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified first by reverse-phase preparative HPLC (Primesphere C-18, 30x100 mm; CH_3CN-H_2O -5 mM NH_4OAc) and then by flash chromatography (SiO_2 /hexane-ethyl acetate, 1:1) to provide the title compound (0.128 g, 17%) as an orange oil. 1H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, $J=2.0$ Hz, 1H), 8.32 (d, $J=2.0$ Hz, 1H), 8.03-8.01 (m, 2H), 7.77 (ddd, $J=8.3, 6.8, 1.5$ Hz, 1H), 7.62 (ddd, $J=8.3, 6.8, 1.5$ Hz, 1H), 4.35 (s, 1H), 4.13 (m, 2H), 2.22 (s, 6H), 1.15 (t, $J=7.0$ Hz, 3H). LCMS: Anal. Calcd. for $C_{15}H_{18}N_2O_2$: 258; found: 259 (M+H)⁺.

[0275] Step 2; (R,S) 2-(Quinolin-3-yl)-2-(N,N-dimethylamino)acetic acid: A mixture of (R,S)-ethyl 2-(quinolin-3-

yl)-2-(N,N-dimethylamino)acetate (0.122 g, 0.472 mmol) and 6M HCl (3 mL) was heated at 100° C. for 12 hours. The solvent was removed in vacuo to provide the dihydrochloride of the title compound (0.169 g, >100%) as a light yellow foam. The unpurified material was used in subsequent steps without further purification. LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_2$: 230; found: 231 (M+H)⁺.

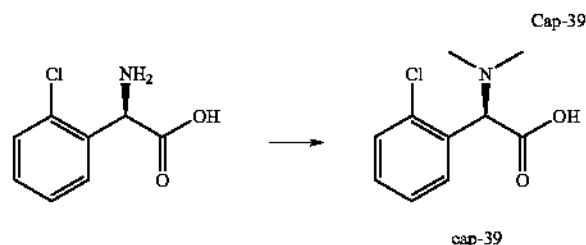


[0276] Step 1; (R)—((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate and (S)—((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate: To a mixture of (RS)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid (2.60 g, 13.19 mmol), DMAP (0.209 g, 1.71 mmol) and (S)-1-phenylethanol (2.09 g, 17.15 mmol) in CH_2Cl_2 (40 mL) was added EDCI (3.29 g, 17.15 mmol) and the mixture was allowed to stir at room temperature for 12 hours. The solvent was then removed in vacuo and the residue partitioned with ethyl acetate- H_2O . The layers were separated, the aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O , brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (Biotage/0-50% diethyl ether-hexane). The resulting pure diastereomeric mix-

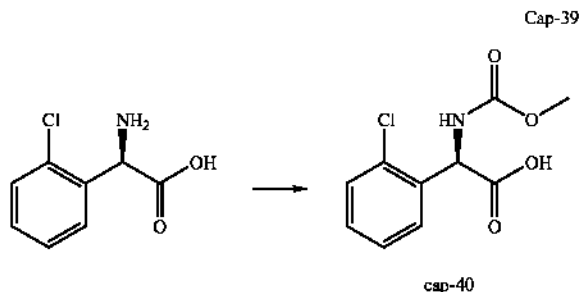
ture was then separated by reverse-phase preparative HPLC (Primesphere C-18, 30x100 mm; CH_3CN-H_2O -0.1% TFA) to give first (S)-1-phenylethyl (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetate (0.501 g, 13%) and then (S)-1-phenylethyl (S)-2-(dimethylamino)-2-(2-fluorophenyl)acetate (0.727 g, 18%), both as their TFA salts. (S,R)-isomer: ¹HNMR (400 MHz, CD_3OD) δ 7.65-7.70 (m, 1H), 7.55-7.60 (ddd, J=9.4, 8.1, 1.5 Hz, 1H), 7.36-7.41 (m, 2H), 7.28-7.34 (m, 5H), 6.04 (q, J=6.5 Hz, 1H), 5.60 (s, 1H), 2.84 (s, 6H), 1.43 (d, J=6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 (M+H)⁺; (S,S)-isomer: ¹HNMR (400 MHz, CD_3OD) δ 7.58-7.63 (m, 1H), 7.18-7.31 (m, 6H), 7.00 (dd, J=8.5, 1.5 Hz, 2H), 6.02 (q, J=6.5 Hz, 1H), 5.60 (s, 1H), 2.88 (s, 6H), 1.54 (d, J=6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 (M+H)⁺.

[0277] Step 2; (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid: A mixture of (R)—((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt (1.25 g, 3.01 mmol) and 20% $Pd(OH)_2/C$ (0.125 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated in vacuo. This gave the title compound as a colorless solid (0.503 g, 98%). ¹HNMR (400 MHz, CD_3OD) δ 7.53-7.63 (m, 2H), 7.33-7.38 (m, 2H), 5.36 (s, 1H), 2.86 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 (M+H)⁺.

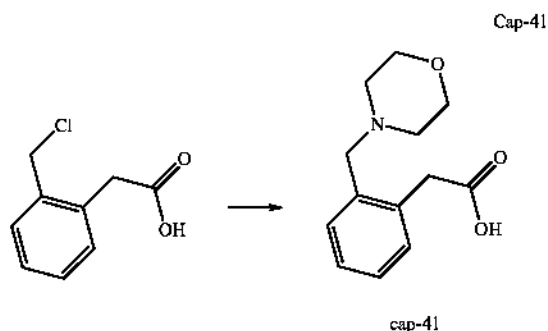
[0278] The S-isomer could be obtained from (S)—((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt in similar fashion.



[0279] A mixture of (R)-2-(2-chlorophenyl)glycine (0.300 g, 1.62 mmol), formaldehyde (35% aqueous solution, 0.80 mL, 3.23 mmol) and 20% $Pd(OH)_2/C$ (0.050 g) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®) and concentrated in vacuo. The residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 30x100 mm; CH_3CN-H_2O -0.1% TFA) to give the TFA salt of the title compound (R)-2-(dimethylamino)-2-(2-chlorophenyl)acetic acid as a colorless oil (0.290 g, 55%). ¹H NMR (400 MHz, CD_3OD) δ 7.59-7.65 (m, 2H), 7.45-7.53 (m, 2H), 5.40 (s, 1H), 2.87 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 216 (M+H)⁺.



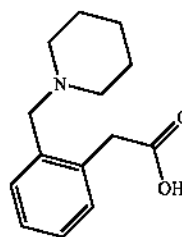
[0280] To an ice-cold solution of (R)-2-(2-chlorophenyl)glycine (1.00 g, 5.38 mmol) and NaOH (0.862 g, 21.6 mmol) in H₂O (5.5 mL) was added methyl chloroformate (1.00 mL, 13.5 mmol) dropwise. The mixture was allowed to stir at 0° C. for 1 hour and then it was acidified by the addition of conc. HCl (2.5 mL). The mixture was extracted with ethyl acetate (2x) and the combined organic phase was washed (H₂O, brine), dried (Na₂SO₄), filtered, and concentrated in vacuo to give the title compound (R)-2-(methoxycarbonylamino)-2-(2-chlorophenyl)acetic acid as a yellow-orange foam (1.31 g, 96%). ¹H NMR (400 MHz, CD₃OD) δ 7.39-7.43 (m, 2H), 7.29-7.31 (m, 2H), 5.69 (s, 1H), 3.65 (s, 3H). LCMS: Anal. Calcd. for C₁₀H₁₀ClNO₄: 243, 245; found: 244, 246 (M+H)⁺.



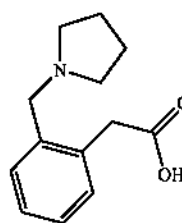
[0281] To a suspension of 2-(2-(chloromethyl)phenyl)acetic acid (2.00 g, 10.8 mmol) in THF (20 mL) was added morpholine (1.89 g, 21.7 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate and extracted with H₂O (2x). The aqueous phase was lyophilized and the residue was purified by silica gel chromatography (Biotage/0-10% methanol-CH₂Cl₂) to give the title compound 2-(2-(morpholinomethyl)phenyl)acetic acid as a colorless solid (2.22 g, 87%). ¹H NMR (400 MHz, CD₃OD) δ 7.37-7.44 (m, 3H), 7.29-7.33 (m, 1H), 4.24 (s, 2H), 3.83 (br s, 4H), 3.68 (s, 2H), 3.14 (br s, 4H). LCMS: Anal. Calcd. for C₁₃H₁₇NO₃: 235; found: 236 (M+H)⁺.

[0282] The following examples were similarly prepared using the method described for Cap-41:

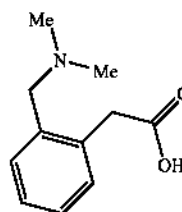
Cap-42 LCMS: Anal. Calcd. for C₁₄H₁₉NO₂: 233; found: 234(M+H)⁺.



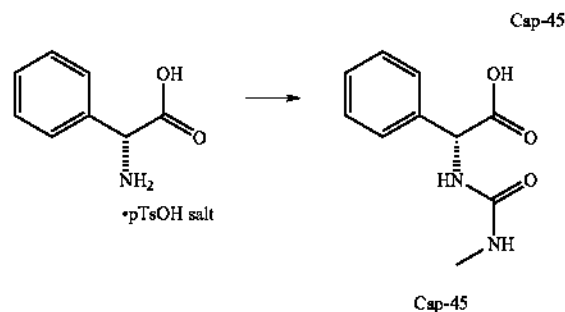
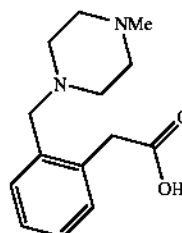
Cap-43 LCMS: Anal. Calcd. for C₁₃H₁₇NO₂: 219; found: 220(M+H)⁺.



Cap-44 LCMS: Anal. Calcd. for C₁₁H₁₅NO₂: 193; found: 194(M+H)⁺.



Cap-45 LCMS: Anal. Calcd. for C₁₄H₂₀N₂O₂: 248; found: 249(M+H)⁺.



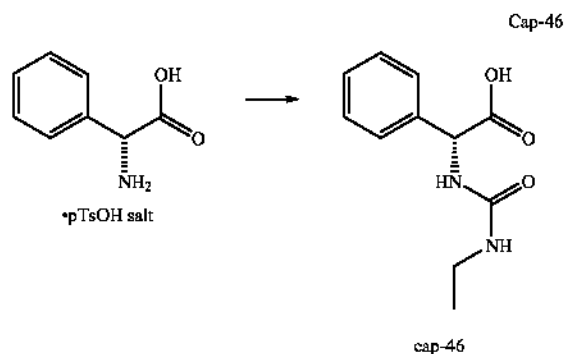
[0283] HMDs (1.85 mL, 8.77 mmol) was added to a suspension of (R)-2-amino-2-phenylacetic acid p-toluenesulfonate (2.83 g, 8.77 mmol) in CH₂Cl₂ (10 mL) and the mixture was stirred at room temperature for 30 minutes. Methyl isocyanate (0.5 g, 8.77 mmol) was added in one portion stirring continued for 30 minutes. The reaction was quenched by addition of H₂O (5 mL) and the resulting pre-

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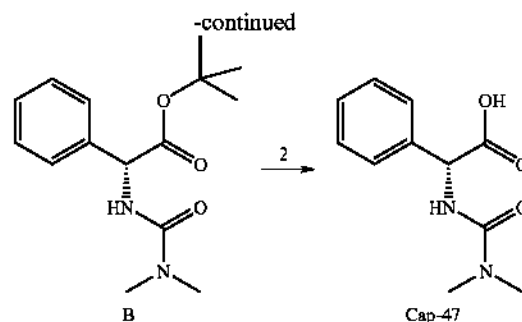
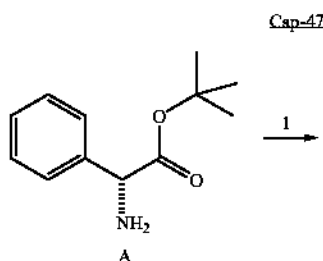
Mar. 12, 2009

precipitate was filtered, washed with H₂O and n-hexanes, and dried under vacuum. (R)-2-(3-methylureido)-2-phenylacetic acid (1.5 g; 82%) was recovered as a white solid and it was used without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 2.54 (d, J=4.88 Hz, 3H) 5.17 (d, J=7.93 Hz, 1H) 5.95 (q, J=4.48 Hz, 1H) 6.66 (d, J=7.93 Hz, 1H) 7.26-7.38 (m, 5H) 12.67 (s, 1H). LCMS: Anal. Calcd. for C₁₀H₁₂N₂O₃ 208.08 found 209.121 (M+H)⁺; HPLC Phenomenex C-18 3.0×46 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=1.38 min, 90% homogeneity index.



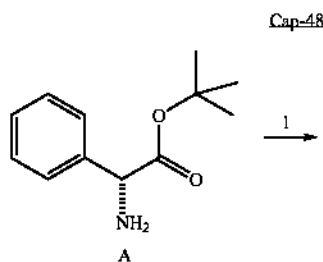
[0284] The desired product was prepared according to the method described for Cap-45. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.96 (t, J=7.17 Hz, 3H) 2.94-3.05 (m, 2H) 5.17 (d, J=7.93 Hz, 1H) 6.05 (t, J=5.19 Hz, 1H) 6.60 (d, J=7.63 Hz, 1H) 7.26-7.38 (m, 5H) 12.68 (s, 1H). LCMS: Anal. Calcd. for C₁₁H₁₄N₂O₃ 222.10 found 209.121 (M+H)⁺.

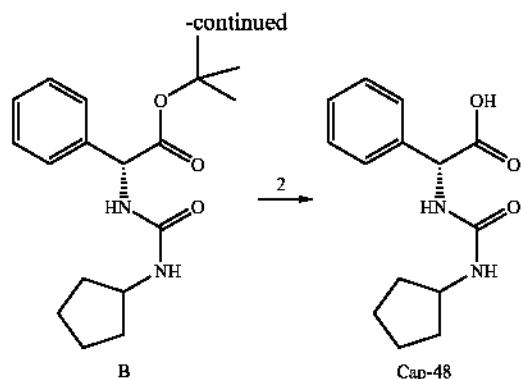
[0285] HPLC XTERRA C-18 3.0×506 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A=90% water, 10% methanol, 0.2% H₃PO₄, B=10% water, 90% methanol, 0.2% H₃PO₄, RT=0.87 min, 90% homogeneity index.



[0286] Step 1; (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate: To a stirred solution of (R)-tert-butyl 2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's base (1.79 mL, 10.25 mmol) in DMF (40 mL) was added dimethylcarbamoyl chloride (0.38 mL, 4.18 mmol) dropwise over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was dissolved in ethyl acetate. The organic layer was washed with H₂O, 1N aq. HCl and brine, dried (MgSO₄), filtered and concentrated under reduced pressure. (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate was obtained as a white solid (0.86 g; 75%) and used without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.33 (s, 9H) 2.82 (s, 6H) 5.17 (d, J=7.63 Hz, 1H) 6.55 (d, J=7.32 Hz, 1H) 7.24-7.41 (m, 5H). LCMS: Anal. Calcd. for C₁₅H₂₂N₂O₃ 278.16 found 279.23 (M+H)⁺; HPLC Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.26 min, 97% homogeneity index.

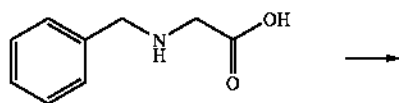
[0287] Step 2; (R)-2-(3,3-dimethylureido)-2-phenylacetic acid: To a stirred solution of (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate (0.86 g, 3.10 mmol) in CH₂Cl₂ (250 mL) was added TFA (15 mL) dropwise and the resulting solution was stirred at rt for 3 h. The desired compound was then precipitated out of solution with a mixture of EtOAc: Hexanes (5:20), filtered off and dried under reduced pressure. (R)-2-(3,3-dimethylureido)-2-phenylacetic acid was isolated as a white solid (0.59 g, 86%) and used without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 2.82 (s, 6H) 5.22 (d, J=7.32 Hz, 1H) 6.58 (d, J=7.32 Hz, 1H) 7.28 (t, J=7.17 Hz, 1H) 7.33 (t, J=7.32 Hz, 2H) 7.38-7.43 (m, 2H) 12.65 (s, 1H). LCMS: Anal. Calcd. for C₁₁H₁₄N₂O₃ 222.24; found: 223.21 (M+H)⁺. HPLC XTERRA C-18 3.0×50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A=90% water, 10% methanol, 0.2% H₃PO₄, B=10% water, 90% methanol, 0.2% H₃PO₄, RT=0.75 min, 93% homogeneity index.





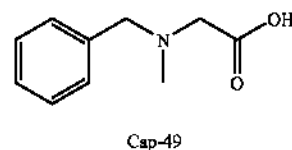
[0288] Step 1; (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate: To a stirred solution of (R)-2-amino-2-phenylacetic acid hydrochloride (1.0 g, 4.10 mmol) and Hunig's base (1.0 mL, 6.15 mmol) in DMF (15 mL) was added cyclopentyl isocyanate (0.46 mL, 4.10 mmol) dropwise and over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was taken up in ethyl acetate. The organic layer was washed with H₂O and brine, dried (MgSO₄), filtered, and concentrated under reduced pressure. (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate was obtained as an opaque oil (1.32 g; 100%) and used without further purification. ¹H NMR (500 MHz, CD₃Cl-D) δ ppm 1.50-1.57 (m, 2H) 1.58-1.66 (m, 2H) 1.87-1.97 (m, 2H) 3.89-3.98 (m, 1H) 5.37 (s, 1H) 7.26-7.38 (m, 5H). LCMS: Anal. Calcd. for C₁₈H₂₆N₂O₃ 318.19 found 319.21 (M+H)⁺; HPLC XTERRA C-18 3.0×50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.82 min, 96% homogeneity index.

[0289] Step 2; (R)-2-(3-cyclopentylureido)-2-phenylacetic acid: To a stirred solution of (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate (1.31 g, 4.10 mmol) in CH₂Cl₂ (25 mL) was added TFA (4 mL) and triethylsilane (1.64 mL; 10.3 mmol) dropwise, and the resulting solution was stirred at room temperature for 6 hours. The volatile components were removed under reduced pressure and the crude product was recrystallized in ethyl acetate/pentanes to yield (R)-2-(3-cyclopentylureido)-2-phenylacetic acid as a white solid (0.69 g, 64%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.17-1.35 (m, 2H) 1.42-1.52 (m, 2H) 1.53-1.64 (m, 2H) 1.67-1.80 (m, 2H) 3.75-3.89 (m, 1H) 5.17 (d, J=7.93 Hz, 1H) 6.12 (d, J=7.32 Hz, 1H) 6.48 (d, J=7.93 Hz, 1H) 7.24-7.40 (m, 5H) 12.73 (s, 1H). LCMS: Anal. Calcd. for C₁₄H₁₈N₂O₃; 262.31; found: 263.15 (M+H)⁺. HPLC XTERRA C-18 3.0×50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A=90% water, 10% methanol, 0.2% H₃PO₄, B=10% water, 90% methanol, 0.2% H₃PO₄, RT=1.24 min, 100% homogeneity index.

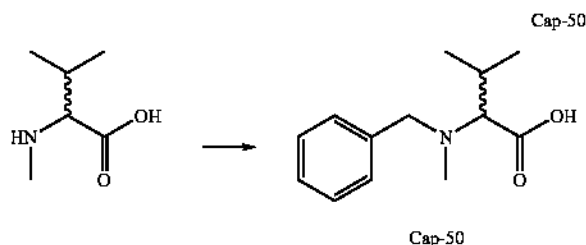


Cap-49

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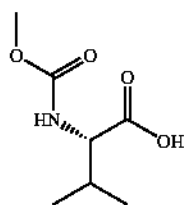


[0290] To a stirred solution of 2-(benzylamino)acetic acid (2.0 g, 12.1 mmol) in formic acid (91 mL) was added formaldehyde (6.94 mL, 93.2 mmol). After five hours at 70° C., the reaction mixture was concentrated under reduced pressure to 20 mL and a white solid precipitated. Following filtration, the mother liquors were collected and further concentrated under reduced pressure providing the crude product. Purification by reverse-phase preparative HPLC (Xterra 30×100 mm, detection at 220 nm, flow rate 35 mL/min, 0 to 35% B over 8 min; A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA) provided the title compound 2-(benzyl(methyl)amino)acetic acid as its TFA salt (723 mg, 33%) as a colorless wax. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29-7.68 (m, 5H). LCMS: Anal. Calcd. for: C₁₀H₁₃NO₂ 179.22; Found: 180.20 (M+H)⁺.



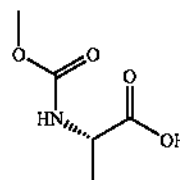
[0291] To a stirred solution of 3-methyl-2-(methylamino)butanoic acid (0.50 g, 3.81 mmol) in water (30 mL) was added K₂CO₃ (2.63 g, 19.1 mmol) and benzyl chloride (1.32 g, 11.4 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was extracted with ethyl acetate (30 mL×2) and the aqueous layer was concentrated under reduced pressure providing the crude product which was purified by reverse-phase preparative HPLC (Xterra 30×100 mm, detection at 220 nm, flow rate 40 mL/min, 20 to 80% B over 6 min; A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA) to provide 2-(benzyl(methyl)amino)-3-methylbutanoic acid, TFA salt (126 mg, 19%) as a colorless wax. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.98 (d, 3H) 1.07 (d, 3H) 2.33-2.48 (m, 1H) 2.54-2.78 (m, 3H) 3.69 (s, 1H) 4.24 (s, 2H) 7.29-7.65 (m, 5H). LCMS: Anal. Calcd. for: C₁₃H₁₉NO₂ 221.30; Found: 222.28 (M+H)⁺.

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Cap-51

(s, 1H), 7.33 (d, $J=8.6$, 1H), 3.84 (dd, $J=8.4$, 6.0, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.87 (m, 6H). HRMS: Anal. Calcd. for $[M+H]^+ C_7H_{14}NO_4$: 176.0923; found 176.0922



Cap-52

[0292] Na_2CO_3 (1.83 g, 17.2 mmol) was added to NaOH (33 mL of 1M/ H_2O , 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled with ice-water bath. Methyl chloroformate (2.8 mL, 36.1 mmol) was added drop-wise over 15 min, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3.25 hr. The reaction mixture was washed with ether (50 mL, 3 \times), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2, and extracted with CH_2Cl_2 (50 mL, 3 \times). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford Cap-51 as a white solid (6 g). 1H NMR for the dominant rotamer (DMSO- d_6 , $\delta=2.5$ ppm, 500 MHz): 12.54

[0293] Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of Cap-51. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O /MeOH/TFA) to afford Cap-52 as a colorless viscous oil. 1H NMR (DMSO- d_6 , $\delta=2.5$ ppm, 500 MHz): 12.49 (br s, 1H), 7.43 (d, $J=7.3$, 0.88H), 7.09 (app br s, 0.12H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, $J=7.3$, 3H).

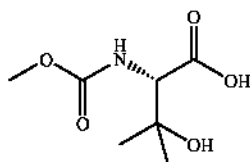
[0294] Cap-53 to -64 were prepared from appropriate starting materials according to the procedure described for the synthesis of Cap-51, with noted modifications if any.

Cap	Structure	Data
Cap-53a: (R) Cap-53b: (S)		1H NMR(DMSO- d_6 , $\delta = 2.5$ ppm, 500 MHz): δ 12.51(br s, 1 H), 7.4(d, $J = 7.9$, 0.9 H), 7.06 (app s, 0.1 H), 3.86-3.82(m, 1 H), 3.53(s, 3 H), 1.75-1.67(m, 1 H), 1.62-1.54(m, 1 H), 0.88(d, $J = 7.3$, 3 H). RT = 0.77 minutes(Cond. 2); LC/MS: Anal. Calcd. for $[M + Na]^+ C_6H_{11}NNaO_4$: 184.06; found 184.07. HRMS Calcd. for $[M + Na]^+ C_6H_{11}NNaO_4$: 184.0586; found 184.0592.
Cap-54a: (R) Cap-54b: (S)		1H NMR(DMSO- d_6 , $\delta = 2.5$ ppm, 500 MHz): δ 12.48(s, 1 H), 7.58(d, $J = 7.6$, 0.9 H), 7.25 (app s, 0.1 H), 3.52(s, 3 H), 3.36-3.33(m, 1 H), 1.10-1.01(m, 1 H), 0.54-0.49(m, 1 H), 0.46-0.40(m, 1 H), 0.39-0.35(m, 1 H), 0.31-0.21(m, 1 H). HRMS Calcd. for $[M + H]^+ C_7H_{12}NO_4$: 174.0766; found 174.0771
Cap-55		1H NMR(DMSO- d_6 , $\delta = 2.5$ ppm, 500 MHz): δ 12.62(s, 1 H), 7.42(d, $J = 8.2$, 0.9 H), 7.07 (app s, 0.1 H), 5.80-5.72(m, 1 H), 5.10(d, $J = 17.1$, 1 H), 5.04(d, $J = 10.4$, 1 H), 4.01-3.96 (m, 1 H), 3.53(s, 3 H), 2.47-2.42(m, 1 H), 2.35-2.29(m, 1 H).
Cap-56		1H NMR(DMSO- d_6 , $\delta = 2.5$ ppm, 500 MHz): δ 12.75(s, 1 H), 7.38(d, $J = 8.3$, 0.9 H), 6.96 (app s, 0.1 H), 4.20-4.16(m, 1 H), 3.60-3.55(m, 2 H), 3.54(s, 3 H), 3.24(s, 3 H).

-continued

Cap	Structure	Data
Cap-57		¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 500 MHz): δ 12.50(s, 1 H), 8.02(d, J = 7.7, 0.08 H), 7.40(d, J = 7.9, 0.76 H), 7.19(d, J = 8.2, 0.07 H), 7.07(d, J = 6.7, 0.09 H), 4.21-4.12(m, 0.08 H), 4.06-3.97(m, 0.07 H), 3.96-3.80(m, 0.85 H), 3.53(s, 3 H), 1.69-1.51(m, 2 H), 1.39-1.26(m, 2 H), 0.85(t, J = 7.4, 3 H). LC(Cond. 2): RT = 1.39 LC/MS: Anal. Calcd. for [M + H] ⁺ C ₇ H ₁₄ NO ₄ : 176.09; found 176.06.
Cap-58		¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 500 MHz): δ 12.63(bs, 1 H), 7.35(s, 1 H), 7.31(d, J = 8.2, 1 H), 6.92(s, 1 H), 4.33-4.29(m, 1 H), 3.54(s, 3 H), 2.54(dd, J = 15.5, 5.4, 1 H), 2.43(dd, J = 15.6, 8.0, 1 H). RT = 0.16 min (Cond. 2); LC/MS: Anal. Calcd. for [M + H] ⁺ C ₆ H ₁₁ N ₂ O ₅ : 191.07; found 191.14.
Cap-59a: (R) Cap-59b: (S)		¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): δ 12.49(br s, 1 H), 7.40(d, J = 7.3, 0.89 H), 7.04(br s, 0.11 H), 4.00-3.95(m, 3 H), 1.24(d, J = 7.3, 3 H), 1.15(t, J = 7.2, 3 H). HRMS: Anal. Calcd. for [M + H] ⁺ C ₆ H ₁₂ NO ₄ : 162.0766; found 162.0771.
Cap-60		The crude material was purified with a reverse phase HPLC(H ₂ O/MeOH/TFA) to afford a colorless viscous oil that crystallized to a white solid upon exposure to high vacuum. ¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): δ 12.38(br s, 1 H), 7.74(s, 0.82 H), 7.48(s, 0.18 H), 3.54/3.51(two s, 3 H), 1.30(m, 2 H), 0.98(m, 2 H). HRMS: Anal. Calcd. for [M + H] ⁺ C ₆ H ₁₀ NO ₄ : 160.0610; found 160.0604.
Cap-61		¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): δ 12.27(br s, 1 H), 7.40(br s, 1 H), 3.50(s, 3 H), 1.32(s, 6 H). HRMS: Anal. Calcd. for [M + H] ⁺ C ₆ H ₁₂ NO ₄ : 162.0766; found 162.0765.
Cap-62		¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): δ 12.74(br s, 1 H), 4.21(d, J = 10.3, 0.6 H), 4.05(d, J = 10.0, 0.4 H), 3.62/3.60(two singlets, 3 H), 3.0(s, 3 H), 2.14-2.05(m, 1 H), 0.95(d, J = 6.3, 3 H), 0.81(d, J = 6.6, 3 H). LC/MS: Anal. Calcd. for [M - H] ⁻ C ₈ H ₁₄ NO ₄ : 188.09; found 188.05.
Cap-63		[Note: the reaction was allowed to run for longer than what was noted for the general procedure.] ¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): 12.21(br s, 1 H), 7.42(br s, 1 H), 3.50(s, 3 H), 2.02-1.85(m, 4 H), 1.66-1.58(m, 4 H). LC/MS: Anal. Calcd. for [M + H] ⁺ C ₈ H ₁₄ NO ₄ : 188.09; found 188.19.
Cap-64		[Note: the reaction was allowed to run for longer than what was noted for the general procedure.] ¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): 12.35(br s, 1 H), 7.77(s, 0.82 H), 7.56/7.52(overlapping br s, 0.18 H), 3.50(s, 3 H), 2.47-2.40(m, 2 H), 2.14-2.07(m, 2 H), 1.93-1.82(m, 2 H).

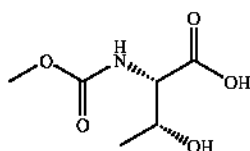
Cap-65



[0295] Methyl chloroformate (0.65 mL, 8.39 mmol) was added dropwise over 5 min to a cooled (ice-water) mixture of Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 mL of 1M/ H_2O , 8.2 mmol) and (S)-3-hydroxy-2-(methoxycarbonylamino)-3-methylbutanoic acid (1.04 g, 7.81 mmol). The reaction mixture was stirred for 45 min, and then the cooling bath was removed and stirring was continued for an additional 3.75 hr. The reaction mixture was washed with CH_2Cl_2 , and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2. The volatile component was removed in vacuo and the residue was taken up in a 2:1 mixture of MeOH/ CH_2Cl_2 (15 mL) and filtered, and the filtrate was rotovaped to afford Cap-65 as a white semi-viscous foam (1.236 g). ^1H NMR (DMSO- d_6 , $\delta=2.5$ ppm, 400 MHz): δ 6.94 (d, $J=8.5$, 0.9H), 6.53 (br s, 0.1H), 3.89 (d, $J=8.8$, 1H), 2.94 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

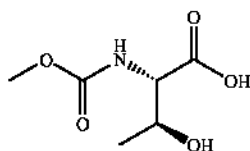
[0296] Cap-66 and -67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of Cap-65.

Cap-66



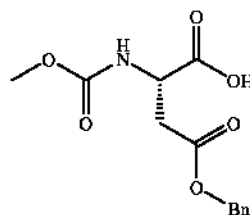
[0297] ^1H NMR (DMSO- d_6 , $\delta=2.5$ ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, $J=8.3$, 0.13H), 6.81 (d, $J=8.8$, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, $J=9.1$, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, $J=6.2$, 3H). [Note: only the dominant signals of NH were noted].

Cap-67



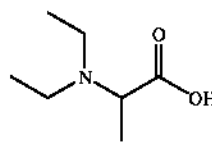
[0298] ^1H NMR (DMSO- d_6 , $\delta=2.5$ ppm, 400 MHz): 12.51 (br s, 1H), 7.25 (d, $J=8.4$, 0.75H), 7.12 (br d, $J=0.4$, 0.05H), 6.86 (br s, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, $J=6.3$, 3H). [Note: only the dominant signals of NH were noted]

Cap-68



[0299] Methyl chloroformate (0.38 mL, 4.9 mmol) was added drop-wise to a mixture of 1N NaOH (aq) (9.0 mL, 9.0 mmol), 1M NaHCO_3 (aq) (9.0 mL, 9.0 mol), L-aspartic acid β -benzyl ester (1.0 g, 4.5 mmol) and Dioxane (9 mL). The reaction mixture was stirred at ambient conditions for 3 hr, and then washed with Ethyl acetate (50 mL, 3 \times). The aqueous layer was acidified with 12N HCl to a pH~1-2, and extracted with ethyl acetate (3 \times 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford Cap-68 as a light yellow oil (1.37 g; mass is above theoretical yield, and the product was used without further purification). ^1H NMR (DMSO- d_6 , $\delta=2.5$ ppm, 500 MHz): δ 12.88 (br s, 1H), 7.55 (d, $J=8.5$, 1H), 7.40-7.32 (m, 5H), 5.13 (d, $J=12.8$, 1H), 5.10 (d, $J=12.9$, 1H), 4.42-4.38 (m, 1H), 3.55 (s, 3H), 2.87 (dd, $J=16.2$, 5.5, 1H), 2.71 (dd, $J=16.2$, 8.3, 1H). LC (Cond. 2): RT=1.90 min; LC/MS: Anal. Calcd. For $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{16}\text{NO}_6$: 282.10; found 282.12.

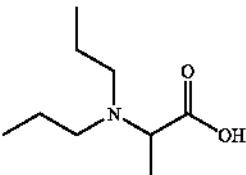
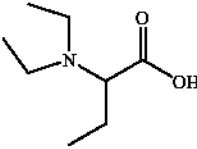
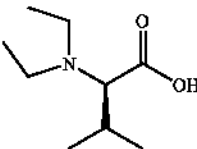
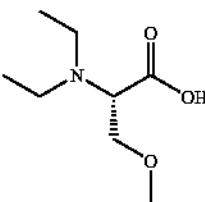
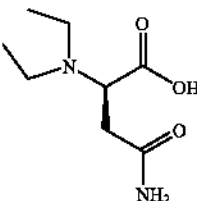
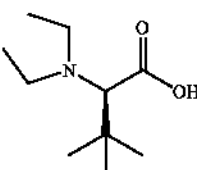
Cap-69a and -69b



Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

[0300] NaCNBH_3 (2.416 g, 36.5 mmol) was added in batches to a chilled ($\sim 15^\circ\text{C}$) water (17 mL)/MeOH (10 mL) solution of alanine (1.338 g, 15.0 mmol). A few minutes later acetaldehyde (4.0 mL, 71.3 mmol) was added drop-wise over 4 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 6 hr. An additional acetaldehyde (4.0 mL) was added and the reaction was stirred for 2 hr. Concentrated HCl was added slowly to the reaction mixture until the pH reached ~ 1.5 , and the resulting mixture was heated for 1 hr at 40°C . Most of the volatile component was removed in vacuo and the residue was purified with a Dowex® 50WX8-100 ion-exchange resin (column was washed with water, and the compound was eluted with dilute NH_4OH , prepared by mixing 18 mL of NH_4OH and 282 mL of water) to afford Cap-69 (2.0 g) as an off-white soft hygroscopic solid. ^1H NMR (DMSO- d_6 , $\delta=2.5$ ppm, 400 MHz): δ 3.44 (q, $J=7.1$, 1H), 2.99-2.90 (m, 2H), 2.89-2.80 (m, 2H), 1.23 (d, $J=7.1$, 3H), 1.13 (t, $J=7.3$, 6H).

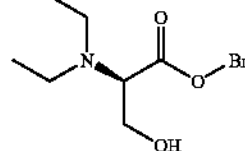
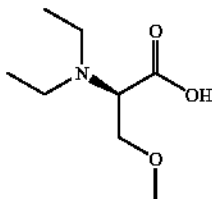
[0301] Cap-70 to -74 were prepared according to the procedure described for the synthesis of Cap-69 by employing appropriate starting materials.

Cap-70a: (R) Cap-70b: (S)		¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): δ 3.42(q, J = 7.1, 1 H), 2.68-2.60(m, 4 H), 1.53-1.44(m, 4 H), 1.19(d, J = 7.3, 3 H), 0.85 (t, J = 7.5, 6 H). LC/MS: Anal. Calcd. for [M + H] ⁺ C ₉ H ₂₀ NO ₂ : 174.15; found 174.13.
Cap-71a: (R) Cap-71b: (S)		¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 500 MHz): δ 3.18-3.14(m, 1 H), 2.84-2.77(m, 2 H), 2.76- 2.68(m, 2 H), 1.69-1.54(m, 2 H), 1.05(t, J = 7.2, 6 H), 0.91(t, J = 7.3, 3 H). LC/MS: Anal. Calcd. for [M + H] ⁺ C ₈ H ₁₈ NO ₂ : 160.13; found 160.06.
Cap-72		¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): δ 2.77-2.66(m, 3 H), 2.39-2.31(m, 2 H), 1.94- 1.85(m, 1 H), 0.98(t, J = 7.1, 6 H), 0.91(d, J = 6.5, 3 H), 0.85(d, J = 6.5, 3 H). LC/MS: Anal. Calcd. for [M + H] ⁺ C ₉ H ₂₀ NO ₂ : 174.15; found 174.15.
Cap-73		¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 500 MHz): δ 9.5(br s, 1 H), 3.77(dd, J = 1.8, 4.1, 1 H), 3.69-3.61(m, 2 H), 3.26(s, 3 H), 2.99-2.88(m, 4 H), 1.13(t, J = 7.2, 6 H).
Cap-74		¹ H NMR(DMSO-d ₆ , δ = 2.5 ppm, 500 MHz): δ 7.54(s, 1 H), 6.89(s, 1 H), 3.81(t, J = 6.6, k, 1 H), 2.82-2.71(m, 4 H), 2.63(dd, J = 15.6, 7.0, 1 H), 2.36(dd, J = 15.4, 6.3, 1 H), 1.09(t, J = 7.2, 6 H). RT = 0.125 minutes (Cond. 2); LC/MS: Anal. Calcd. for [M + H] ⁺ C ₈ H ₁₇ N ₂ O ₃ : 189.12; found 189.13.
Cap-74x		LC/MS: Anal. Calcd. for [M + H] ⁺ C ₁₀ H ₂₂ NO ₂ : 188.17; found 188.21

-continued

Cap-75, step a

Cap-75

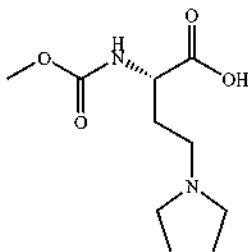


[0302] NaBH₃CN (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient

condition for 2 hr. The reaction was carefully quenched with 12N HCl and concentrated in vacuo. The residue was dissolved in water and purified with a reverse phase HPLC (MeOH/H₂O/TFA) to afford the TFA salt of (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate as a colorless viscous oil (1.9 g). ¹H NMR (DMSO-d₆, δ=2.5 ppm, 500 MHz): δ 9.73 (br s, 1H), 7.52-7.36 (m, 5H), 5.32 (d, J=12.2, 1H), 5.27 (d, J=12.5, 1H), 4.54-4.32 (m, 1H), 4.05-3.97 (m, 2H), 3.43-3.21 (m, 4H), 1.23 (t, J=7.2, 6H). LC/MS (Cond. 2): RT=1.38 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₄H₂₂NO₃: 252.16; found 252.19.

Cap-75

[0303] NaH (0.0727 g, 1.82 mmol, 60%) was added to a cooled (ice-water) THF (3.0 mL) solution of the TFA salt (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate (0.3019 g, 0.8264 mmol) prepared above, and the mixture was stirred for 15 min. Methyl iodide (56 μL, 0.90 mmol) was added and stirring was continued for 18 hr while allowing the bath to thaw to ambient condition. The reaction was quenched with water and loaded onto a MeOH pre-conditioned MCX (6 g) cartridge, and washed with methanol followed by compound elution with 2N NH₃/Methanol. Removal of the volatile component in vacuo afforded Cap-75, contaminated with (R)-2-(diethylamino)-3-hydroxypropanoic acid, as a yellow semi-solid (100 mg). The product was used as is without further purification.

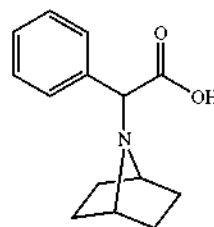


Cap-76

[0304] NaCNBH₃ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15° C.) water/MeOH (12 mL each) solution of (S)-4-amino-2-(tert-butoxycarbonylamino)butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 3.5 hr. An additional acetaldehyde (2.7 mL, 48.1 mmol) was added and the reaction was stirred for 20.5 hr. Most of the MeOH component was removed in vacuo, and the remaining mixture was treated with concentrated HCl until its pH reached ~1.0 and then heated for 2 hr at 40° C. The volatile component was removed in vacuo, and the residue was treated with 4 M HCl/dioxane (20 mL) and stirred at ambient condition for 7.5 hr. The volatile component was removed in vacuo and the residue was purified with Dowex ® 50WX8-100 ion-exchange resin (column was washed with water and the compound was eluted with dilute NH₄OH, prepared from 18 mL of NH₄OH and 282 mL of water) to afford intermediate (S)-2-amino-4-(diethylamino)butanoic acid as an off-white solid (1.73 g).

[0305] Methyl chloroformate (0.36 mL, 4.65 mmol) was added drop-wise over 11 min to a cooled (ice-water) mixture of Na₂CO₃ (0.243 g, 2.29 mmol), NaOH (4.6 mL of 1M/H₂O,

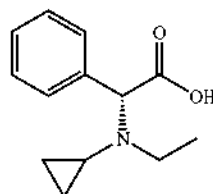
4.6 mmol) and the above product (802.4 mg). The reaction mixture was stirred for 55 min, and then the cooling bath was removed and stirring was continued for an additional 5.25 hr. The reaction mixture was diluted with equal volume of water and washed with CH₂Cl₂ (30 mL, 2×), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 2. The volatile component was then removed in vacuo and the crude material was free-based with MCX resin (6.0 g; column was washed with water, and sample was eluted with 2.0 M NH₃/MeOH) to afford impure Cap-76 as an off-white solid (704 mg). ¹H NMR (MeOH-d₄, δ=3.29 ppm, 400 MHz): δ 3.99 (dd, J=7.5, 4.7, 1H), 3.62 (s, 3H), 3.25-3.06 (m, 6H), 2.18-2.09 (m, 1H), 2.04-1.96 (m, 1H), 1.28 (t, J=7.3, 6H). LC/MS: Anal. Calcd. for [M+H]⁺ C₁₀H₂₁N₂O₄: 233.15; found 233.24.



Cap-77a and -77b

Cap-77a: enantiomer-1
Cap-77b: enantiomer-2

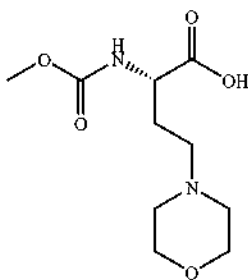
[0306] The synthesis of Cap-77 was conducted according to the procedure described for Cap-7 by using 7-azabicyclo[2.2.1]heptane for the SN₂ displacement step, and by effecting the enantiomeric separation of the intermediate benzyl 2-(7-azabicyclo[2.2.1]heptan-7-yl)-2-phenylacetate using the following condition: the intermediate (303.7 mg) was dissolved in ethanol, and the resulting solution was injected on a chiral HPLC column (Chiracel AD-H column, 30×250 mm, 5 μm) eluting with 90% CO₂-10% EtOH at 70 mL/min, and a temperature of 35° C. to provide 124.5 mg of enantiomer-1 and 133.8 mg of enantiomer-2. These benzyl esters were hydrogenolysed according to the preparation of Cap-7 to provide Cap-77: ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 7.55 (m, 2H), 7.38-7.30 (m, 3H), 4.16 (s, 1H), 3.54 (app br s, 2H), 2.08-1.88 (m, 4H), 1.57-1.46 (m, 4H). LC (Cond. 1): RT=0.67 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₄H₁₈BrNO₂: 232.13; found 232.18. HRMS: Anal. Calcd. for [M+H]⁺ C₁₄H₁₈BrNO₂: 232.1338; found 232.1340.



Cap-78

[0307] NaCNBH₃ (0.5828 g, 9.27 mmol) was added to a mixture of the HCl salt of (R)-2-(ethylamino)-2-phenylacetic acid (an intermediate in the synthesis of Cap-3; 0.9923 mg, 4.60 mmol) and (1-ethoxycyclopropoxy)trimethylsilane (1.640 g, 9.40 mmol) in MeOH (10 mL), and the semi-het-

erogeneous mixture was heated at 50° C. with an oil bath for 20 hr. More (1-ethoxycyclopropoxy)trimethylsilane (150 mg, 0.86 mmol) and NaCNBH₃ (52 mg, 0.827 mmol) were added and the reaction mixture was heated for an additional 3.5 hr. It was then allowed to cool to ambient temperature and acidified to a ~pH region of 2 with concentrated HCl, and the mixture was filtered and the filtrate was rotovaped. The resulting crude material was taken up in i-PrOH (6 mL) and heated to effect dissolution, and the non-dissolved part was filtered off and the filtrate concentrated in vacuo. About 1/3 of the resultant crude material was purified with a reverse phase HPLC (H₂O/MeOH/TFA) to afford the TFA salt of Cap-78 as a colorless viscous oil (353 mg). ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz; after D₂O exchange): δ 7.56-7.49 (m, 5H), 5.35 (s, 1H), 3.35 (m, 1H), 3.06 (app br s, 1H), 2.66 (m, 1H), 1.26 (t, J=7.3, 3H), 0.92 (m, 1H), 0.83-0.44 (m, 3H). LC (Cond. 1): RT=0.64 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₃H₁₈NO₂: 220.13; found 220.21. HRMS: Anal. Calcd. for [M+H]⁺ C₁₃H₁₈NO₂: 220.1338; found 220.1343.



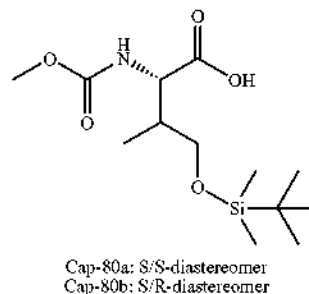
Cap-79

[0308] Ozone was bubbled through a cooled (-78° C.) CH₂Cl₂ (5.0 mL) solution Cap-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of blue color. Me₂S (10 pipet drops) was added, and the reaction mixture was stirred for 35 min. The -78° C. bath was replaced with a -10° C. bath and stirring continued for an additional 30 min, and then the volatile component was removed in vacuo to afford a colorless viscous oil.

[0309] NaBH₃CN (149 mg, 2.25 mmol) was added to a MeOH (5.0 mL) solution of the above crude material and morpholine (500 μL, 5.72 mmol) and the mixture was stirred at ambient condition for 4 hr. It was cooled to ice-water temperature and treated with concentrated HCl to bring its pH to ~2.0, and then stirred for 2.5 hr. The volatile component was removed in vacuo, and the residue was purified with a combination of MCX resin (MeOH wash; 2.0 N NH₃/MeOH elution) and a reverse phase HPLC (H₂O/MeOH/TFA) to afford Cap-79 containing unknown amount of morpholine.

[0310] In order to consume the morpholine contaminant, the above material was dissolved in CH₂Cl₂ (1.5 mL) and treated with Et₃N (0.27 mL, 1.94 mmol) followed by acetic anhydride (0.10 mL, 1.06 mmol) and stirred at ambient condition for 18 hr. THF (1.0 mL) and H₂O (0.5 mL) were added and stirring continued for 1.5 hr. The volatile component was removed in vacuo, and the resultant residue was passed through MCX resin (MeOH wash; 2.0 N NH₃/MeOH elution) to afford impure Cap-79 as a brown viscous oil, which was used for the next step without further purification.

Cap-80a and -80b

Cap-80a: S/S-diastereomer
Cap-80b: S/R-diastereomer

[0311] SOCl₂ (6.60 mL, 90.5 mmol) was added drop-wise over 15 min to a cooled (ice-water) mixture of (S)-3-amino-4-(benzyloxy)-4-oxobutanoic acid (10.04 g, 44.98 mmol) and MeOH (300 mL), the cooling bath was removed and the reaction mixture was stirred at ambient condition for 29 hr. Most of the volatile component was removed in vacuo and the residue was carefully partitioned between EtOAc (150 mL) and saturated NaHCO₃ solution. The aqueous phase was extracted with EtOAc (150 mL, 2×), and the combined organic phase was dried (MgSO₄), filtered, and concentrated in vacuo to afford (S)-1-benzyl 4-methyl 2-aminosuccinate as a colorless oil (9.706 g). ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 7.40-7.32 (m, 5H), 5.11 (s, 2H), 3.72 (app t, J=6.6, 1H), 3.55 (s, 3H), 2.68 (dd, J=15.9, 6.3, 1H), 2.58 (dd, J=15.9, 6.8, 1H), 1.96 (s, 2H). LC (Cond. 1): RT=0.90 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₂H₁₆NO₄: 238.11; found 238.22.

[0312] Pb(NO₃)₂ (6.06 g, 18.3 mmol) was added over 1 min to a CH₂Cl₂ (80 mL) solution of (S)-1-benzyl 4-methyl 2-aminosuccinate (4.50 g, 19.0 mmol), 9-bromo-9-phenyl-9H-fluorene (6.44 g, 20.0 mmol) and Et₃N (3.0 mL, 21.5 mmol), and the heterogeneous mixture was stirred at ambient condition for 48 hr. The mixture was filtered and the filtrate was treated with MgSO₄ and filtered again, and the final filtrate was concentrated. The resulting crude material was submitted to a Biotage purification (350 g silica gel, CH₂Cl₂ elution) to afford (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate as highly viscous colorless oil (7.93 g). ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 7.82 (m, 2H), 7.39-7.13 (m, 16H), 4.71 (d, J=12.4, 1H), 4.51 (d, J=12.6, 1H), 3.78 (d, J=9.1, NH), 3.50 (s, 3H), 2.99 (m, 1H), 2.50-2.41 (m, 2H, partially overlapped with solvent). LC (Cond. 1): RT=2.16 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₃₁H₂₈NO₄: 478.20; found 478.19.

[0313] LiHMDS (9.2 mL of 1.0 M/THF, 9.2 mmol) was added drop-wise over 10 min to a cooled (-78° C.) THF (50 mL) solution of (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.907 g, 8.18 mmol) and stirred for 1 hr. MeI (0.57 mL, 9.2 mmol) was added drop-wise over 8 min to the mixture, and stirring was continued for 16.5 hr while allowing the cooling bath to thaw to room temperature. After quenching with saturated NH₄Cl solution (5 mL), most of the organic component was removed in vacuo and the residue was partitioned between CH₂Cl₂ (100 mL) and water (40 mL). The organic layer was dried (MgSO₄), filtered, and concentrated in vacuo, and the resulting crude material was purified with a Biotage (350 g silica gel; 25% EtOAc/hexanes) to afford 3.65 g of a 2S/3S and 2S/3R diastereomeric

mixtures of 1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate in ~1.0:0.65 ratio (^1H NMR). The stereochemistry of the dominant isomer was not determined at this juncture, and the mixture was submitted to the next step without separation. Partial ^1H NMR data (DMSO- d_6 , δ =2.5 ppm, 400 MHz): major diastereomer, δ 4.39 (d, J =12.3, 1H of CH_2), 3.33 (s, 3H, overlapped with H_2O signal), 3.50 (d, J =10.9, NH), 1.13 (d, J =7.1, 3H); minor diastereomer, δ 4.27 (d, J =12.3, 1H of CH_2), 3.76 (d, J =10.9, NH), 3.64 (s, 3H), 0.77 (d, J =7.0, 3H). LC (Cond. 1): RT=2.19 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{32}\text{H}_{30}\text{NO}_4$: 492.22; found 492.15.

[0314] Diisobutylaluminum hydride (20.57 ml of 1.0 M in hexanes, 20.57 mmol) was added drop-wise over 10 min to a cooled (-78°C) THF (120 mL) solution of (2S,3R)-1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.37 g, 6.86 mmol) prepared above, and stirred at -78°C for 20 hr. The reaction mixture was removed from the cooling bath and rapidly poured into -1M $\text{H}_3\text{PO}_4/\text{H}_2\text{O}$ (250 mL) with stirring, and the mixture was extracted with ether (100 mL, 2x). The combined organic phase was washed with brine, dried (MgSO_4), filtered and concentrated in vacuo. A silica gel mesh of the crude material was prepared and submitted to chromatography (25% EtOAc/hexanes; gravity elution) to afford 1.1 g of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate, contaminated with benzyl alcohol, as a colorless viscous oil and (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate containing the (2S,3R) stereoisomer as an impurity. The latter sample was resubmitted to the same column chromatography purification conditions to afford 750 mg of purified material as a white foam. [Note: the (2S,3S) isomer elutes before the (2S,3R) isomer under the above condition]. (2S,3S) isomer: ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): 7.81 (m, 2H), 7.39-7.08 (m, 16H), 4.67 (d, J =12.3, 1H), 4.43 (d, J =12.4, 1H), 4.21 (app t, J =5.2, OH), 3.22 (d, J =10.1, NH), 3.17 (m, 1H), 3.08 (m, 1H), ~2.5 (m, 1H, overlapped with the solvent signal), 1.58 (m, 1H), 0.88 (d, J =6.8, 3H). LC (Cond. 1): RT=2.00 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{31}\text{H}_{30}\text{NO}_3$: 464.45; found 464.22. (2S,3R) isomer: ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): 7.81 (d, J =7.5, 2H), 7.39-7.10 (m, 16H), 4.63 (d, J =12.1, 1H), 4.50 (app t, J =4.9, 1H), 4.32 (d, J =12.1, 1H), 3.59-3.53 (m, 2H), 3.23 (m, 1H), 2.44 (dd, J =9.0, 8.3, 1H), 1.70 (m, 1H), 0.57 (d, J =6.8, 3H). LC (Cond. 1): RT=1.92 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{31}\text{H}_{30}\text{NO}_3$: 464.45; found 464.52.

[0315] The relative stereochemical assignments of the DIBAL-reduction products were made based on NOE studies conducted on lactone derivatives prepared from each isomer by employing the following protocol: LiHMDS (50 μL of 1.0 M/THF, 0.05 mmol) was added to a cooled (ice-water) THF (2.0 mL) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (62.7 mg, 0.135 mmol), and the reaction mixture was stirred at similar temperature for ~2 hr. The volatile component was removed in vacuo and the residue was partitioned between CH_2Cl_2 (30 mL), water (20 mL) and saturated aqueous NH_4Cl solution (1 mL). The organic layer was dried (MgSO_4), filtered, and concentrated in vacuo, and the resulting crude material was submitted to a Biotage purification (40 g silica gel; 10-15% EtOAc/hexanes) to afford (3S,4S)-4-methyl-3-(9-phenyl-9H-fluoren-9-ylamino)dihydrofuran-2(3H)-one as a colorless film of solid (28.1 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was

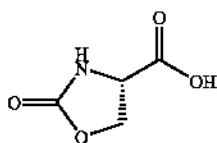
elaborated similarly to (3S,4R)-4-methyl-3-(9-phenyl-9H-fluoren-9-ylamino)dihydrofuran-2(3H)-one. (3S,4S)-lactone isomer: ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz), 7.83 (d, J =7.5, 2H), 7.46-7.17 (m, 11H), 4.14 (app t, J =8.3, 1H), 3.60 (d, J =5.8, NH), 3.45 (app t, J =9.2, 1H), ~2.47 (m, 1H, partially overlapped with solvent signal), 2.16 (m, 1H), 0.27 (d, J =6.6, 3H). LC (Cond. 1): RT=1.98 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{Na}]^+ \text{C}_{24}\text{H}_{21}\text{NNaO}_2$: 378.15; found 378.42. (3S,4R)-lactone isomer: ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz), 7.89 (d, J =7.6, 1H), 7.85 (d, J =7.3, 1H), 7.46-7.20 (m, 11H), 3.95 (dd, J =9.1, 4.8, 1H), 3.76 (d, J =8.8, 1H), 2.96 (d, J =3.0, NH), 2.92 (dd, J =6.8, 3, NCH), 1.55 (m, 1H), 0.97 (d, J =7.0, 3H). LC (Cond. 1): RT=2.03 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{Na}]^+ \text{C}_{24}\text{H}_{21}\text{NNaO}_2$: 378.15; found 378.49.

[0316] TBDMS-Cl (48 mg, 0.312 mmol) followed by imidazole (28.8 mg, 0.423 mmol) were added to a CH_2Cl_2 (3 mL) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (119.5 mg, 0.258 mmol), and the mixture was stirred at ambient condition for 14.25 hr. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with water (15 mL), and the organic layer was dried (MgSO_4), filtered, and concentrated in vacuo. The resultant crude material was purified with a Biotage (40 g silica gel; 5% EtOAc/hexanes) to afford (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate, contaminated with TBDMS based impurities, as a colorless viscous oil (124.4 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was elaborated similarly to (2S,3R)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate. (2S,3S)-silyl ether isomer: ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz), 7.82 (d, J =4.1, 1H), 7.80 (d, J =4.0, 1H), 7.38-7.07 (m, 16H), 4.70 (d, J =12.4, 1H), 4.42 (d, J =12.3, 1H), 3.28-3.19 (m, 3H), 2.56 (dd, J =10.1, 5.5, 1H), 1.61 (m, 1H), 0.90 (d, J =6.8, 3H), 0.70 (s, 9H), -0.13 (s, 3H), -0.16 (s, 3H). LC (Cond. 1, where the run time was extended to 4 min): RT=3.26 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{37}\text{H}_{44}\text{NO}_3\text{Si}$: 578.31; found 578.40. (2S,3R)-silyl ether isomer: ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz), 7.82 (d, J =3.0, 1H), 7.80 (d, J =3.1, 1H), 7.39-7.10 (m, 16H), 4.66 (d, J =12.4, 1H), 4.39 (d, J =12.4, 1H), 3.61 (dd, J =9.9, 5.6, 1H), 3.45 (d, J =9.5, 1H), 3.41 (dd, J =10.6, 6.2, 1H), 2.55 (dd, J =9.5, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, J =7.1, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

[0317] A balloon of hydrogen was attached to a mixture of (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (836 mg, 1.447 mmol) and 10% Pd/C (213 mg) in EtOAc (16 mL) and the mixture was stirred at room temperature for ~21 hr, where the balloon was recharged with H_2 as necessary. The reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of diatomaceous earth (Celite-545), and the pad was washed with EtOAc (200 mL), EtOAc/MeOH (1:1 mixture, 200 mL) and MeOH (750 mL). The combined organic phase was concentrated, and a silica gel mesh was prepared from the resulting crude material and submitted to a flash chromatography (8:2:1 mixture of EtOAc/i-PrOH/ H_2O) to afford (2S,3S)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid as a white fluffy solid (325 mg). (2S,3R)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was similarly elaborated to (2S,3R)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid. (2S,3S)-amino acid isomer: ^1H NMR (Methanol- d_4 , δ =3.29 ppm, 400 MHz), 3.76 (dd, J =10.5, 5.2, 1H), 3.73 (d,

$J=3.0$, 1H), 3.67 (dd, $J=10.5$, 7.0, 1H), 2.37 (m, 1H), 0.97 (d, $J=7.0$, 3H), 0.92 (s, 9H), 0.10 (s, 6H). LC/MS: Anal. Calcd. for $[M+H]^+ C_{11}H_{26}NO_3Si$: 248.17; found 248.44. (2S,3R)-amino acid isomer: 1H NMR (Methanol- d_4 , $\delta=3.29$ ppm, 400 MHz), 3.76-3.75 (m, 2H), 3.60 (d, $J=4.1$, 1H), 2.16 (m, 1H), 1.06 (d, $J=7.3$, 3H), 0.91 (s, 9H), 0.09 (s, 6H). Anal. Calcd. for $[M+H]^+ C_{11}H_{26}NO_3Si$: 248.17; found 248.44.

[0318] Water (1 mL) and NaOH (0.18 mL of 1.0 M/ H_2O , 0.18 mmol) were added to a mixture of (2S,3S)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid (41.9 mg, 0.169 mmol) and Na_2CO_3 (11.9 mg, 0.112 mmol), and sonicated for about 1 min to effect dissolution of reactants. The mixture was then cooled with an ice-water bath, methyl chloroformate (0.02 mL, 0.259 mmol) was added over 30 s, and vigorous stirring was continued at similar temperature for 40 min and then at ambient temperature for 2.7 hr. The reaction mixture was diluted with water (5 mL), cooled with ice-water bath and treated drop-wise with 1.0 N HCl aqueous solution (~0.23 mL). The mixture was further diluted with water (10 mL) and extracted with CH_2Cl_2 (15 mL, 2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford Cap-80a as an off-white solid. (2S,3R)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid was similarly elaborated to Cap-80b. Cap-80a: 1H NMR (DMSO- d_6 , $\delta=2.5$ ppm, 400 MHz), 12.57 (br s, 1H), 7.64 (d, $J=8.3$, 0.3H), 7.19 (d, $J=8.8$, 0.7H), 4.44 (dd, $J=8.1$, 4.6, 0.3H), 4.23 (dd, $J=8.7$, 4.4, 0.7H), 3.56/3.53 (two singlets, 3H), 3.48-3.40 (m, 2H), 2.22-2.10 (m, 1H), 0.85 (s, 9H), ~0.84 (d, 0.9H, overlapped with t-Bu signal), 0.79 (d, $J=7$, 2.1H), 0.02/0.01/0.00 (three overlapping singlets, 6H). LC/MS: Anal. Calcd. for $[M+Na]^+ C_{13}H_{27}NNaO_5Si$: 328.16; found 328.46. Cap-80b: 1H NMR ($CDCl_3$, $\delta=7.24$ ppm, 400 MHz), 6.00 (br d, $J=6.8$, 1H), 4.36 (dd, $J=7.1$, 3.1, 1H), 3.87 (dd, $J=10.5$, 3.0, 1H), 3.67 (s, 3H), 3.58 (dd, $J=10.6$, 4.8, 1H), 2.35 (m, 1H), 1.03 (d, $J=7.1$, 3H), 0.90 (s, 9H), 0.08 (s, 6H). LC/MS: Anal. Calcd. for $[M+Na]^+ C_{13}H_{27}NNaO_5Si$: 328.16; found 328.53. The crude products were utilized without further purification.

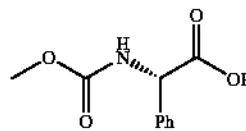


Cap-81

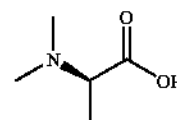
[0319] Prepared according to the protocol described by Falb et al. *Synthetic Communications* 1993, 23, 2839.

Cap-82 to Cap-85

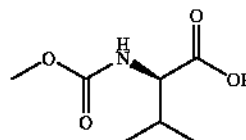
[0320] Cap-82 to Cap-85 were synthesized from appropriate starting materials according to the procedure described for Cap-51. The samples exhibited similar spectral profiles as that of their enantiomers (i.e., Cap-4, Cap-13, Cap-51 and Cap-52, respectively)



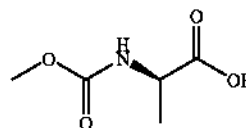
Cap-82



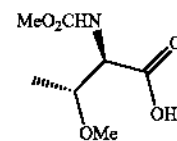
Cap-83



Cap-84

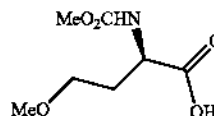


Cap-85



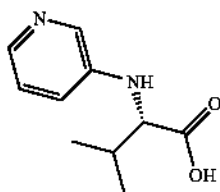
Cap-86

[0321] To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0° C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and 10% MeOH in CH_2Cl_2 (250 mL) and the combined organic phases were concentrated under in vacuo to afford a colorless oil (4.18 g, 97%) which was of sufficient purity for use in subsequent steps. 1H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.92-3.97 (m, 1H), 3.66 (s, 3H), 1.17 (d, $J=7.7$ Hz, 3H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 190 ($M-H$)⁻.



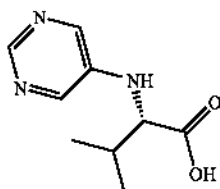
Cap-87

[0322] To a mixture of L-homoserine (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (0.76 mL, 9.79 mmol) dropwise at 0° C. The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and the combined organic phases were concentrated under in vacuo to afford a colorless solid (0.719 g, 28%) which was of sufficient purity for use in subsequent steps. 1H NMR (400 MHz, $CDCl_3$) δ 4.23 (dd, $J=4.5$, 9.1 Hz, 1H), 3.66 (s, 3H), 3.43-3.49 (m, 2H), 2.08-2.14 (m, 1H), 1.82-1.89 (m, 1H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 192 ($M+H$)⁺.



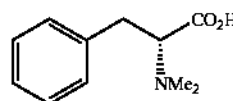
Cap-88

[0323] A mixture of L-valine (1.0 g, 8.54 mmol), 3-bromopyridine (1.8 mL, 18.7 mmol), K_2CO_3 (2.45 g, 17.7 mmol) and CuI (169 mg, 0.887 mmol) in DMSO (10 mL) was heated at 100° C. for 12 h. The reaction mixture was cooled to rt, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20 g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25 g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2x200 mL). The appropriate fractions was concentrated in vacuo and the residue (ca. 1.1 g) was dissolved in H_2O , frozen and lyophilized. The title compound was obtained as a foam (1.02 g, 62%). 1H NMR (400 MHz, DMSO- d_6) δ 8.00 (s, br, 1H), 7.68-7.71 (m, 1H), 7.01 (s, br, 1H), 6.88 (d, J=7.5 Hz, 1H), 5.75 (s, br, 1H), 3.54 (s, 1H), 2.04-2.06 (m, 1H), 0.95 (d, J=6.0 Hz, 3H), 0.91 (d, J=6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{10}H_{14}N_2O_2$: 194; found: 195 (M+H) $^+$.



Cap-89

[0324] A mixture of L-valine (1.0 g, 8.54 mmol), 5-bromopyrimidine (4.03 g, 17.0 mmol), K_2CO_3 (2.40 g, 17.4 mmol) and CuI (179 mg, 0.94 mmol) in DMSO (10 mL) was heated at 100° C. for 12 h. The reaction mixture was cooled to RT, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20 g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25 g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2x200 mL). The appropriate fractions was concentrated in vacuo and the residue (ca. 1.1 g) was dissolved in H_2O , frozen and lyophilized. The title compound was obtained as a foam (1.02 g, 62%). 1H NMR (400 MHz, CD_3OD) showed the mixture to contain valine and the purity could not be estimated. The material was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_9H_{13}N_3O_2$: 195; found: 196 (M+H) $^+$.



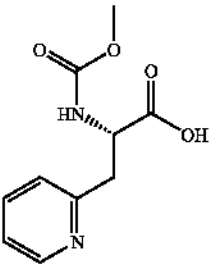
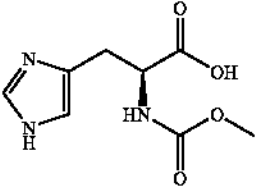
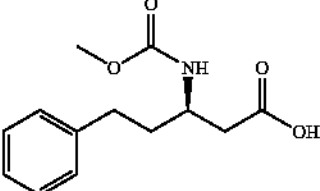
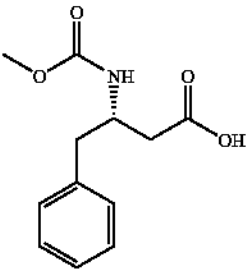
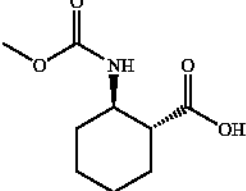
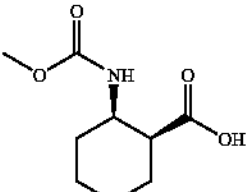
Cap-90

[0325] Cap-90 was prepared according to the method described for the preparation of Cap-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 (M-H) $^-$.

[0326] The following caps were prepared according to the method of example 51:

Cap	Structure	LCMS
Cap-91		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 (M-H) $^-$.
Cap-92		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 (M-H) $^-$.

-continued

Cap	Structure	LCMS
Cap-93		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 ($M + H$) ⁺ .
Cap-94		LCMS: Anal. Calcd. for $C_9H_{11}N_3O_4$: 213; found: 214 ($M + H$) ⁺ .
Cap-95		LCMS: Anal. Calcd. for $C_{13}H_{17}NO_4$: 251; found: 250 ($M - H$) ⁻ .
Cap-96		LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 236 ($M - H$) ⁻ .
Cap-97		LCMS: Anal. Calcd. for $C_9H_{13}NO_4$: 201; found: 200 ($M - H$) ⁻ .
Cap-98		LCMS: Anal. Calcd. for $C_9H_{13}NO_4$: 201; found: 202 ($M + H$) ⁺ .

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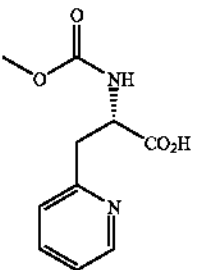
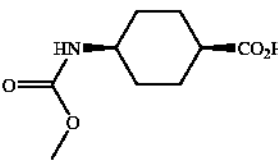
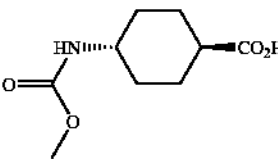
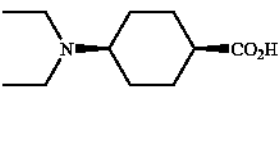
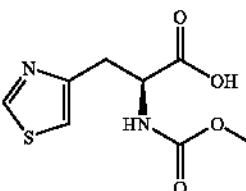
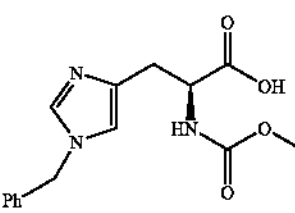
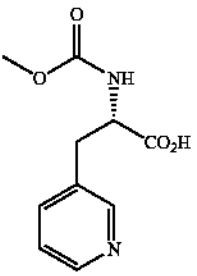
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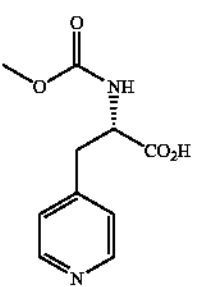
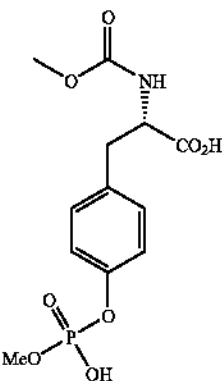
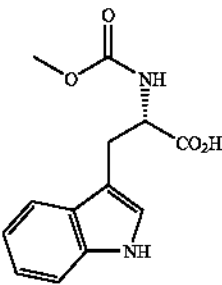
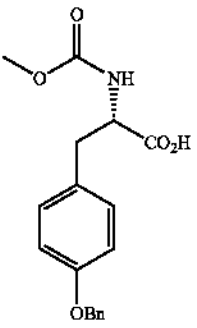
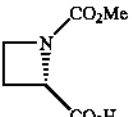
-continued

Cap	Structure	LCMS
Cap-99		¹ HNMR(400 MHz, CD ₃ OD) δ 3.88-3.94(m, 1 H), 3.60, 3.61(s, 3 H), 2.80(m, 1 H), 2.20(m, 1 H), 1.82-1.94(m, 3 H), 1.45-1.71(m, 2 H).
Cap-99a		¹ HNMR(400 MHz, CD ₃ OD) δ 3.88-3.94(m, 1 H), 3.60, 3.61(s, 3 H), 2.80(m, 1 H), 2.20(m, 1 H), 1.82-1.94(m, 3 H), 1.45-1.71(m, 2 H).
Cap-100		LCMS: Anal. Calcd. for C ₁₂ H ₁₄ NO ₄ F: 255; found: 256(M + H) ⁺ .
Cap-101		LCMS: Anal. Calcd. for C ₁₁ H ₁₃ NO ₄ : 223; found: 222 (M - H) ⁻ .
Cap-102		LCMS: Anal. Calcd. for C ₁₁ H ₁₃ NO ₄ : 223; found: 222 (M - H) ⁻ .

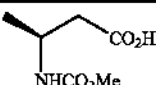
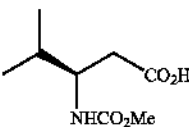
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Cap	Structure	LCMS
Cap-103		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 ($M + H$) ⁺ .
Cap-104		¹ HNMR(400 MHz, CD ₃ OD) δ 3.60(s, 3 H), 3.50-3.53(m, 1 H), 2.66-2.69 and 2.44-2.49(m, 1 H), 1.91-2.01(m, 2 H), 1.62-1.74(m, 4 H), 1.51-1.62(m, 2 H).
Cap-105		¹ HNMR(400 MHz, CD ₃ OD) δ 3.60(s, 3 H), 3.33-3.35(m, 1 H, partially obscured by solvent), 2.37-2.41 and 2.16-2.23(m, 1 H), 1.94-2.01(m, 4 H), 1.43-1.53(m, 2 H), 1.17-1.29(m, 2 H).
Cap-106		¹ HNMR(400 MHz, CD ₃ OD) δ 3.16(q, J = 7.3 Hz, 4 H), 2.38-2.41(m, 1 H), 2.28-2.31(m, 2 H), 1.79-1.89(m, 2 H), 1.74(app, ddd J = 3.5, 12.5, 15.9 Hz, 2 H), 1.46(app dt J = 4.0, 12.9 Hz, 2 H), 1.26(t, J = 7.3 Hz, 6 H).
Cap-107		LCMS: Anal. Calcd. for $C_8H_{10}N_2O_4S$: 230; found: 231 ($M + H$) ⁺ .
Cap-108		LCMS: Anal. Calcd. for $C_{15}H_{17}N_3O_4$: 303; found: 304 ($M + H$) ⁺ .
Cap-109		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 ($M + H$) ⁺ .

-continued

Cap	Structure	LCMS
Cap-110		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M + H)^+$.
Cap-111		LCMS: Anal. Calcd. for $C_{12}H_{16}NO_8P$: 333; found: 334 $(M + H)^+$.
Cap-112		LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_4$: 262; found: 263 $(M + H)^+$.
Cap-113		LCMS: Anal. Calcd. for $C_{18}H_{19}NO_5$: 329; found: 330 $(M + H)^+$.
Cap-114		1H NMR(400 MHz, $CDCl_3$) δ 4.82-4.84(m, 1 H), 4.00-4.05(m, 2 H), 3.77(s, 3 H), 2.56(s, br, 2 H)

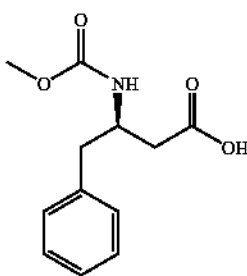
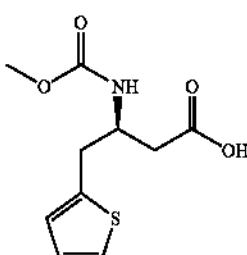
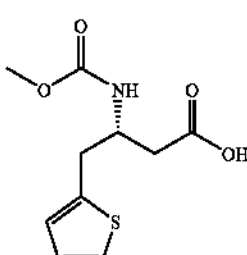
-continued

Cap	Structure	LCMS
Cap-115		¹ HNMR(400 MHz, CDCl ₃) δ 5.13(s, br, 1 H), 4.13(s, br, 1 H), 3.69(s, 3 H), 2.61(d, J = 5.0 Hz, 2 H), 1.28(d, J = 9.1 Hz, 3 H).
Cap-116		¹ HNMR(400 MHz, CDCl ₃) δ 5.10(d, J = 8.6 Hz, 1 H), 3.74-3.83(m, 1 H), 3.69(s, 3 H), 2.54-2.61(m, 2 H), 1.88(sept, J = 7.0 Hz, 1 H), 0.95(d, J = 7.0 Hz, 6 H).

Cap-117 to Cap-123

[0327] For the preparation of caps Cap-117 to Cap-123 the Boc amino acids were commercially available and were deprotected by treatment with 25% TFA in CH₂Cl₂. After

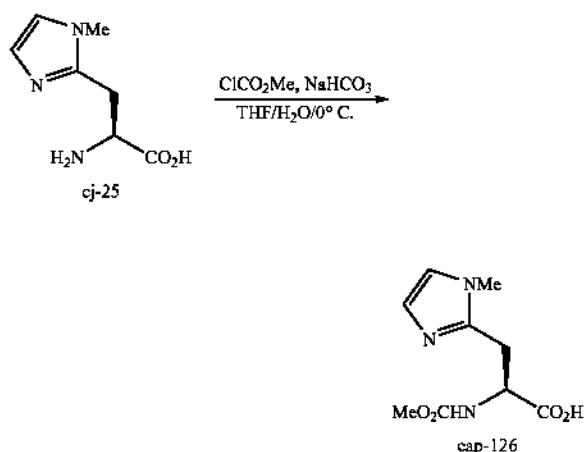
complete reaction as judged by LCMS the solvents were removed in vacuo and the corresponding TFA salt of the amino acid was carbamoylated with methyl chloroformate according to the procedure for Cap-51.

Cap	Structure	LCMS
Cap-117		LCMS: Ansl. Calcd. for C ₁₂ H ₁₅ NO ₄ S: 237; found: 238(M + H) ⁺ .
Cap-118		LCMS: Ansl. Calcd. for C ₁₀ H ₁₃ NO ₄ S: 243; found: 244(M + H) ⁺ .
Cap-119		LCMS: Ansl. Calcd. for C ₁₀ H ₁₃ NO ₄ S: 243; found: 244(M + H) ⁺ .

in subsequent reactions. LCMS: Anal. Calcd. for $C_{11}H_{22}N_2O_4$: 246; found: 247 (M+H)⁺.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1-methyl-1H-imidazol-2-yl)propanoic acid (Cap-126)

[0332]



[0333] This procedure is a modification of that used to prepare Cap-51. To a suspension of (S)-2-amino-3-(1-methyl-1H-imidazol-2-yl)propanoic acid (0.80 g, 4.70 mmol) in THF (10 mL) and H_2O (10 mL) at $0^\circ C$, was added $NaHCO_3$ (0.88 g, 10.5 mmol). The resulting mixture was treated with $ClCO_2Me$ (0.40 mL, 5.20 mmol) and the mixture allowed to stir at $0^\circ C$. After stirring for ca. 2 h LCMS showed no starting material remaining. The reaction was acidified to pH 2 with 6 N HCl.

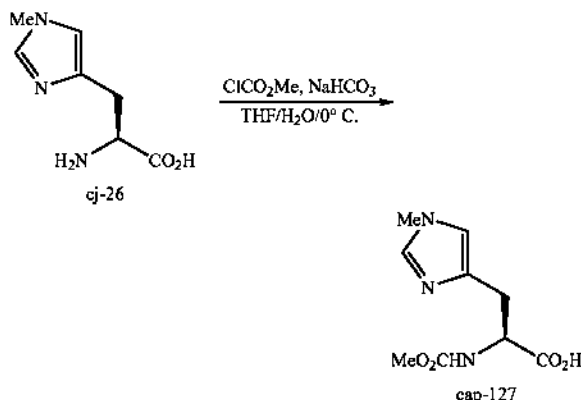
[0334] The solvents were removed in vacuo and the residue was suspended in 20 mL of 20% MeOH in CH_2Cl_2 . The mixture was filtered and concentrated to give a light yellow foam (1.21 g.). LCMS and 1H NMR showed the material to be a 9:1 mixture of the methyl ester and the desired product. This material was taken up in THF (10 mL) and H_2O (10 mL), cooled to $0^\circ C$, and LiOH (249.1 mg, 10.4 mmol) was added. After stirring ca. 1 h LCMS showed no ester remaining. Therefore the mixture was acidified with 6N HCl and the solvents removed in vacuo. LCMS and 1H NMR confirm the absence of the ester. The title compound was obtained as its HCl salt contaminated with inorganic salts (1.91 g, >100%). The compound was used as is in subsequent steps without further purification.

[0335] 1H NMR (400 MHz, CD_3OD) δ 8.84, (s, 1H), 7.35 (s, 1H), 4.52 (dd, $J=5.0, 9.1$ Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (dd, $J=4.5, 15.6$ Hz, 1H, partially obscured by solvent), 3.12 (dd, $J=9.0, 15.6$ Hz, 1H).

[0336] LCMS: Anal. Calcd. for $C_{17}H_{15}NO_2$: 392; found: 393 (M+H)⁺.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (Cap-127)

[0337]



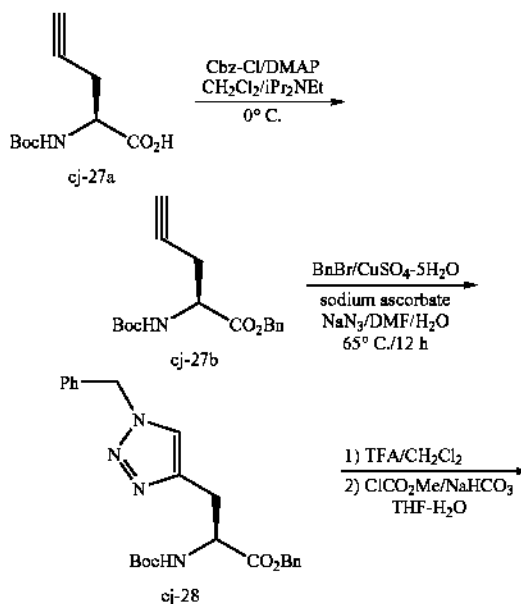
[0338] Cap-127 was prepared according to the method for Cap-126 above starting from (S)-2-amino-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (1.11 g, 6.56 mmol), $NaHCO_3$ (1.21 g, 14.4 mmol) and $ClCO_2Me$ (0.56 mL, 7.28 mmol). The title compound was obtained as its HCl salt (1.79 g, >100%) contaminated with inorganic salts. LCMS and 1H NMR showed the presence of ca. 5% of the methyl ester. The crude mixture was used as is without further purification.

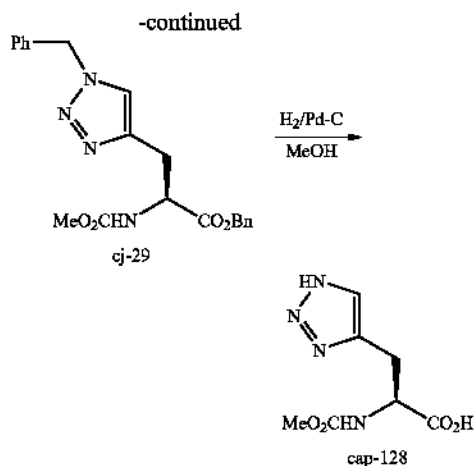
[0339] 1H NMR (400 MHz, CD_3OD) δ 8.90 (s, 1H), 7.35 (s, 1H), 4.48 (dd, $J=5.0, 8.6$ Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (m, 1H), 3.08 (m, 1H).

[0340] LCMS: Anal. Calcd. for $C_{17}H_{15}NO_2$: 392; found: 393 (M+H)⁺.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (Cap-128)

[0341]





Step 1. Preparation of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (cj-27b)

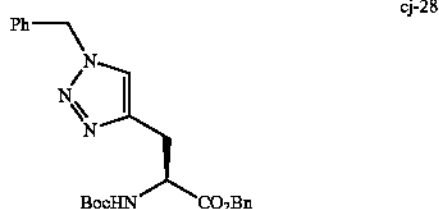
[0342]



[0343] To a solution of cj-27a (1.01 g, 4.74 mmol), DMAP (58 mg, 0.475 mmol) and $i\text{Pr}_2\text{NEt}$ (1.7 mL, 9.8 mmol) in CH_2Cl_2 (100 mL) at 0°C . was added Cbz-Cl (0.68 mL, 4.83 mmol). The solution was allowed to stir for 4 h at 0°C ., washed (1N H_2SO_4 , brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (TLC 6:1 hex:EtOAc) to give the title compound (1.30 g, 91%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.35 (s, 5H), 5.35 (d, br, $J=8.1$ Hz, 1H), 5.23 (d, $J=12.2$ Hz, 1H), 5.17 (d, $J=12.2$ Hz, 1H), 4.48-4.53 (m, 1H), 2.68-2.81 (m, 2H), 2.00 (t, $J=2.5$ Hz, 1H), 1.44 (s, 9H). LCMS: Anal. Calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_4$: 303; found: 304 ($\text{M}+\text{H}$) $^+$.

Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (cj-28)

[0344]

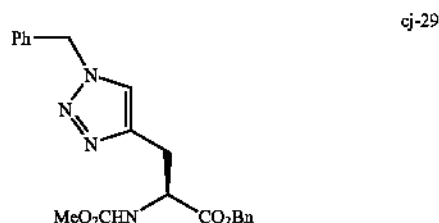


[0345] To a mixture of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (0.50 g, 1.65 mmol), sodium ascorbate (0.036 g, 0.18 mmol), $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ (0.022 g, 0.09 mmol) and NaN_3 (0.13 g, 2.1 mmol) in $\text{DMF-H}_2\text{O}$ (5 mL, 4:1) at rt was added BuBr (0.24 mL, 2.02 mmol) and the mixture was warmed to 65°C . After 5 h LCMS indicated low conversion. A further portion of NaN_3 (100 mg) was added and heating was continued for 12 h. The reaction was poured into EtOAc and H_2O and shaken. The layers were separated and the aqueous layer extracted 3 \times with EtOAc and the combined organic phases washed ($\text{H}_2\text{O}\times 3$, brine), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash (Biotage, 40+M 0-5% MeOH in CH_2Cl_2 ; TLC 3% MeOH in CH_2Cl_2) to afford a light yellow oil which solidified on standing (748.3 mg, 104%). The NMR was consistent with the desired product but suggests the presence of DMF. The material was used as is without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.27-7.32 (m, 10H), 5.54 (s, 2H), 5.07 (s, 2H), 4.25 (m, 1H), 3.16 (dd, $J=1.0, 5.3$ Hz, 1H), 3.06 (dd, $J=5.3, 14.7$ Hz), 2.96 (dd, $J=9.1, 14.7$ Hz, 1H), 1.31 (s, 9H).

[0346] LCMS: Anal. Calcd. for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_4$: 436; found: 437 ($\text{M}+\text{H}$) $^+$.

Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29)

[0347]



[0348] A solution of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (0.52 g, 1.15 mmol) in CH_2Cl_2 was added TFA (4 mL). The mixture was allowed to stir at room temperature for 2 h. The mixture was concentrated in vacuo to give a colorless oil which solidified on standing. This material was dissolved in $\text{THF-H}_2\text{O}$ and cooled to 0°C . Solid NaHCO_3 (0.25 g, 3.00 mmol) was added followed by ClCO_2Me (0.25 mL, 3.25 mmol). After stirring for 1.5 h the mixture was acidified to pH~2 with 6N HCl and then poured into $\text{H}_2\text{O-EtOAc}$. The layers were separated and the aq phase extracted 2 \times with EtOAc. The combined org layers were washed (H_2O , brine), dried (Na_2SO_4),

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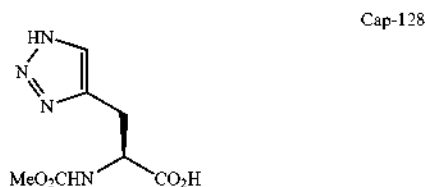
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filtered, and concentrated in vacuo to give a colorless oil (505.8 mg, 111%, NMR suggested the presence of an unidentified impurity) which solidified while standing on the pump. The material was used as is without further purification. ¹HNMR (400 MHz, DMSO-d₆) δ 7.87 (s, 1H), 7.70 (d, J=8.1 Hz, 1H), 7.27-7.32 (m, 10H), 5.54 (s, 2H), 5.10 (d, J=12.7 Hz, 1H), 5.06 (d, J=12.7 Hz, 1H), 4.32-4.37 (m, 1H), 3.49 (s, 3H), 3.09 (dd, J=5.6, 14.7 Hz, 1H), 2.98 (dd, J=9.6, 14.7 Hz, 1H). LCMS: Anal. Calcd. for C₂₁H₂₂N₄O₄: 394; found: 395 (M+H)⁺.

Step 3. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (Cap-128)

[0349]

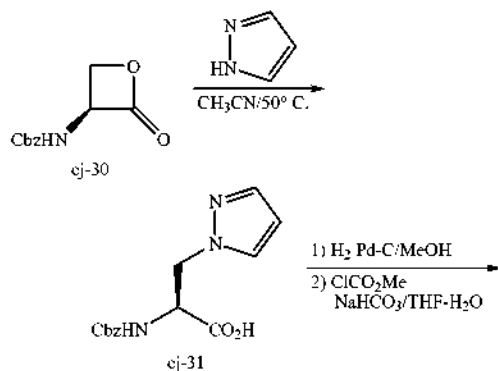


[0350] (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd—C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12 h. The mixture was filtered through diatomaceous earth (Celite®) and concentrated in vacuo. (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid was obtained as a colorless gum (266 mg, 111%) which was contaminated with ca. 10% of the methyl ester. The material was used as is without further purification.

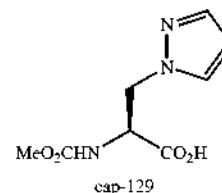
[0351] ¹HNMR (400 MHz, DMSO-d₆) δ 12.78 (s, br, 1H), 7.59 (s, 1H), 7.50 (d, J=8.0 Hz, 1H), 4.19-4.24 (m, 1H), 3.49 (s, 3H), 3.12 (dd, J=4.8 Hz, 14.9 Hz, 1H), 2.96 (dd, J=9.9, 15.0 Hz, 1H). LCMS: Anal. Calcd. for C₇H₁₀N₄O₄: 214; found: 215 (M+H)⁺.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (Cap-129)

[0352]

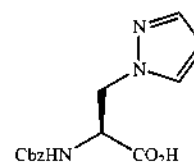


-continued



Step 1. Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (cj-31)

[0353]



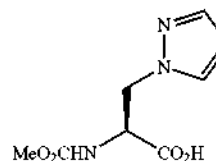
[0354] A suspension of (S)-benzyl 2-oxooxetan-3-ylcarbamate (0.67 g, 3.03 mmol), and pyrazole (0.22 g, 3.29 mmol) in CH₃CN (12 mL) was heated at 50° C. for 24 h. The mixture was cooled to rt overnight and the solid filtered to afford (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (330.1 mg). The filtrate was concentrated in vacuo and then triturated with a small amount of CH₃CN (ca. 4 mL) to afford a second crop (43.5 mg). Total yield 370.4 mg (44%).

[0355] m.p. 165.5-168° C. lit m.p. 168.5-169.5 Vederas et al. *J. Am. Chem. Soc.* 1985, 107, 7105.

[0356] ¹HNMR (400 MHz, CD₃OD) δ 7.51 (d, J=2.0, 1H), 7.48 (s, J=1.5 Hz, 1H), 7.24-7.34 (m, 5H), 6.23 (m, 1H), 5.05 (d, 12.7 Hz, 1H), 5.03 (d, J=12.7 Hz, 1H), 4.59-4.66 (m, 2H), 4.42-4.49 (m, 1H). LCMS: Anal. Calcd. for C₁₄H₁₅N₃O₄: 289; found: 290 (M+H)⁺.

Step 2. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (Cap-129)

[0357]

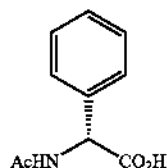


[0358] (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (0.20 g, 0.70 mmol) was hydrogenated in the presence of Pd—C (45 mg) in MeOH (5 mL) at atmospheric pressure for 2 h. The product appeared to be insoluble in MeOH, therefore the rxn mixture was diluted with 5 mL H₂O and a few drops of 6N HCl. The homogeneous solution was filtered through diatomaceous earth (Celite®), and the

MeOH removed in vacuo. The remaining solution was frozen and lyophilized to give a yellow foam (188.9 mg). This material was suspended in THF—H₂O (1:1, mL) and then cooled to 0° C. To the cold mixture was added NaHCO₃ (146.0 mg, 1.74 mmol) carefully (evolution of CO₂). After gas evolution had ceased (ca. 15 min) ClCO₂Me (0.06 mL, 0.78 mmol) was added dropwise. The mixture was allowed to stir for 2 h and was acidified to pH~2 with 6N HCl and poured into EtOAc. The layers were separated and the aqueous phase extract with EtOAc (x5). The combined organic layers were washed (brine), dried (Na₂SO₄), filtered, and concentrated to give the title compound as a colorless solid (117.8 mg, 79%).

[0359] ¹HNMR (400 MHz, DMSO-d₆) δ 13.04 (s, 1H), 7.63 (d, J=2.6 Hz, 1H), 7.48 (d, J=8.1 Hz, 1H), 7.44 (d, J=1.5 Hz, 1H), 6.19 (app t, J=2.0 Hz, 1H), 4.47 (dd, J=3.0, 12.9 Hz, 1H), 4.29-4.41 (m, 2H), 3.48 (s, 3H). LCMS: Anal. Calcd. for C₈H₁₁N₃O₄: 213; found: 214 (M+H)⁺.

cap-130



Cap-130. N-Acetyl-(R)-Phenylglycine

[0360] Cap-130 was prepared by acylation of commercially available (R)-phenylglycine analogous to the procedure given in: Calmes, M.; Dannis, J.; Jacquier, R.; Verducci, J. *Tetrahedron*, 1987, 43(10), 2285.

EXAMPLES

[0361] The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

[0362] Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker 300, 400, or 500 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO₂) according to Still's flash chromatography technique (*J. Org. Chem.* 1978, 43, 2923).

[0363] Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Condition 1

Column=Phenomenex-Luna 3.0x50 mm S10

Start % B=0

Final % B=100

[0364] Gradient time=2 min

Stop time=3 min

Flow Rate=4 mL/min

Wavelength=220 nm

[0365] Solvent A=0.1% TFA in 10% methanol/90% H₂O

Solvent B=0.1% TFA in 90% methanol/10% H₂O

Condition 2

Column=Phenomenex-Luna 4.6x50 mm S10

Start % B=0

Final % B=100

[0366] Gradient time=2 min

Stop time=3 min

Flow Rate=5 mL/min

Wavelength=220 nm

[0367] Solvent A=0.1% TFA in 10% methanol/90% H₂O

Solvent B=0.1% TFA in 90% methanol/10% H₂O

Condition 3

Column=HPLC XTERRA C18 3.0x50 mm S7

Start % B=0

Final % B=100

[0368] Gradient time=3 min

Stop time=4 min

Flow Rate=4 mL/min

Wavelength=220 nm

[0369] Solvent A=0.1% TFA in 10% methanol/90% H₂O
Solvent B=0.1% TFA in 90% methanol/10% H₂O

[0370] Method A: LCMS—Xterra MS C-18 3.0x50 mm, 0 to 100% B over 30.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate.

[0371] Method B: HPLC—X-Terra C-18 4.6x50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA

[0372] Method C: HPLC—YMC C-18 4.6x50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.2% H₃PO₄, B=90% methanol 10% water 0.2% H₃PO₄.

[0373] Method D: HPLC—Phenomenex C-18 4.6x150 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.2% H₃PO₄, B=90% methanol 10% water 0.2% H₃PO₄.

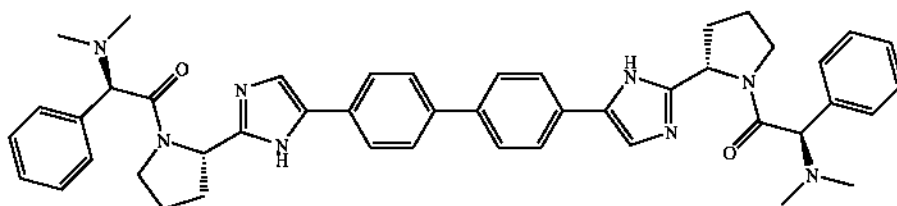
[0374] Method E: LCMS—Gemini C-18 4.6x50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate.

[0375] Method F: LCMS—Luna C-18 3.0x50 mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate.

Example 1

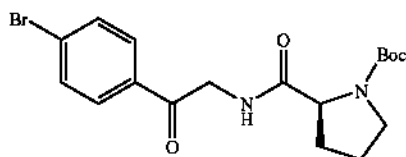
(1R,1'R)-2,2'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

[0376]



Example 1, Step a

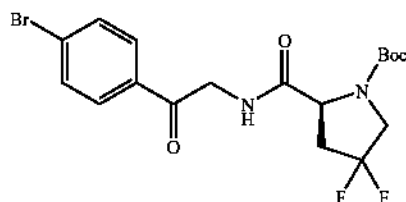
[0377]



1a

[0378] N,N-Diisopropylethylamine (18 mL, 103.3 mmol) was added dropwise, over 15 minutes, to a heterogeneous mixture of N-Boc-L-proline (7.139 g, 33.17 mmol), HATU (13.324 g, 35.04 mmol), the HCl salt of 2-amino-1-(4-bromophenyl)ethanone (8.127 g, 32.44 mmol), and DMF (105 mL), and stirred at ambient condition for 55 minutes. Most of the volatile component was removed in vacuo, and the resulting residue was partitioned between ethyl acetate (300 mL) and water (200 mL). The organic layer was washed with water (200 mL) and brine, dried (MgSO_4), filtered, and concentrated in vacuo. A silica gel mesh was prepared from the residue and submitted to flash chromatography (silica gel; 50-60% ethyl acetate/hexanes) to provide ketoamide 1a as a white solid (12.8 g). ^1H NMR ($\text{DMSO}-d_6$, δ =2.5 ppm, 400 MHz): δ 8.25-8.14 (m, 1H), 7.92 (br d, J =8.0, 2H), 7.75 (br d, J =8.6, 2H), 4.61 (dd, J =18.3, 5.7, 1H), 4.53 (dd, J =18.1, 5.6, 1H), 4.22-4.12 (m, 1H), 3.43-3.35 (m, 1H), 3.30-3.23 (m, 1H), 2.18-2.20 (m, 1H), 1.90-1.70 (m, 3H), 1.40/1.34 (two app br s, 9H). LC (Cond. 1): RT=1.70 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{Na}]^+$ $\text{C}_{18}\text{H}_{23}\text{BrN}_2\text{NaO}_4$: 433.07; found 433.09.

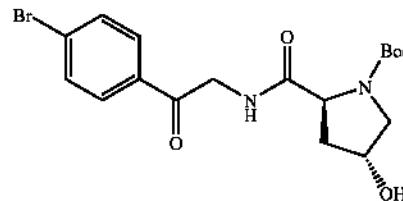
[0379] Analogous compounds such as intermediate 1-1a to 1-5a can be prepared by incorporating the appropriately substituted amino acid and aryl bromide isomer.



1-1a

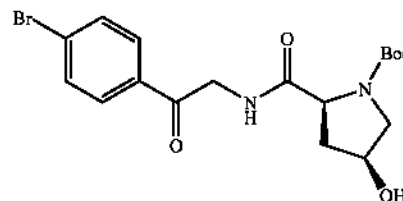
[0380] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 1.35/1.40 (two br s, 9H), 2.27-2.42 (m, 1H), 2.73-2.95 (m, 1H), 3.62-

3.89 (m, 2H), 4.36-4.50 (m, 1H), 4.51-4.60 (m, 1H), 4.62-4.73 (m, 1H), 7.75 (d, J =8.24 Hz, 2H), 7.92 (d, J =7.63 Hz, 2H), 8.31-8.49 (m, 1H). HPLC XTERRA C-18 4.6x30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H_3PO_4 , B=10% water, 90% methanol, 0.2% H_3PO_4 , RT=1.59 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{BrF}_2\text{N}_2\text{O}_4$: 446.06; found: 445.43 (M-H) $^-$.



1-2a

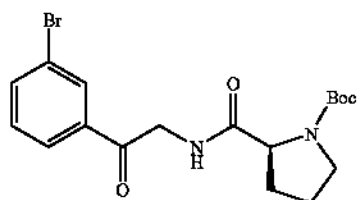
[0381] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm (8.25 1H, s), 7.91 (2H, d, J =8.24 Hz), 7.75 (2H, d, J =8.24 Hz), 4.98 (1H, s), 4.59-4.63 (1H, m), 4.46-4.52 (1H, m), 4.23 (1H, m), 3.37 (1H, s), 3.23-3.28 (1H, m), 2.06 (1H, m), 1.88 (1H, s), 1.38 (3H, s), 1.33 (6H, s). LCMS—Phenomenex C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA mobile phase, RT=3.34 minutes, Anal Calcd. for $\text{C}_{18}\text{H}_{23}\text{BrN}_2\text{O}_5$ 427.30; found 428.08 (M+H) $^+$.



1-3a

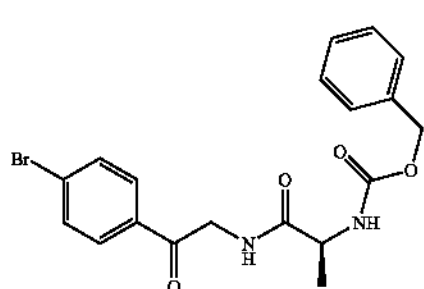
[0382] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.30 (1H, s) 7.93-7.96 (2H, m) 7.76 (2H, d, J =8.24 Hz) 5.13 (1H, s) 4.66-4.71 (1H, m) 4.52-4.55 (1H, m) 4.17 (1H, m) 3.51 (1H, s) 3.16-3.19 (1H, m) 2.36 (1H, m) 1.78 (1H, s) 1.40 (s, 3H), 1.34

(s, 6H). LCMS—Phenomenex C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, RT=3.69 minutes, Anal. Calcd. for $C_{18}H_{23}BrN_2O_5$ 427.30; found 428.16 (M+H)⁺.



1-4a

[0383] ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.29-1.47 (m, 9H), 1.67-1.90 (m, 3H), 2.00-2.20 (m, 1H), 3.23-3.30 (m, 1H), 3.34-3.44 (m, 1H), 4.16 (dd, 1H), 4.57 (q, 2H), 7.51 (t, J=7.78 Hz, 1H), 7.86 (dd, J=7.93, 1.22 Hz, 1H), 7.98 (d, J=7.63 Hz, 1H), 8.11 (s, 1H), 8.15-8.29 (m, 1H). LC/MS (M+Na)⁺=433.12/435.12.

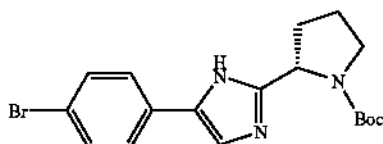


1-5a

[0384] LCMS conditions: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume. RT=1.93 min; LRMS: Anal. Calcd. for $C_{19}H_{18}BrN_2O_4$ 418.05; found: 419.07 (M+H)⁺.

Example 1, Step b

[0385]



1b

[0386] A mixture of ketoamide 1a (12.8 g, 31.12 mmol) and NH_4OAc (12.0 g, 155.7 mmol) in xylenes (155 mL) was heated in a sealed tube at 140° C. for 2 hours. The volatile component was removed in vacuo, and the residue was partitioned carefully between ethyl acetate and water, whereby enough saturated $NaHCO_3$ solution was added so as to make the pH of the aqueous phase slightly basic after the shaking of the biphasic system. The layers were separated, and the aqueous

layer was extracted with an additional ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting material was recrystallized from ethyl acetate/hexanes to provide two crops of imidazole 1b as a light-yellow dense solid, weighing 5.85 g. The mother liquor was concentrated in vacuo and submitted to a flash chromatography (silica gel; 30% ethyl acetate/hexanes) to provide an additional 2.23 g of imidazole 1b. ¹H NMR (DMSO-*d*₆, δ=2.5 ppm, 400 MHz): δ 12.17/11.92/11.86 (m, 1H), 7.72-7.46/7.28 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.30-1.75 (m, 4H), 1.40/1.15 (app br s, 9H). LC (Cond. 1): RT=1.71 min; >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ $C_{18}H_{23}BrN_3O_2$: 392.10; found 391.96; HRMS: Anal. Calcd. for [M+H]⁺ $C_{18}H_{23}BrN_3O_2$: 392.0974; found 392.0959

[0387] The optical purity of the two samples of 1b were assessed using the chiral HPLC conditions noted below (ee>99% for the combined crops; ee=96.7% for the sample from flash chromatography):

Column: Chiralpak AD, 10 μm, 4.6×50 mm

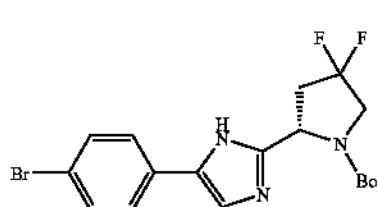
[0388] Solvent: 2% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 254 nm

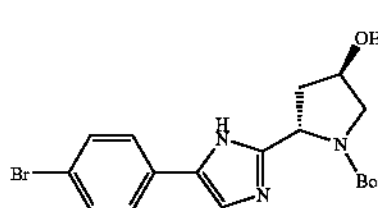
Relative retention time: 2.83 minutes (R), 5.34 minutes (S)

[0389] Analogous compounds such as intermediates 1-1b to 1-4b can be prepared by incorporating the appropriate ketoamide.



1-1b

[0390] ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.17/1.40 (two br s, 9H), 2.50-2.74 (m, J=25.64 Hz, 1H), 2.84-3.07 (m, 1H), 3.88 (d, J=10.07 Hz, 2H), 5.03 (s, 1H), 7.50 (d, J=8.55 Hz, 2H), 7.60 (s, 1H), 7.70 (d, J=8.55 Hz, 2H), 12.10 (s, 1H). HPLC XTERRA C-18 4.6×30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H_3PO_4 , B=10% water, 90% methanol, 0.2% H_3PO_4 , RT=1.59 minutes, 99% homogeneity index; LCMS: Anal. Calcd. for $C_{18}H_{20}BrF_2N_3O_2$: 428.27; found: 428.02 (M)⁺.



1-2b

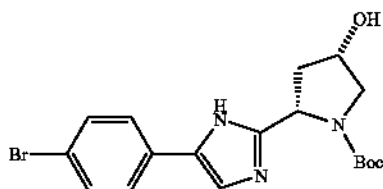
[0391] ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.89-11.99 (1H, m), 7.68 (2H, d, J=8.54 Hz), 7.52-7.59 (1H, m), 7.48 (2H, d, J=8.54 Hz), 4.80 (1H, m), 4.33 (1H, s), 3.51-3.60 (1H, m), 3.34 (1H, d, J=10.99 Hz), 2.14 (1H, s), 1.97-2.05 (1H, m),

US 2009/0068140 A1

Mar. 12, 2009

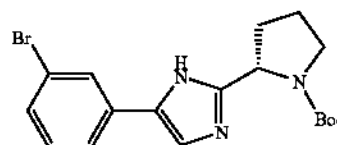
67

1.37 (3H, s), 1.10 (6H, s); LCMS—Phenomenex C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, (RT=3.23 min) Anal Calcd. for $C_{18}H_{22}BrN_3O_3$ 408.30; found 409.12 (M+H)⁺.



1-3b

[0392] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 12.06-12.24 (1H, m), 7.58-7.69 (5H, m), 4.84-4.95 (1H, m), 4.34 (1H, s), 3.61 (1H, s), 3.34-3.40 (1H, m), 2.52 (1H, s), 1.92-2.20 (1H, m), 1.43 (3H, s), 1.22 (6H, s); LCMS—Phenomenex C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, (RT=3.41 min) Anal Calcd. for $C_{18}H_{22}BrN_3O_3$ 408.30; found 409.15 (M+H)⁺.



1-4b

[0393] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.98-1.51 (m, 9H), 1.82-2.12 (m, 3H), 2.31-2.48 (m, 1H), 3.30-3.51 (m, 1H), 3.52-3.66 (m, 1H), 4.88-5.16 (m, 1H), 7.47 (t, J=7.93 Hz, 1H), 7.61 (d, J=7.93 Hz, 1H), 7.81 (d, J=7.93 Hz, 1H), 8.04 (s, 1H), 8.12 (d, J=28.38 Hz, 1H), 14.65 (s, 1H). LC/MS (M+H)⁺=391.96/393.96.

[0394] Additional imidazole analogs made following procedures similar to those described above.

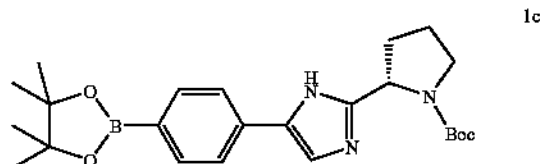
[0395] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

[0396] Condition 2: Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

Example	Structure	Data
1-5b		RT = 1.70 minutes (condition 2, 98%); LRMS: Anal. Calcd. for $C_{19}H_{18}BrN_3O_2$ 399.05; found: 400.08(M + H) ⁺ .
1-6b		RT = 1.64 minutes (condition 2, 98%); LRMS: Anal. Calcd. for $C_{17}H_{22}N_3O_2$ 379.09; found: 380.06(M + H) ⁺ .
1-7b		RT = 2.28 minutes (95%); LRMS: Anal. Calcd. for $C_{20}H_{21}BrN_3O_2$ 414.08; found: 414.08 (M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{20}H_{21}BrN_3O_2$ 414.0817; found: 414.0798(M + H) ⁺ .

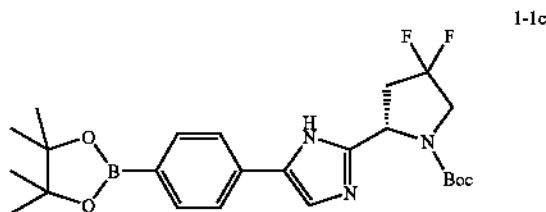
Example 1, Step c

[0397]



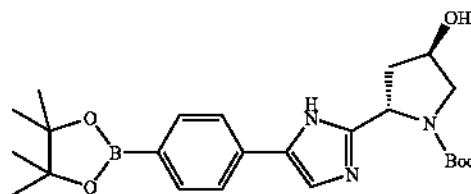
[0398] $\text{Pd}(\text{Ph}_3\text{P})_4$ (469 mg, 0.406 mmol) was added to a pressure tube containing a mixture of bromide 1b (4.008 g, 10.22 mmol), bis(pinacolato)diboron (5.422 g, 21.35 mmol), potassium acetate (2.573 g, 26.21 mmol) and 1,4-dioxane (80 mL). The reaction flask was purged with nitrogen, capped and heated with an oil bath at 80° C. for 16.5 hours. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude material was partitioned carefully between CH_2Cl_2 (150 mL) and an aqueous medium (50 mL water+10 mL saturated NaHCO_3 solution). The aqueous layer was extracted with CH_2Cl_2 , and the combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The resulting material was purified with flash chromatography (sample was loaded with eluting solvent; 20-35% ethyl acetate/ CH_2Cl_2) to provide boronate 1c, contaminated with pinacol, as an off-white dense solid; the relative mole ratio of 1c to pinacol was about 10:1 (^1H NMR). The sample weighed 3.925 g after ~2.5 days exposure to high vacuum. ^1H NMR ($\text{DMSO}-d_6$, δ =2.5 ppm, 400 MHz): 12.22/11.94/11.87 (m, 1H), 7.79-7.50/7.34-7.27 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app brs, 1H), 3.36 (m, 1H), 2.27-1.77 (m, 4H), 1.45-1.10 (m, 21H). LC (Cond. 1): RT=1.64 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{24}\text{H}_{35}\text{BN}_3\text{O}_4$: 440.27; found 440.23.

[0399] Analogous compounds such as intermediates 1-1c to 1-4c can be prepared by incorporating the appropriate aryl bromide.



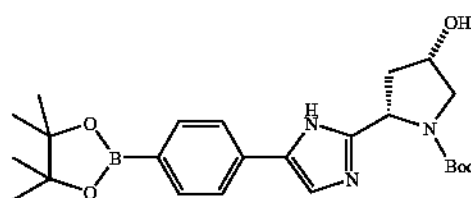
[0400] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 1.16 (s, 8H), 1.29 (s, 13H), 2.51-2.72 (m, 1H), 2.84-3.03 (m, 1H), 3.79-4.00 (m, 2H), 4.88-5.21 (m, 1H), 7.62 (d, J =7.93 Hz, 2H), 7.67 (s, 1H), 7.76 (d, J =7.93 Hz, 2H), 12.11/12.40 (two br s, 1H). HPLC GEMINI C-18 4.6x50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=95% water, 5% acetonitrile, 0.1% NH_4OAc , B=5% water, 95% acetonitrile, 0.1% NH_4OAc , RT=1.62 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $\text{C}_{34}\text{H}_{32}\text{BF}_2\text{N}_3\text{O}_4$: 475.34; found: 474.78 ($\text{M}-\text{H}$) $^-$.

1-2c



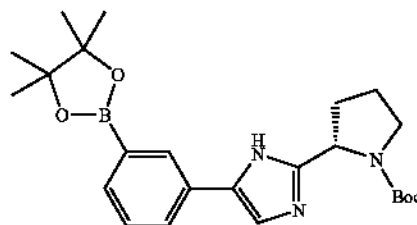
[0401] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 11.97 (1H, m), 7.62-7.75 (5H, m), 5.05 (1H d, J =3.36 Hz), 4.82 (m, 1H), 4.35 (m, 1H), 3.58 (1H, m), 2.389 (1H, s), 2.17 (1H, m), 1.38 (3H, s), 1.30 (12H, s), 1.1 (6H, s); LCMS—Phenomenex C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate, RT=3.63 minutes, Anal. Calcd. for $\text{C}_{24}\text{H}_{34}\text{BN}_3\text{O}_5$ 455.30; found 456.31 ($\text{M}+\text{H}$) $^+$.

1-3c



[0402] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 12.05-12.24 (1H, m), 7.61-7.73 (5H, m), 4.83-5.01 (1H, m), 4.33 (1H, s), 3.54-3.63 (1H, m), 3.39-3.80 (1H, m), 2.38-2.49 (1H, m), 1.98-2.01 (1H, m), 1.42 (3H, s), 1.34 (12H, s), 1.21 (6H, s); LCMS—Phenomenex C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, RT=3.64 minutes, Anal. Calcd. for $\text{C}_{24}\text{H}_{34}\text{BN}_3\text{O}_5$ 455.30; found 456.30 ($\text{M}+\text{H}$) $^+$.

1-4c



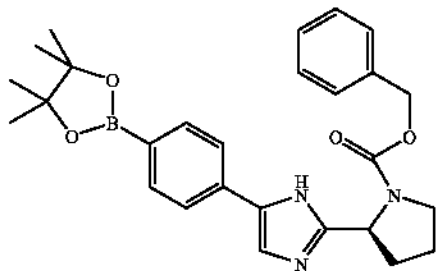
[0403] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 1.02-1.54 (m, 21H), 1.75-2.07 (m, 3H), 2.09-2.33 (m, 1H), 3.32-3.44 (m, 1H), 3.55 (s, 1H), 4.69-4.94 (m, 1H), 7.33 (t, J =7.32 Hz, 1H), 7.41-7.57 (m, 2H), 7.84 (d, J =7.32 Hz, 1H), 8.08 (s, 1H), 11.62-12.07 (m, 1H). LC/MS ($\text{M}+\text{H}$) $^+$ =440.32.

[0404] Additional boronic esters: Conditions for 1-5c through 1-10c

LCMS conditions: Condition 1: Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

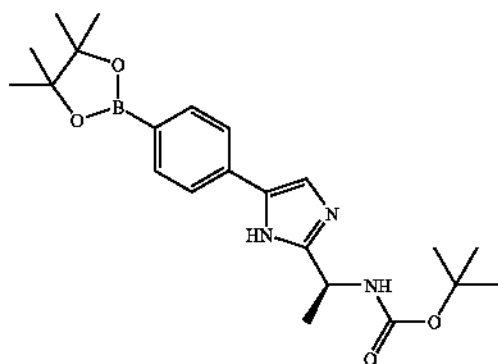
[0405] Condition 2: Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

1-5c



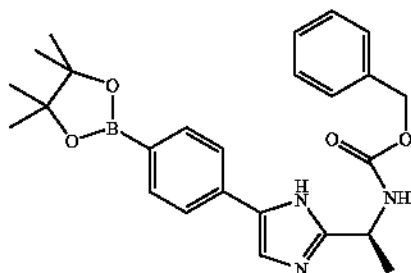
RT = 1.84 minutes
(condition 2); LCMS:
Anal. Calcd. for
 $C_{27}H_{32}BN_3O_4$ 473;
found: 474(M + H)⁺.

1-6c



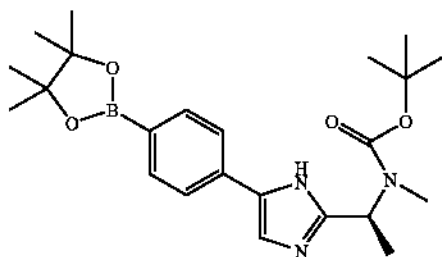
RT = 1.84 minutes
(condition 2); LCMS:
Anal. Calcd. for
 $C_{22}H_{32}BN_3O_4$ 413;
found: 414(M + H)⁺.

1-7c



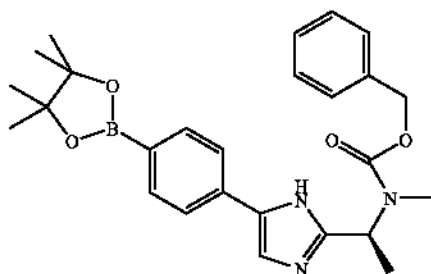
RT = 1.85 minutes
(condition 2); LRMS:
Anal. Calcd. for
 $C_{25}H_{31}BN_3O_4$ 448; found:
448(M + H)⁺.

1-8c



RT = 2.49(76%, boronic
ester) and 1.81(21.4%,
boronic acid); LCMS:
Anal. Calcd. for
 $C_{23}H_{35}N_3O_4B$ 428.27;
found: 428.27(M + H)⁺;
HRMS: Anal. Calcd.
for $C_{23}H_{35}N_3O_4B$
428.2721; found:
428.2716(M + H)⁺.

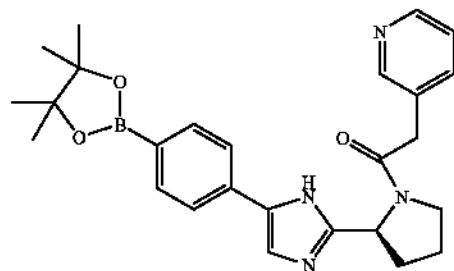
1-9c



RT = 2.54(74.2%,
boronic ester) and 1.93
(25.8%, boronic acid);
LRMS: Anal. Calcd. for
 $C_{26}H_{33}N_3O_4B$ 462.26;
found: 462.25(M + H)⁺;
HRMS: Anal. Calcd.
for $C_{26}H_{33}N_3O_4B$
462.2564; found:
462.2570(M + H)⁺.

-continued

1-10c

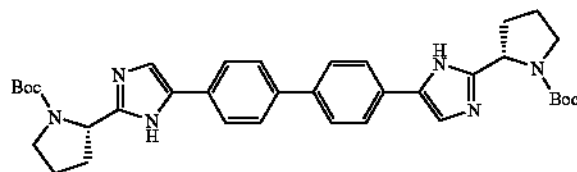


RT = 1.91(64.5%, boronic ester) and 1.02 (33.8%, boronic acid); LRMS: Anal. Calcd. for $C_{26}H_{32}N_4O_3^{10}B$ 458.26; found: 458.28(M + H)⁺; HRMS: Anal. Calcd. for $C_{26}H_{32}N_4O_3^{10}B$ 458.2604; found: 458.2617(M + H)⁺.

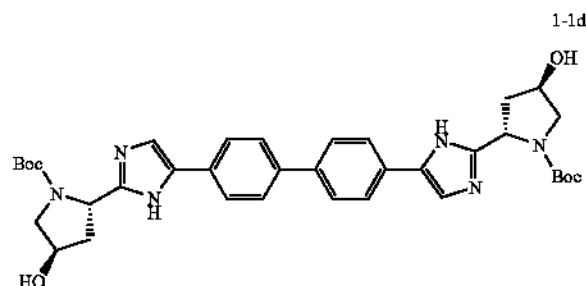
Example 1, Step d

di-tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl)di(1-pyrrolidinecarboxylate)

[0406]



1d

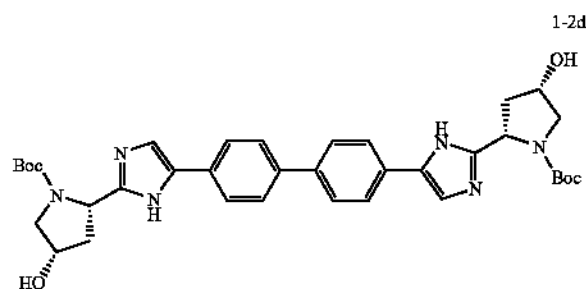


1-1d

[0409] Example 1-1d was prepared using intermediates 1-2c and 1-2b. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 11.94-12.22 (2H, m) 7.53-7.82 (10H, m) 4.82-4.92 (2H, m) 4.34-4.43 (2H, m) 3.55-3.64 (2H, m) 3.36 (2H, d, J=11.29 Hz) 2.12-2.22 (2H, m) 2.02-2.11 (2H, m) 1.40 (6H, s) 1.14 (12H, s); LCMS—Phenomenex C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, RT=3.32 min, Anal. Calcd. for 656.79; found 657.40 (M+H)⁺. Nominal/LRMS-(M+H)⁺ 657.42, (M-H)⁻ 655.28.

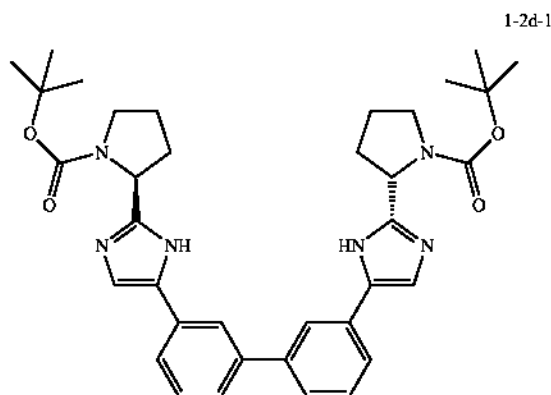
[0407] Pd(Ph₃P)₄ (59.9 mg, 0.0518 mmol) was added to a mixture of bromide 1b (576.1 mg, 1.469 mmol), boronate 1c (621.8 mg, 1.415 mmol), NaHCO₃ (400.4 mg, 4.766 mmol) in 1,2-dimethoxyethane (12 mL) and water (4 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 80° C. for 5.75 hours, and then the volatile component was removed in vacuo. The residue was partitioned between 20% methanol/CHCl₃ (60 mL) and water (30 mL), and the aqueous phase was extracted with 20% methanol/CHCl₃ (30 mL). The combined organic phase was washed with brine, dried (MgSO₄), filtered, and concentrated in vacuo. A silica gel mesh was prepared from the resulting crude material and submitted to flash chromatography (ethyl acetate) to provide dimer 1d, contaminated with Ph₃PO, as an off-white solid (563 mg). ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 12.21-12.16/11.95-11.78 (m, 2H), 7.85-7.48/7.32-7.25 (m, 10H), 4.90-4.71 (m, 2H), 3.60-3.32 (m, 4H), 2.30-1.79 (m, 8H), 1.46-1.10 (m, 18H). LC (Cond. 1b): RT=1.77 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₃₆H₄₅BN₆O₄: 625.35; found 625.48.

[0408] Additional symmetric analogs can be prepared in similar fashion.



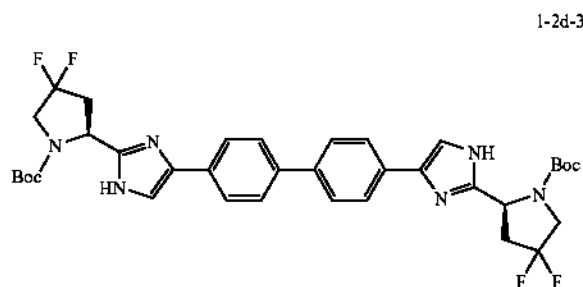
1-2d

[0410] Example 1-2d was prepared using intermediates 1-3b and 1-3c. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 12.00-12.20 (2H, m) 7.56-7.76 (10H, m) 4.90 (1H, s) 4.82 (1H, s) 4.25-4.34 (2H, m) 3.56 (2H, s) 3.34-3.47 (2H, m) 1.97-2.13 (4H, m) 1.39 (9H, m) 1.20 (9H, s); LCMS—Phenomenex C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA; RT=3.35 min, Anal. Calcd. for 656.79; found 657.30 (M+H)⁺.



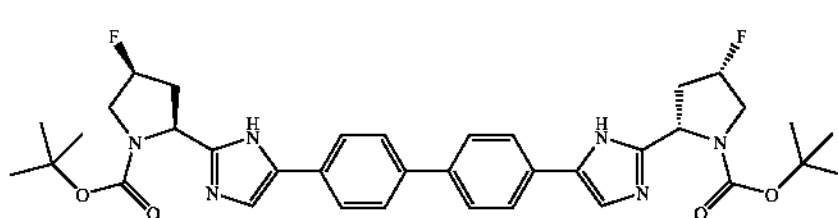
tert-butyl (2S)-2-(4-(3'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

[0411] Example 1-2d-1 was prepared using intermediates 1-4c and 1-4b. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.09-1.51 (m, 18H), 1.84-2.15 (m, 6H), 2.34-2.50 (m, 2H), 3.35-3.52 (m, 2H), 3.54-3.67 (m, 2H), 5.08 (d, J=5.49 Hz, 2H), 7.68 (t, J=7.78 Hz, 2H), 7.78-7.92 (m, 4H), 8.11-8.30 (m, 4H), 14.81 (s, 2H). LC/MS (M+H)⁺=625.48.



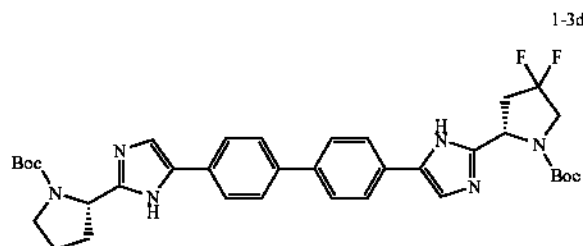
[0413] Prepared from 1-1b and 1-1c in the same manner as the preparation of 1d from 1b and 1c. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.18/1.40 (two br. s., 18H), 2.53-2.75 (m, J=25.94 Hz, 2H), 2.86-3.06 (m, 2H), 3.78-4.02 (m, 4H), 5.04 (br s, 2H), 7.17-8.24 (m, 10H), 12.07/12.37 (two br. s., 2H); HPLC XTERRA C-18 3.0x50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A=90% water, 10% methanol, 0.2% H₃PO₄, B=10% water, 90% methanol, 0.2% H₃PO₄, RT=1.31 min, 99% homogeneity index. LCMS: Anal. Calcd. for C₃₆H₄₀F₄N₆O₄: 696.73; found: 967.64 (M+H)⁺.

[0414] Dissymmetric compounds such as intermediate 1-3d and 1-4d can be prepared by the same method. For example, reaction of 1-1c with 1b in the same manner as described above for the preparation of 1d provided 1-3d.



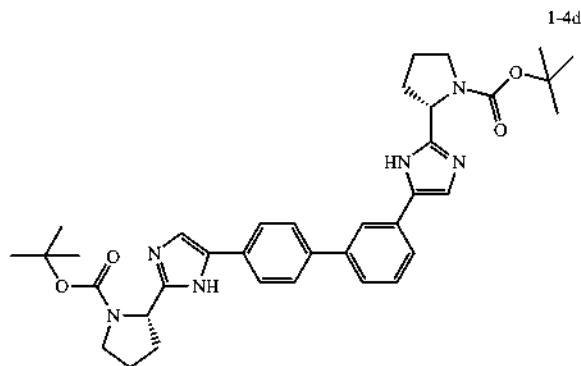
[0412] Diol 1-1d (0.15 g, 0.23 mmol) was added as a solid to a solution of bis(2-methoxyethyl)aminosulfur trifluoride (0.1 mL, 0.51 mmol) in 11.0 mL CH₂Cl₂ cooled to -78° C. The reaction was stirred at -78° C. for two hours and then warmed to room temperature and stirred for 2 hours. The reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. The layers were separated and the aqueous layer was extracted one time with CH₂Cl₂. The combined organics were washed with brine, dried (MgSO₄), filtered, and concentrated to give a yellow oil. The oil was triturated with CH₂Cl₂ and pentane to provide the desired product as a tan solid (0.092 g, 61%). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.76-11.94 (2H, m), 7.77-7.85 (4H, m), 7.66-7.72 (4H, m), 7.60-7.66 (2H, m, J=11.60 Hz), 5.39 (1H, s), 5.28 (1H, s), 5.03 (2H, s), 3.66-3.79 (4H, m), 2.61-2.70 (2H, m), 2.28-2.38 (2H, m), 1.42 (10H, s), 1.24 (8H, s). LCMS—Phenomenex C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, (t_R=3.58 min) Anal. Calcd. for C₃₆H₄₂F₂N₆O₄ 660.70; found 661.68 (M+H)⁺.

Similarly, reaction of 1-4c with 1b in the same manner as described above for the preparation of 1d provided 1-4d.



[0415] ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.40/1.18 (two br. s., 18H), 1.90-2.02 (m, 2H), 2.02-2.12 (m, 1H), 2.28-2.46 (m, 2H), 2.68-2.87 (m, 1H), 3.35-3.49 (m, 1H), 3.53-3.62 (m, 1H), 3.82-4.10 (m, 2H), 4.92-5.11 (m, 1H), 5.28 (s, 1H), 7.79-8.00 (m, 8H), 8.03-8.25 (m, 2H), 13.77-15.16 (m, 2H); HPLC XTERRA C-18 3.0x50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H₃PO₄, B=10% water, 90% methanol, 0.2% H₃PO₄,

RT=1.22 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{36}H_{42}F_2N_6O_4$: 660.75; found: 661.98 ($M+H$)⁺.



[0416] Example 1-4d was prepared from 1-4c and 1b in similar fashion to the preparation of 1d from 1b and 1c. ¹H

NMR (500 MHz, DMSO-*d*₆) δ ppm 0.99-1.60 (m, 18H) 1.75-2.11 (m, *J*=73.24 Hz, 6H) 2.12-2.32 (m, 2H) 3.32-3.41 (m, 2H) 3.56 (s, 2H) 4.63-5.02 (m, 2H) 6.98-8.28 (m, 10H) 11.67-12.33 (m, 2H); LC conditions: Phenomenex Luna 3.0×5.0 mm S10, Solvent A—0.1% TFA in 10% MeOH/90% H₂O, Solvent B—0.1% TFA in 90% MeOH/10% H₂O, 0 to 100% B over 2 min, Stop time=3 min, Flow rate=4 ml/min, Wavelength=220 nm, LC/MS ($M+H$)⁺=625.32. Retention time=1.438 min

[0417] Additional biphenyl analogs were prepared similarly.

LC conditions for Examples 1-5d through 1-7d: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

[0418] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

Example	Compound Name	Structure	Characterization Data
1-5d	di-tert-butyl(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl)bis(methylcarbamate)		RT = 1.64 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{34}H_{42}N_6O_4$ 601.35; found: 601.48($M+H$) ⁺ ; LRMS: Anal. Calcd. for $C_{34}H_{44}N_6O_4$ 600.34; found: 601.32($M+H$) ⁺ .
Prepared from 1-8c and 1-6b			
1-6d	tert-butyl (2S)-2-(5-(4'-(2-((1S)-1-(tert-butoxycarbonyl)(methylamino)ethyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		RT = 1.63 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{35}H_{45}N_6O_4$ 613.34; found: 613.56($M+H$) ⁺ ; LRMS: Anal. Calcd. for $C_{35}H_{44}N_6O_4$ 612.34; found: 613.33($M+H$) ⁺ .
Prepared from 1-8c and 1b			

-continued

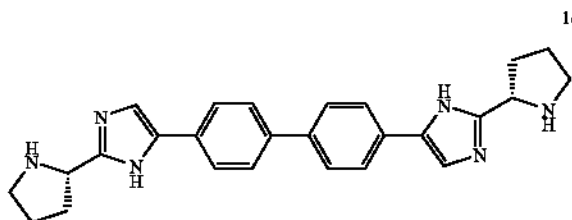
Example	Compound Name	Structure	Characterization Data
1-7d	benzyl (2 <i>S</i>)-2-(5-(4'-(2-((1 <i>S</i>)-1-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1 <i>H</i> -imidazol-5-yl)-4-biphenyl)-1 <i>H</i> -imidazol-2-yl)-1-pyrrolidinecarboxylate		RT = 1.65 minutes (>95%); Condition 2; LCMS: Anal. Calcd. C ₃₈ H ₄₃ N ₆ O ₄ 647.33; found: 647.44(M + H) ⁺ ; LRMS: Anal. Calcd. for C ₃₈ H ₄₂ N ₆ O ₄ 646.33; found: 647.34(M + H) ⁺ .

Prepared from 1-6b and 1-5c

Example 1, Step e

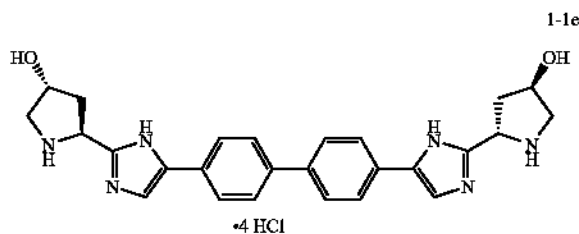
5,5'-(4,4'-biphenyldiyl)bis(2-((2*S*)-2-pyrrolidinyl)-1*H*-imidazole)

[0419]

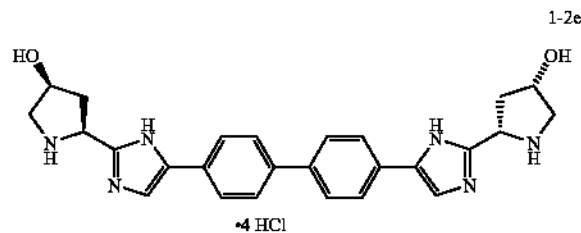


[0420] A mixture of carbamate 1d (560 mg) and 25% TFA/CH₂Cl₂ (9.0 mL) was stirred at ambient condition for 3.2 hours. The volatile component was removed in vacuo, and the resulting material was free based using an MCX column (methanol wash; 2.0 M NH₃/methanol elution) to provide pyrrolidine 1e as a dull yellow solid (340 mg). ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.80 (d, J=8.1, 4H), 7.66 (d, J=8.3, 4H), 7.46 (br s, 2H), 4.16 (app t, J=7.2, 2H), 2.99-2.69 (m, 6H), 2.09-2.00 (m, 2H), 1.94-1.66 (m, 6H). LC (Cond. 1): RT=1.27 min; >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₂₆H₂₉N₆: 425.25; found 425.25; HRMS: Anal. Calcd. for [M+H]⁺ C₂₆H₂₉N₆: 425.2454; found 425.2448

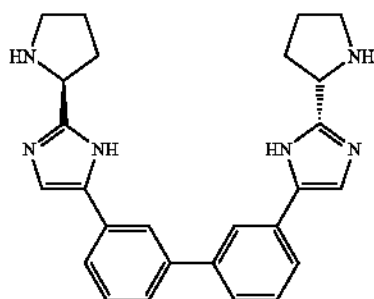
[0421] Additional analogs such as 1-1e to 1-4e can be prepared in a similar fashion.



[0422] To a solution of 1-1d (3*R*,3'*R*,5*S*,5'*S*)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1*H*-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) in 3 mL dioxane was added 0.8 mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 1-1e (3*R*,3'*R*,5*S*,5'*S*)-5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1*H*-imidazole-5,2-diyl))dipyrrolidine-3-ol-tetrahydrochloride (0.55 g, 100% yield). Used without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 10.33 (s, 2H), 9.85 (s, 2H), 8.09 (s, 2H), 8.01 (d, J=8.24 Hz, 4H), 7.88 (d, J=8.24 Hz, 4H), 5.14 (m, 2H), 4.62 (m, 2H), 3.61 (m, 2H), 3.23 (d, J=11.29 Hz, 2H), 2.64 (m, 2H), 2.44 (dd, J=13.43, 6.71 Hz, 2H); LCMS—Waters-Sunfire C-18 4.6x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, RT=1.35 minutes Anal. Calcd. for 456.30; found 457.25 (M+H)⁺; Nominal/LRMS-(M+H)⁺ 457.35.



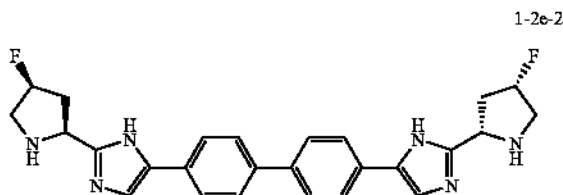
[0423] Example 1-2e was prepared in similar fashion to the method described for the preparation of 1-1e. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 10.32 (1H, s) 8.01 (2H, s) 7.97 (4H, d, J=8.24 Hz) 7.86 (4H, d, J=8.24 Hz) 5.01-5.10 (2H, m) 4.52-4.60 (2H, m) 3.36-3.45 (2H, m) 3.25 (2H, s) 2.60-2.68 (2H, m) 2.40-2.48 (2H, m); LCMS—Phenomenex C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, RT=2.10 min., Anal. Calcd. for 456.30; found 457.22 (M+H)⁺



1-2e-1

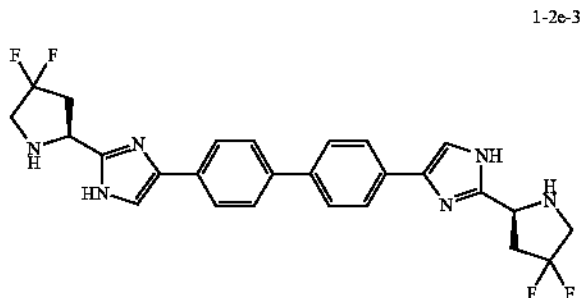
2-((2S)-2-pyrrolidinyl)-4-(3'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenyl)-1H-imidazole

[0424] Example 1-2e-1 was prepared from 1-2d-1 in similar fashion described for the preparation of 1-1e. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.74-2.44 (m, 12H), 4.83 (s, 2H), 7.37-7.72 (m, 4H), 7.74-8.03 (m, 4H), 8.10 (s, 2H), 9.14 (s, 2H), 9.81 (s, 2H). LC/MS (M+H)⁺=425.30.



1-2e-2

[0425] To a solution of 1-2d-2 (0.084 g, 0.13 mmol) in 1 mL dioxane was added 0.5 mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 1-2e-2 (0.077 g, 100% yield). The compound was used without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.00 (2H, s), 7.97 (4H, d, J=8.55 Hz), 7.85 (4H, d, J=8.24 Hz), 5.63 (1H, s), 5.52 (1H, s), 5.09-5.17 (2H, m), 3.67-3.74 (2H, m), 3.63-3.67 (2H, m), 3.07-3.14 (1H, m), 2.89-2.96 (1H, m), 2.81-2.87 (2H, m); LCMS—Phenomenex C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, (t_R=222 min) Anal Calcd. for C₂₆H₂₆F₂N₆ 460.53; found 461.37 (M+H)⁺.

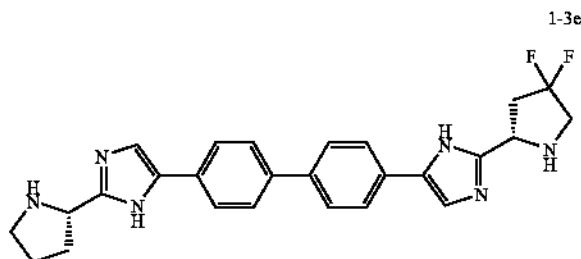


1-2e-3

[0426] Prepared from 1-2d-3 in the same manner as the preparation of 1-1e from 1-1d. ¹H NMR (500 MHz, DMSO-

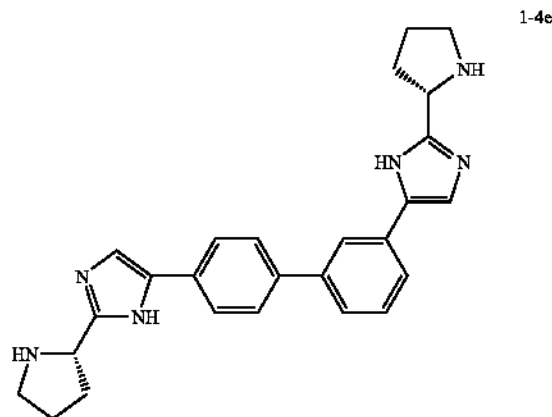
d₆) δ ppm 2.97-3.13 (m, 4H), 3.64-3.91 (m, 4H), 5.16 (d, J=6.41 Hz, 2H), 7.84 (d, J=7.93 Hz, 4H), 7.96 (d, J=7.93 Hz, 4H), 8.00 (s, 2H); HPLC XTERRA C-18 3.0x50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A=90% water, 10% methanol, 0.2% H₃PO₄, B=10% water, 90% methanol, 0.2% H₃PO₄, RT=1.66 min, 92% homogeneity index. LCMS: Anal. Calcd. for C₂₆H₂₄F₄N₆: 496.50; found: 495.53 (M-H)⁻.

[0427] Analogous dissymmetric compounds such as intermediates 1-3e and 1-4e can be prepared by the same method.



1-3e

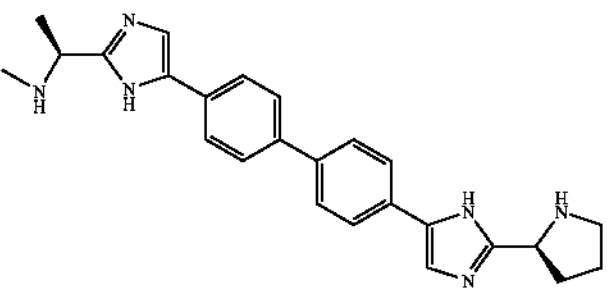
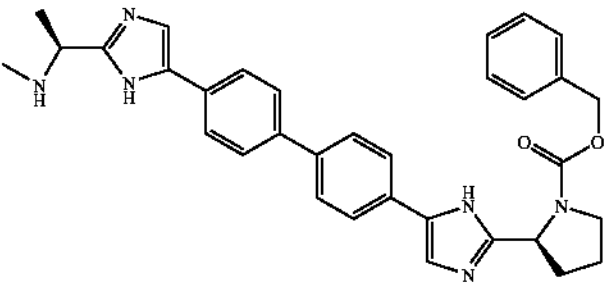
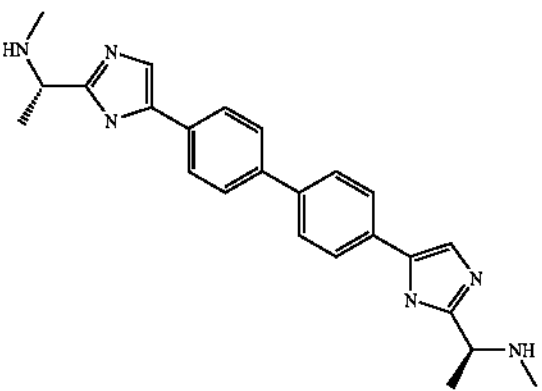
[0428] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.87-2.09 (m, 1H), 2.13-2.26 (m, 1H), 2.37-2.47 (m, 2H), 2.92-3.12 (m, 2H), 3.37 (s, 1H), 3.40-3.49 (m, 1H), 3.67-3.91 (m, 2H), 4.96-5.05 (m, 1H), 5.14 (t, J=8.70 Hz, 1H), 7.86 (t, J=9.00 Hz, 4H), 7.93-8.03 (m, 5H), 8.10 (s, 1H), 10.26/9.75 (two br s., 2H); HPLC XTERRA C-18 3.0x50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H₃PO₄, B=10% water, 90% methanol, 0.2% H₃PO₄, RT=0.8622 minutes, 99% homogeneity index; LCMS: Anal. Calcd. for C₂₆H₂₆F₂N₆: 460.52; found: 461.45 (M+H)⁺.



1-4e

[0429] Example 1-4e was prepared from 1-4d in similar fashion to that described for the preparation of 1-1e from 1-1d. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.90-2.13 (m, 2H), 2.12-2.31 (m, 2H), 2.36-2.60 (m, 4H), 3.29-3.55 (m, 4H), 5.00 (s, 2H), 7.35-8.50 (m, 10H), 9.76 (s, 2H), 10.12-10.45 (m, 2H). LC conditions: Phenomenex Luna 3.0x5.0 mm S10, Solvent A—0.1% TFA in 10% MeOH/90% H₂O, Solvent B—0.1% TFA in 90% MeOH/10% H₂O, 0 to 100% B over 2 min, Stop time=3 min, Flow rate=4 ml/min, Wavelength=220 nm, LC/MS (M+H)⁺=425.28. Retention time=0.942 min

[0430] Additional analogs were prepared similarly:

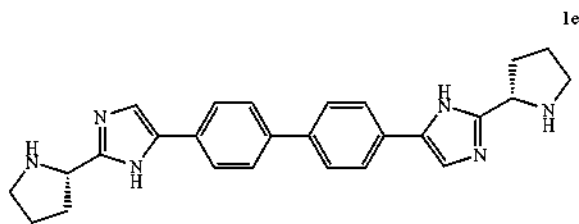
Example	Compound Name	Structure	Data
1-5e			RT = 1.37 min; LCMS: Anal. Calcd. for $C_{25}H_{28}N_6$ 412; found: 413 (M + H) ⁺ .
		Prepared from 1-6d	
1-6e			RT = 1.43 min; LCMS: Anal. Calcd. for $C_{33}H_{35}N_6O_2$ 547; found: 547 (M + H) ⁺ .
		Prepared from 1-7d	
1-7e			RT = 1.12 min; LRMS: Anal. Calcd. for $C_{24}H_{28}N_6$ 400.24; found: 401.22 (M + H) ⁺ .
		Prepared from 1-5d	

LC Conditions for 1-5e through 1-7e; Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

Alternative Synthesis of Example 1, Step e

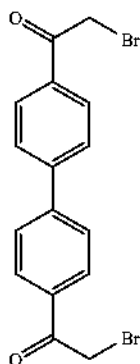
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)

[0431]



Example A-1e-1

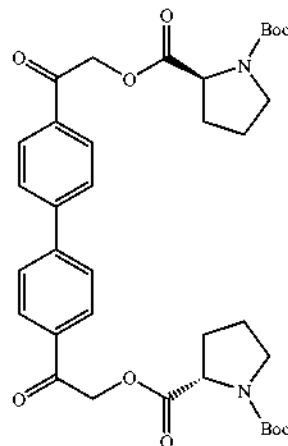
[0432]



[0433] A 1 L, 3-neck round bottom flask, fitted with a nitrogen line, overhead stirrer and thermocouple was charged with 20 g (83.9 mmol, 1 equiv) 1,1'-(biphenyl-4,4'-diyl)diethanone, 200 mL CH_2Cl_2 and 8.7 mL (27.1 g, 169.3 mmol, 2.02 equiv) bromine. The mixture was allowed to stir under nitrogen for about 20 h under ambient conditions. The resulting slurry was charged with 200 mL CH_2Cl_2 and concentrated down to about 150 mL via vacuum distillation. The slurry was then solvent exchanged into THF to a target volume of 200 mL via vacuum distillation. The slurry was cooled to 20-25° C. over 1 h and allowed to stir at 20-25° C. for an additional hour. The off-white crystalline solids were filtered and washed with 150 mL CH_2Cl_2 . The product was dried under vacuum at 60° C. to provide 27.4 g (69.2 mmol, 82%) of the desired product: ^1H NMR (400 MHz, CDCl_3) δ 7.95-7.85 (m, 4H), 7.60-7.50 (m, 4H), 4.26 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.0, 145.1, 133.8, 129.9, 127.9, 30.8; IR (KBr, cm^{-1}) 3007, 2950, 1691, 1599, 1199; Anal calcd for $\text{C}_{16}\text{H}_{12}\text{Br}_2\text{O}_2$: C, 48.52; H, 3.05; Br, 40.34. Found: C, 48.53; H, 3.03; Br, 40.53. HRMS calcd for $\text{C}_{16}\text{H}_{12}\text{Br}_2\text{O}_2$ ($\text{M}+\text{H}^+$, DCI^+): 394.9282. Found: 394.9292. mp 224-226° C.

Example A-1e-2

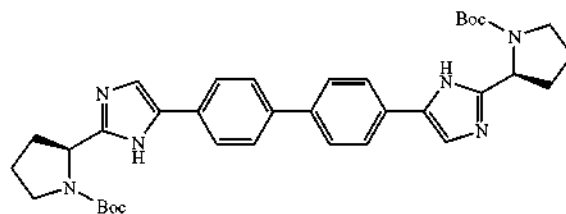
[0434]



[0435] A 500 mL jacketed flask, fitted with a nitrogen line, thermocouple and overhead stirrer, was charged with 20 g (50.5 mmol, 1 equiv) of Example A-1e-1, 22.8 g (105.9 moles, 2.10 equiv) 1-(tert-butoxycarbonyl)-L-proline, and 200 mL acetonitrile. The slurry was cooled to 20° C. followed by the addition of 18.2 mL (13.5 g, 104.4 mmol, 2.07 equiv) DIPEA. The slurry was warmed to 25° C. and allowed to stir for 3 h. The resulting clear, organic solution was washed with 3x100 mL 13 wt % aqueous NaCl. The rich acetonitrile solution was solvent exchanged into toluene (target volume=215 mL) by vacuum distillation until there was less than 0.5 vol % acetonitrile.

Example A-1e-3

[0436]



[0437] The above toluene solution of Example A-1e-2 was charged with 78 g (1.011 moles, 20 equiv) ammonium acetate and heated to 95-100° C. The mixture was allowed to stir at 95-100° C. for 15 h. After reaction completion, the mixture was cooled to 70-80° C. and charged with 7 mL acetic acid, 40 mL n-butanol, and 80 mL of 5 vol % aqueous acetic acid. The resulting biphasic solution was split while maintaining a temperature >50° C. The rich organic phase was charged with 80 mL of 5 vol % aqueous acetic acid, 30 mL acetic acid and 20 mL n-butanol while maintaining a temperature >50° C. The resulting biphasic solution was split while maintaining a temperature >50° C. and the rich organic phase was washed with an additional 80 mL of 5 vol % aqueous acetic acid. The rich organic phase was then solvent exchanged into toluene to a target volume of 215 mL by vacuum distillation. While maintaining a temperature >60° C., 64 mL MeOH was charged. The resulting slurry was heated to 70-75° C. and aged for 1 h.

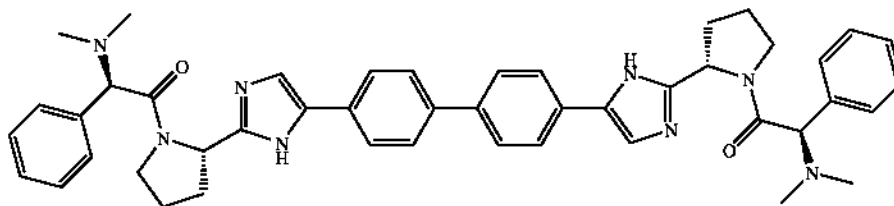
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Mar. 12, 2009

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The slurry was cooled to 20-25° C. over 1 h and aged at that temperature for an additional hour. The slurry was filtered and the cake was washed with 200 mL 10:3 toluene:MeOH. The product was dried under vacuum at 70° C., resulting in 19.8 g (31.7 mmol, 63%) of the desired product: ¹H NMR (400 MHz, DMSO-d₆) δ 13.00-11.00 (s, 2H), 7.90-7.75 (m, 4H), 7.75-7.60 (m, 4H), 7.60-7.30 (s, 2H), 4.92-4.72 (m, 2H), 3.65-3.49 (m, 2H), 3.49-3.28 (m, 2H), 2.39-2.1 (m, 2H), 2.10-1.87 (m, 6H), 1.60-1.33 (s, 8H), 1.33-1.07 (s, 10H); ¹³C NMR (100 MHz, DMSO-d₆) δ 154.1, 153.8, 137.5, 126.6, 125.0, 78.9, 78.5, 55.6, 55.0, 47.0, 46.7, 33.7, 32.2, 28.5, 28.2,

25 (br, 2H), 10.1-9.75 (br, 2H), 8.19 (s, 2H), 7.05 (d, J=8.4, 4H), 7.92 (d, J=8.5, 4H), 5.06 (m, 2H), 3.5-3.35 (m, 4H), 2.6-2.3 (m, 4H), 2.25-2.15 (m, 2H), 2.18-1.96 (m, 2H); ¹³C NMR (100 MHz, DMSO-d₆) δ 156.6, 142.5, 139.3, 128.1, 127.5, 126.1, 116.9, 53.2, 45.8, 29.8, 24.3; IR (KBr, cm⁻¹) 3429, 2627, 1636, 1567, 1493, 1428, 1028. Anal calcd for C₂₆H₃₂N₆Cl₄: C, 54.75; H, 5.65; Cl, 24.86; Adjusted for 1.9% water: C, 53.71; H, 5.76; N, 14.46; Cl, 24.39. Found: C, 53.74; H, 5.72; N, 14.50; Cl, 24.49; KF=1.9. mp 240° C. (decomposed)



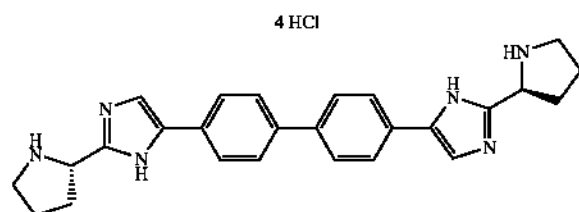
24.2, 23.5; IR (KBr, cm⁻¹) 2975, 2876, 1663, 1407, 1156, 1125; HRMS calcd for C₃₆H₄₅N₆O₄ (M+H; ESI⁺): 625.3502. Found: 625.3502. mp 190-195° C. (decomposed).

Example A-1e-4

Example 1

(1R,1'R)-2,2'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

[0438]



[0439] To a 250 ml reactor equipped with a nitrogen line and overhead stirrer, 25.0 g of Example A-1e-3 (40.01 mmol, 1 equiv) was charged followed by 250 mL methanol and 32.85 mL (400.1 mmol, 10 equiv) 6M aqueous hydrogen chloride. The temperature was increased to 50° C. and agitated at 50° C. for 5 h. The resulting slurry was cooled to 20-25° C. and held with agitation for ca. 18 h. Filtration of the slurry afforded a solid which was washed successively with 100 ml 90% methanol/water (V/V) and 2x100 ml of methanol. The wet cake was dried in a vacuum oven at 50° C. overnight to give 18.12 g (31.8 mmol, 79.4%) of the desired product.

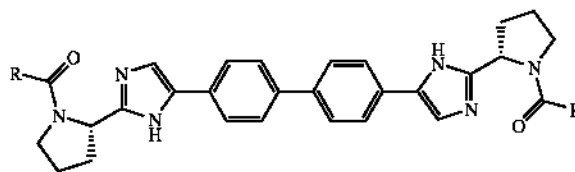
Recrystallization of Example A-1e-4

[0440] To a 250 ml reactor equipped with a nitrogen line and an overhead stirrer, 17.8 g of crude Example A-1e-4 was charged followed by 72 mL methanol. The resulting slurry was agitated at 50° C. for 4 h, cooled to 20-25° C. and held with agitation at 20-25° C. for 1 h. Filtration of the slurry afforded a crystalline solid which was washed with 60 ml methanol. The resulting wet cake was dried in a vacuum oven at 50° C. for 4 days to yield 14.7 g (25.7 mmol, 82.6%) of the desired product: ¹H NMR (400 MHz, DMSO-d₆) δ 10.5-10.

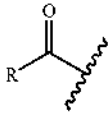
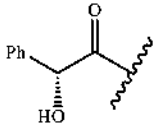
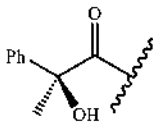
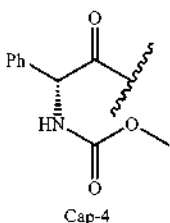
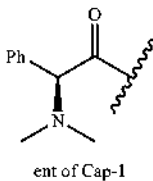
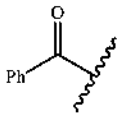
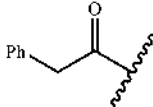
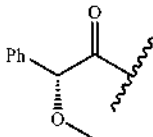
[0441] HATU (44.6 mg, 0.117 mmol) was added to a mixture of pyrrolidine 1e (22.9 mg, 0.054 mmol), diisopropylethylamine (45 μL, 0.259 mmol) and Cap-1 (28.1 mg, 0.13 mmol) in DMF (1.5 mL), and the resulting mixture was stirred at ambient for 90 minutes. The volatile component was removed in vacuo, and the residue was purified first by MCX (methanol wash; 2.0 M NH₃/methanol elution) and then by a reverse phase HPLC system (H₂O/methanol/TFA) to provide the TFA salt of Example 1 as an off-white foam (44.1 mg). ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 10.25 (br s, 2H), 8.20-7.10 (m, 20H), 5.79-5.12 (m, 4H), 4.05-2.98 (m, 4H), 2.98-2.62 (m, 6H), 2.50-1.70 (m, 14H), [Note: the signal of the imidazole NH was too broad to assign a chemical shift]; LC (Cond. 1): RT=1.40 min; >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₆H₅₁N₈O₂: 747.41; found 747.58

Examples 2 to 24-4d

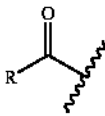
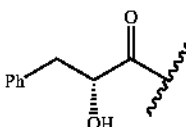
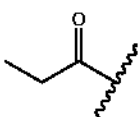
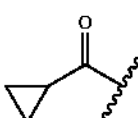
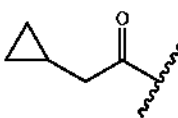
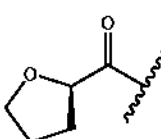
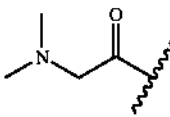
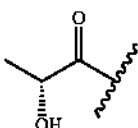
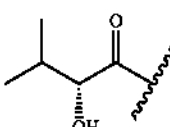
[0442]



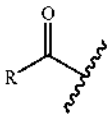
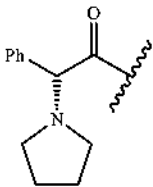
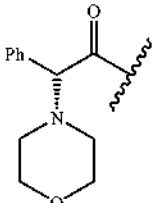
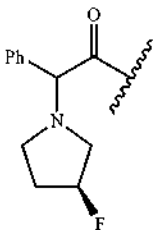
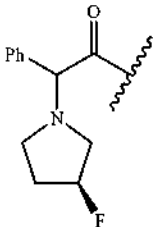
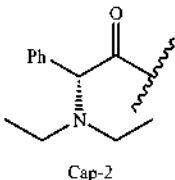
[0443] Examples 2 to 24-4 h were prepared as TFA salts by substituting the respective acids for Cap-1 using the same method described for Example 1. Caps in the following table without a number are commercially available.

Example	Compound Name		RT(LC-Cond.); % homogeneity index; MS data
2	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol)		1.55 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₁ N ₆ O ₄ ; 693.32; found 693.46; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₁ N ₆ O ₄ ; 693.3189; found 693.3182
3	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-2-phenyl-2-propanol)		1.77 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₃ N ₆ O ₄ ; 721.35; found 721.52; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₃ N ₆ O ₄ ; 721.3502; found 721.3515
4	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy))biscarbamate		1.64 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₄₇ N ₈ O ₈ ; 807.36; found 807.58
5	(1S,1'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanimine)		1.33 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₁ N ₈ O ₂ ; 747.41; found 747.64; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₁ N ₈ O ₂ ; 747.4135; found 747.4103
6	5,5'-(4,4'-biphenyldiylbis(2-((2S)-1-benzoyl-2-pyrrolidinyl)-1H-imidazole)		1.65 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₃₇ N ₆ O ₂ ; 633.30; found 633.51
7	5,5'-(4,4'-biphenyldiylbis(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazole)		1.71 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₁ N ₆ O ₂ ; 661.33; found 661.53; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₁ N ₆ O ₂ ; 661.3291; found 661.3300
8	5,5'-(4,4'-biphenyldiylbis(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazole)		1.63 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₅ N ₆ O ₄ ; 721.35; found 721.59; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₅ N ₆ O ₄ ; 721.3502; found 721.3536

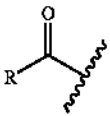
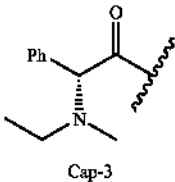
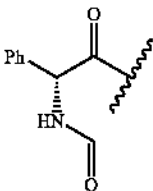
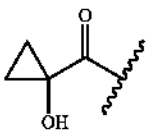
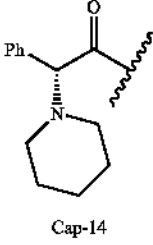
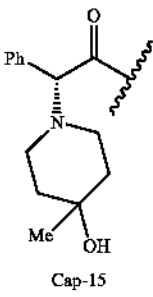
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Example	Compound Name		RT(LC-Cond.); % homogeneity index; MS data
9	(2R,2'R)-1,1'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-3-phenyl-2-propanol)		1.71 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₅ N ₆ O ₄ : 721.35; found 721.58; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₅ N ₆ O ₄ : 721.3502; found 721.3497
10	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-propionyl-2-pyrrolidinyl)-1H-imidazole)		1.47 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₂ H ₃₇ N ₆ O ₂ : 537.30; found 537.40; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₂ H ₃₇ N ₆ O ₂ : 537.2978; found 537.2952
11	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(cyclopropylcarbonyl)-2-pyrrolidinyl)-1H-imidazole)		1.48 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₄ H ₃₇ N ₆ O ₂ : 561.30; found 561.44
12	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-imidazole)		1.57 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₁ N ₆ O ₂ : 589.33; found 589.48; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₁ N ₆ O ₂ : 589.3291; found 589.3268
13	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazole)		1.44 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₁ N ₆ O ₄ : 621.32; found 621.52; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₁ N ₆ O ₄ : 621.3189; found 621.3191
14	2,2'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxoethanamine)		1.27 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₄ H ₄₃ N ₈ O ₂ : 595.35; found 595.54; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₄ H ₄₃ N ₈ O ₂ : 595.3509; found 595.3503
15	(2R,2'R)-1,1'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-2-propanol)		1.36 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₂ H ₃₇ N ₆ O ₄ : 569.29; found 569.44; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₂ H ₃₇ N ₆ O ₄ : 569.2876; found 569.2872
16	(2R,2'R)-1,1'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol)		1.51 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₅ N ₆ O ₄ : 625.35; found 625.50; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₅ N ₆ O ₄ : 625.3517

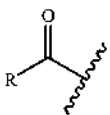
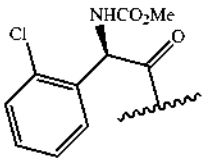
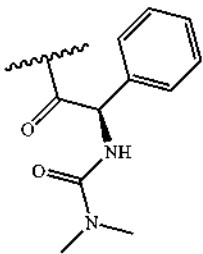
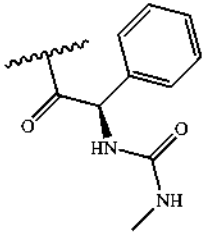
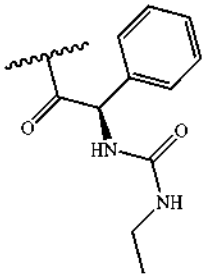
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Example	Compound Name		RT(LC-Cond. 1); % homogeneity index; MS data
17	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazole)	 Cap-5	1.13 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₅ N ₈ O ₂ : 799.45; found 799.67
18	4,4'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dimorpholine	 Cap-6	1.11 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₅ N ₈ O ₄ : 831.44; found 831.71
19	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(((3S)-3-fluoro-1-pyrrolidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazole)	 Diastereomer-1 Cap-9a	1.17 minutes(Cond. 1); 97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₃ F ₂ N ₈ O ₂ : 835.43; found 835.51; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₃ F ₂ N ₈ O ₂ : 835.4260; found 835.4261
20	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(((3S)-3-fluoro-1-pyrrolidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazole)	 Diastereomer-2 Cap-9b	1.03 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₃ F ₂ N ₈ O ₂ : 835.43; found 835.51; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₃ F ₂ N ₈ O ₂ : 835.4260; found 835.4261
21	(1R,1'R)-2,2'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)bis(N,N-diethyl-2-oxo-1-phenylethanamine)	 Cap-2	1.13 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₉ N ₈ O ₂ : 803.48; found 803.56; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₉ N ₈ O ₂ : 803.4761; found 803.4728

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Example	Compound Name		RT(LC-Cond.); % homogeneity index; MS data
22	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-ethyl-N-methyl-2-oxo-1-phenylethanamine)		1.10 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₅₅ N ₈ O ₂ : 775.45; found 775.52; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₉ N ₈ O ₂ : 775.4448; found 775.4456
23	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)))diformamide		1.22 minutes(Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₃ N ₈ O ₄ : 747.34; found 747.38
24	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))dicyclopropanol		1.77 minutes(Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₄ H ₃₇ N ₈ O ₄ : 593.29; found 593.16
24-1	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)))dipiperidine		¹ HNMR(400 MHz, DMSO-d ₆) δ 12.18(m, 0.4 H), 11.96(m, 0.4 H), 11.79(m, 1.2 H), 7.84-7.70(m, 4 H), 7.69-7.65(m, 4 H), 7.53-7.50(m, 2 H), 7.43-7.28(m, 4 H), 7.09-7.01(m, 2 H), 6.87-6.85(m, 2 H), 5.51-5.48(m, 0.5 H), 5.01-4.98(m, 1.5 H), 4.29(m, 1.5 H), 4.16(m, 0.5 H), 3.98(m, 2 H), 3.65-3.49(m, 2 H), 3.43-3.36(m, 2 H), 2.41-2.31(m, 8 H), 2.14-1.82(m, 8 H), 1.47-1.31(m, 12 H); LCMS: Anal. Calcd. for C ₅₂ H ₅₈ N ₈ O ₂ : 826; found: 827(M + H) ⁺ .
24-2	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)))bis(4-methyl-4-piperidinol)		¹ HNMR(400 MHz, DMSO-d ₆) δ 12.02(br s, 1 H), 11.82(br s, 1 H), 7.90-7.79(m, 4 H), 7.79-7.65(m, 5 H), 7.55(br s, 2 H), 7.45(d, J = 7.6 Hz, 2 H), 7.39-7.25(m, 3 H), 7.34(d, J = 7.6 Hz, 2 H), 7.04(t, J = 7.6 Hz, 2 H), 6.85(d, J = 8.1 Hz, 2 H), 5.15-4.96(m, 2 H), 4.31-3.96(m, 6 H), 2.35-2.20(m, 2 H), 2.05-1.94(m, 4 H), 1.94-1.81(m, 4 H), 1.50-1.35(m, 9 H), 1.35-1.20(m, 5 H), 1.09(s, 2 H), 1.05(s, 4 H); LCMS: Anal. Calcd. for C ₆₄ H ₆₇ N ₈ O ₄ : 886; found: 887(M + H) ⁺ .

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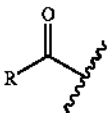
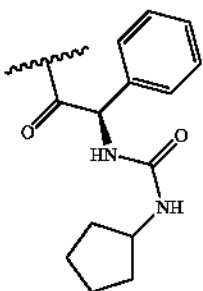
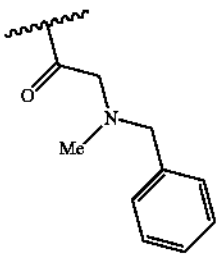
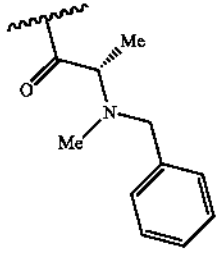
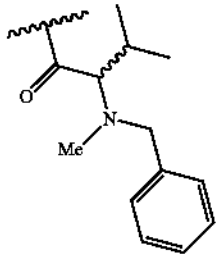
Example	Compound Name		RT(LC-Cond.): % homogeneity index; MS data
24-3	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S))-2,1-pyrrolidinediyl((1R)-1-(2-chlorophenyl)-2-oxo-2,1-ethanediy))biscarbamate		LCMS: Anal. Calcd. for $C_{36}H_{34}Cl_2N_8O_6$: 874; found: 875(M + H) ⁺ .
24-4a	N',N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S))-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy))bis(1,1-dimethylurea)	 Cap-47	¹ H NMR(500 MHz, DMSO-d ₆) δ ppm 1.89-2.00 (m, J = 17.09, 7.02 Hz, 4 H), 2.06-2.13 (m, J = 14.95, 3.97 Hz, 3 H), 2.24-2.33 (m, J = 8.70, 6.56 Hz, 2 H), 2.79-2.84 (m, 12 H), 3.29 (q, 2 H), 3.95-4.03 (m, 3 H), 5.26 (dd, J = 8.55, 2.14 Hz, 3 H), 5.52 (d, J = 5.80 Hz, 3 H), 6.72 (d, J = 6.10 Hz, 3 H), 7.02-7.07 (m, 1 H), 7.29-7.36 (m, 3 H), 7.39 (t, J = 7.17 Hz, 4 H), 7.46 (d, J = 7.02 Hz, 3 H), 7.92 (s, 8 H), 8.12 (s, 2 H); HPLC XTERRA C-184.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H ₃ PO ₄ , B = 10% water, 90% methanol, 0.2% H ₃ PO ₄ , RT = 2.13 minutes, 96% homogeneity index; LCMS: Anal. Calcd. for $C_{48}H_{53}N_{10}O_4$: 832.42; found: 833.43(M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{48}H_{54}N_{10}O_4$: 833.4251; found: 833.4267(M + H) ⁺ .
24-4b	N',N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S))-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy))bis(1-methylurea)	 Cap-45	RT = 4.45 minutes (Gemini C-184.6 × 50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10 mm ammonium acetate, B = 95% acetonitrile, 5% water, 10 mm ammonium acetate); LCMS: Anal. Calcd. for $C_{46}H_{48}N_{10}O_4$: 804.95; found: 805.41(M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{46}H_{49}N_{10}O_4$: 805.3938; found: 805.3929(M + H) ⁺ .
24-4c	N',N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S))-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy))bis(1-ethylurea)	 Cap-46	RT = 4.20 minutes (Gemini C-184.6 × 50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10 mm ammonium acetate, B = 95% acetonitrile, 5% water, 10 mm ammonium acetate); LCMS: Anal. Calcd. for $C_{48}H_{53}N_{10}O_4$: 833.00; found: 833.48 (M + H) ⁺ .

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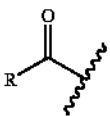
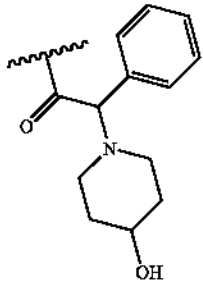
Example	Compound Name		RT(LC-Cond.); % homogeneity index; MS data
24-4d	N',N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-cyclopentylurea)		RT = 4.92 minutes (Gemini C-184.6 x 50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 0 mm ammonium acetate, B = 95% acetonitrile, 5% water, 10 mm ammonium acetate); LCMS: Anal. Calcd. for C ₅₄ H ₆₀ N ₁₀ O ₄ 912.49; found: 913.68 (M + H) ⁺ ; HRMS: Anal. Calcd. for C ₅₄ H ₆₁ N ₁₀ O ₄ 913.4877; found: 913.4899 (M + H) ⁺ .
24-4e	2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N-methyl-2-oxoethanamine)		¹ H NMR(500 MHz, DMSO-d ₆) δ ppm 1.97-2.43(m, 8 H), 2.64-2.91(m, 6 H), 3.45-3.63(m, 2 H), 3.62-3.76(m, 2 H), 4.14(dd, 4 H), 4.22-4.45(m, 4 H), 5.29(s, 2 H), 7.28-7.65(m, 10 H), 7.90(s, 8 H), 8.06(s, 2 H), 14.62(s, 2 H); HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid. RT = 3.06 min; LCMS: Anal. Calcd. for: C ₄₆ H ₅₀ N ₈ O ₂ 746.96; Found: 747.41 (M + H) ⁺ .
24-4f	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N-methyl-1-oxo-2-propanamine)		RT = 2.95 minutes (99%); HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C ₄₈ H ₅₄ N ₈ O ₂ 775.02; Found: 775.45(M + H) ⁺ .
24-4g	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N,3-dimethyl-1-oxo-2-butanamine)		RT = 3.86 minutes(100%); HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C ₅₂ H ₆₂ N ₈ O ₂ 831.13; Found: 831.51(M + H) ⁺ .

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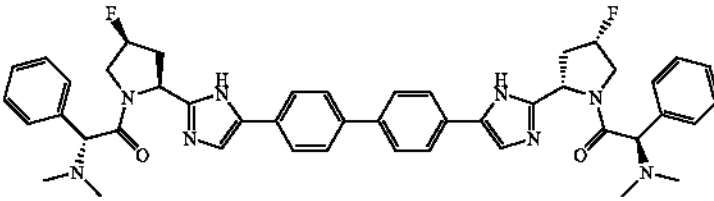
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Example	Compound Name		RT(LC-Cond.); % homogeneity index; MS data
24-4h	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))di(4-piperidinol)		RT = 2.86 minutes(100%); HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C ₃₂ H ₃₈ N ₈ O ₄ 859.09; Found: 859.45(M + H) ⁺ .

Cap-8

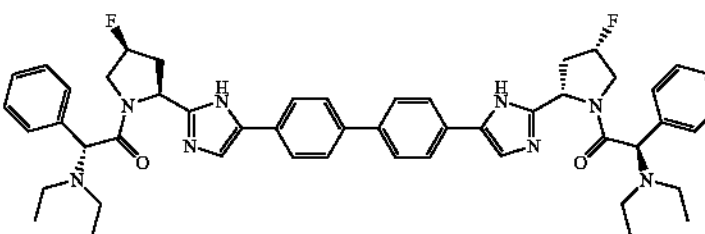
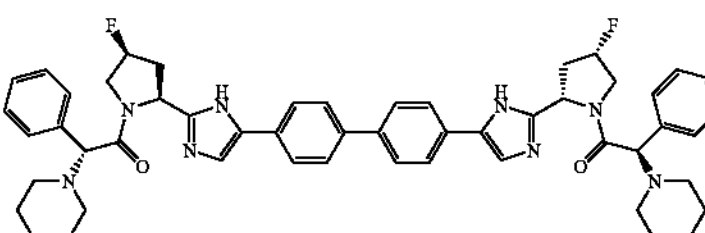
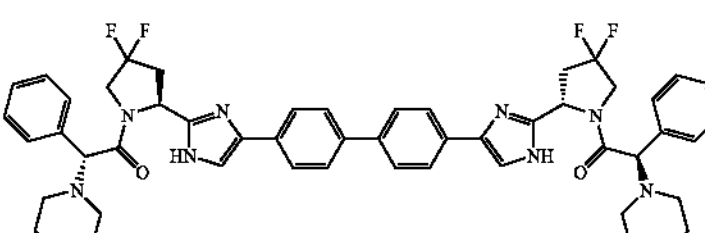
Examples 24-5 to 24-18

[0444]

Example	Compound Name	Structure	Data
24-5	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S,4S)-4-fluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine		Gemini C-18 4.6 x 50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10 mM ammonium acetate, B = 95% acetonitrile, 5% water, 10 mM ammonium acetate. (RT = 4.163 min); Nominal/LRMS-Calcd. for C ₄₆ H ₄₈ F ₂ N ₈ O ₂ 782.93; found 783.40 (M + H) ⁺ ; Accurate/HRMS-Calcd. for C ₄₆ H ₄₈ F ₂ N ₈ O ₂ 783.3946; 783.3934 (M + H) ⁺ .

from 1-2e-2 and Cap-1

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Example	Compound Name	Structure	Data
24-6	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl))))bis(N,N-diethyl-2-oxo-1-phenylethanamine)		Gemini C-18 4.6 x 50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10 mm ammonium acetate, B = 95% acetonitrile, 5% water, 10 mm ammonium acetate. (RT = 3.76 min); LCMS: Anal. Calcd. for C ₅₀ H ₃₆ F ₂ N ₈ O ₂ 839.04; found: 839.49 (M + H) ⁺ ; HRMS: Anal. Calcd. for C ₅₀ H ₃₇ F ₂ N ₈ O ₂ 839.4572; found: 839.4590 (M + H) ⁺ .
		from 1-2e-2 and Cap-2	
24-7	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl))))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)		Gemini C-18 4.6 x 50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10 mm ammonium acetate, B = 95% acetonitrile, 5% water, 10 mm ammonium acetate. RT = 3.99 min; LCMS: Anal. Calcd. for C ₅₂ H ₃₆ F ₂ N ₈ O ₂ 863.06; found: 863.47 (M + H) ⁺ ; HRMS: Anal. Calcd. for C ₅₂ H ₃₇ F ₂ N ₈ O ₂ 863.4572; found: 863.4553 (M + H) ⁺ .
		from 1-2e-2 and Cap-14	
24-8	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl))((1R)-2-oxo-1-phenyl-2,1-ethanediy))))dipiperidine		RT = 1.64 minutes, method B; LCMS: Anal. Calcd. for C ₅₂ H ₃₄ F ₄ N ₈ O ₆ 898.43; found: 899.46 (M + H) ⁺ ; HRMS: Anal. Calcd. for C ₅₂ H ₃₅ F ₄ N ₈ O ₆ 899.4384; found: 899.4380 (M + H) ⁺ .
		from 1-2e-3 and Cap-14	

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Example	Compound Name	Structure	Data
24-9	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl))) bismethylcarbamate		RT = 2.62 minutes, method C; LCMS: Anal. Calcd. for $C_{46}H_{42}F_4N_8O_6$: 878.88; found: 879.81 (M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{46}H_{43}F_4N_8O_6$: 879.33242; found: 879.3273 (M + H) ⁺ .
		from 1-2e-3 and Cap-4	
24-10	1-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidiny)-1H-imidazole-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidiny)-2-oxo-1-phenylethyl) piperidine		RT = 1.54 minutes, method B; LCMS: Anal. Calcd. for $C_{52}H_{56}F_2N_8O_6$: 862.45; found: 863.46 (M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_6$: 863.4573; found: 863.4572 (M + H) ⁺ .
		from 1-3e and Cap-14.	
24-11	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl))) bismethylcarbamate		RT = 8.54 minutes, method A; LCMS: Anal. Calcd. for $C_{46}H_{46}N_8O_8$: 838.93; found: 839.41 (M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{46}H_{47}N_8O_8$: 839.9300; found: 839.3527 (M + H) ⁺ .
		from 1-1e and Cap-4	
24-12	(3R,5S,3'R,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-hydroxy-2-phenylacetyl)-3-pyrrolidinol)		RT = 6.92 minutes, method A; LCMS: Anal. Calcd. for $C_{42}H_{40}N_8O_6$: 724.81; found: 725.43 (M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{42}H_{41}N_8O_6$: 725.3087; found: 725.3088 (M + H) ⁺ .
		from 1-1e and mandelic acid	
24-13	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(3-methylurea)		RT = 3.80 minutes, method C; LCMS: Anal. Calcd. for $C_{46}H_{48}N_{10}O_6$: 836.95; found: 837.52 (M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{46}H_{49}N_{10}O_6$: 837.3836; found: 837.3809 (M + H) ⁺ .
		Prepared from 1-1e and Cap-45	

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Example	Compound Name	Structure	Data
24-14	N',N''-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediy)))bis(1-ethylurea)		RT = 4.39 minutes, method C; LRMS: Anal. Calcd. for $C_{48}H_{52}N_{10}O_6$ 865.003; found: 865.56 (M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{48}H_{53}N_{10}O_6$ 865.4149; found: 865.4139 (M + H) ⁺ .
		Prepared from 1-1e and Cap-46	
24-15	N',N''-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediy)))bis(1-cyclopentylurea)		RT = 4.88 minutes, method B; LRMS: Anal. Calcd. for $C_{54}H_{60}N_{10}O_6$ 944.13; found: 945.65 (M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{54}H_{61}N_{10}O_6$ 945.4775; found: 945.4769 (M + H) ⁺ .
		Prepared from 1-1e and Cap-48	
24-16	(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-(dimethylamino)-2-phenylacetyl)-3-pyrrolidinol)		RT = 3.66 minutes, method D; LRMS: Anal. Calcd. for $C_{46}H_{50}N_8O_4$ 778.39; found: 779.39 (M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{46}H_{51}N_8O_4$ 779.4033; found: 779.4021 (M + H) ⁺ .
		Prepared from 1-2e and Cap-1	
24-17	dimethyl (4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl((2S,4S)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediy))) bis carbamate		RT = 5.75 minutes, method C; LRMS: Anal. Calcd. for $C_{46}H_{46}N_8O_8$ 838.93; found: 839.44 (M + H) ⁺ ; HRMS: Anal. Calcd. for $C_{46}H_{47}N_8O_8$ 839.3517; found: 839.3519 (M + H) ⁺ .
		Prepared from 1-2e and Cap-4	
24-18	(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-hydroxy-2-phenylacetyl)-3-pyrrolidinol)		RT = 4.41 minutes, method D; LRMS: Anal. Calcd. for $C_{42}H_{40}N_6O_6$ 724.81; found: 725.13 (M + H) ⁺ .
		from 1-2e and mandelic acid	

-continued

Example	Compound Name	Structure	Data
24-18-1	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethandiyl (methylimino) ((1R)-2-oxo-1-phenyl-2,1-ethandiyl))) biscarbamate		RT = 1.55 min ¹ ; LRMS: Anal. Calcd. for C ₄₄ H ₄₆ N ₈ O ₆ 782.35; found: 783.37 (M + H) ⁺ ; HRMS: Anal. Calcd. for C ₄₄ H ₄₇ N ₈ O ₆ 783.3619 found: 783.3630 (M + H) ⁺ .
		from 1-7e and Cap-4	
24-18-2	(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethandiyl))bis(2-(dimethylamino)-N-methyl-2-phenylacetamide)		RT = 1.16 min ¹ ; LRMS: Anal. Calcd. for C ₄₄ H ₅₀ N ₈ O ₂ 722.41; found: 723.41 (M + H) ⁺ ; HRMS: Anal. Calcd. for C ₄₄ H ₅₁ N ₈ O ₂ 723.4135 found: 723.4152 (M + H) ⁺ .
		from 1-7e and Cap-1	
24-18-3	(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethandiyl))bis(N-methyl-2-phenyl-2-(1-piperidinyl)acetamide)		RT = 1.28 min ¹ ; LRMS: Anal. Calcd. for C ₅₀ H ₄₈ N ₈ O ₂ 802.47; found: 803.50 (M + H) ⁺ ; HRMS: Anal. Calcd. for C ₅₀ H ₄₉ N ₈ O ₂ 803.4761 found: 803.4778 (M + H) ⁺ .
		from 1-7e and Cap-14	

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Example	Compound Name	Structure	Data
24-18-4	methyl ((1R)-2-((2S)-2-(5-(4'-((1S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)methylamino)ethyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl carbamate		RT = 1.53 min ¹ ; LRMS: Anal. Calcd. for C ₄₅ H ₄₆ N ₈ O ₆ 794.35; found: 795.39 (M + H) ⁺ ; HRMS: Anal. Calcd. for C ₄₅ H ₄₇ N ₈ O ₆ 795.3619 found: 795.3616 (M + H) ⁺ .
		Prepared from 1-5e and Cap-4	
24-18-5	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4'-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)ethyl)-N-methyl-2-phenylacetamide		RT = 1.21 ¹ ; LRMS: Anal. Calcd. for C ₄₅ H ₅₀ N ₈ O ₂ 734.41; found: 735.46 (M + H) ⁺ ; HRMS: Anal. Calcd. for C ₄₅ H ₅₁ N ₈ O ₂ 735.4135 found: 735.4136 (M + H) ⁺ .
		Prepared from 1-5e and Cap-1	
24-18-6	(2R)-N-methyl-2-phenyl-N-((1S)-1-(5-(4'-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)ethyl)-2-(1-piperidinyl)acetamide		RT = 1.30 ¹ ; LRMS: Anal. Calcd. for C ₅₁ H ₅₈ N ₈ O ₂ 814.47; found: 815.48 (M + H) ⁺ ; HRMS: Anal. Calcd. for C ₅₁ H ₅₉ N ₈ O ₂ 815.4761 found: 815.4744 (M + H) ⁺ .
		Prepared from 1-5e and Cap-14	

¹LC Conditions for 24-18-1 through 24-18-6: Phenomenex LUNA C-18 4.6 x 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220 nm, 5 µL injection volume.

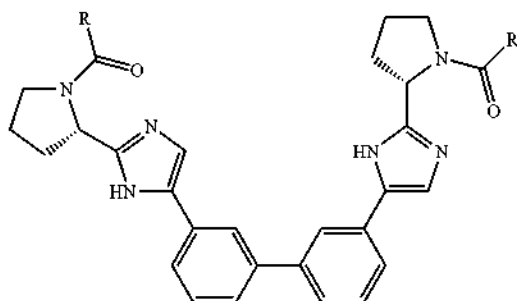
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Examples 24-19 to 24-20

[0445]



[0446] Example 24-19 and 24-20 were prepared as TFA salts from 1-2e-1 and the respective acids using the same method described for Example 1.

LC conditions for 24-19 and 24-20:

Column=Phenomenex-Luna 3.0×50 mm S10

Start % B=0

Final % B=100

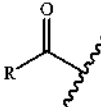
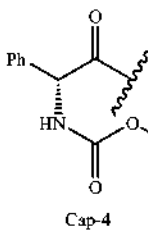
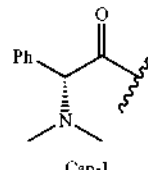
[0447] Gradient time=2 min

Stop time=3 min

Flow Rate=4 mL/min

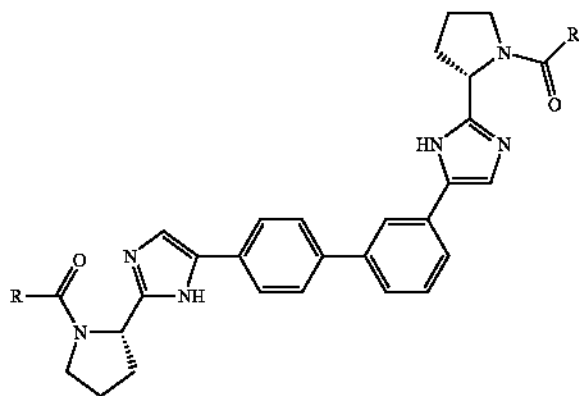
Wavelength=220 nm

[0448] Solvent A=0.1% TFA in 10% methanol/90% H₂O
Solvent B=0.1% TFA in 90% methanol/10% H₂O

Example	Compound Name		Data
24-19	methyl ((1R)-2-((2S)-2-(4-(3'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidiny)-1H-imidazol-5-yl)-3-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidiny)-2-oxo-1-phenylethyl)carbamate		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.82-1.97 (m, 2 H), 1.97-2.17 (m, 4 H), 2.18-2.37 (m, 2 H), 3.18 (d, J = 9.77 Hz, 2 H), 3.44-3.58 (m, 6 H), 3.79-4.04 (m, 2 H), 5.09-5.46 (m, 2 H), 5.45-5.84 (m, 2 H), 6.97-7.49 (m, 10 H), 7.61-7.74 (m, 4 H), 7.75-7.93 (m, 4 H), 8.10-8.32 (m, 4 H), 14.48 (app br s, 2 H); RT = 1.34 min; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₄₇ N ₈ O ₆ ; 807.36; found 807.40
24-20	(1R)-2-((2S)-2-(4-(3'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidiny)-1H-imidazol-5-yl)-3-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidiny)-N,N-dimethyl-2-oxo-1-phenylethyl)aniline		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.71-2.32 (m, 8 H), 3.33-3.68 (m, 2 H), 3.89-4.16 (m, J = 2.75 Hz, 2 H), 4.96 (app br s, 12 H), 5.26 (s, 2 H), 5.45 (s, 2 H), 7.03-7.78 (m, 12 H), 7.84 (s, 4 H), 8.07-8.43 (m, 4 H), 9.90-10.87 (m, 2 H); RT = 1.10 min; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₁ N ₈ O ₂ ; 747.41; found 747.45

Examples 24-21 to 24-22

[0449]



[0450] Example 24-21 and 24-22 were prepared as TFA salts from 1-4e and the respective carboxylic acids using the same method described for Example 1.

Example	Compound Name		Data
24-21	methyl ((1R)-2-((2R)-2-(4-(3'-(2-((2S)-1-((2R)-2-(methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.73-2.37 (m, 8 H), 3.13 (s, 2 H), 3.36-4.29 (m, 8 H), 5.26 (s, 2 H), 5.53 (s, 2 H), 6.99-8.61 (m, 22 H), 14.51 (s, 2 H); RT = 1.33 min; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₄₇ N ₈ O ₆ : 807.36; found 807.58
24-22	(1R)-2-((2R)-2-(4-(3'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethyl)carbamate		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.84-2.32 (m, 8 H), 2.92-3.10 (m, 2 H), 3.92-4.08 (m, 2 H), 4.43 (app br s, 12 H), 5.16-5.37 (m, 2 H), 5.39-5.58 (m, 2 H), 7.16-8.24 (m, 20 H), 9.60-10.46 (m, 2 H); RT = 1.08 min; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₁ N ₈ O ₂ : 747.41; found 747.45

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LC conditions for 24-21 and 24-22:

Column=Phenomenex-Luna 3.0x50 mm S10

Start % B=0

Final % B=100

[0451] Gradient time=2 min

Stop time=3 min

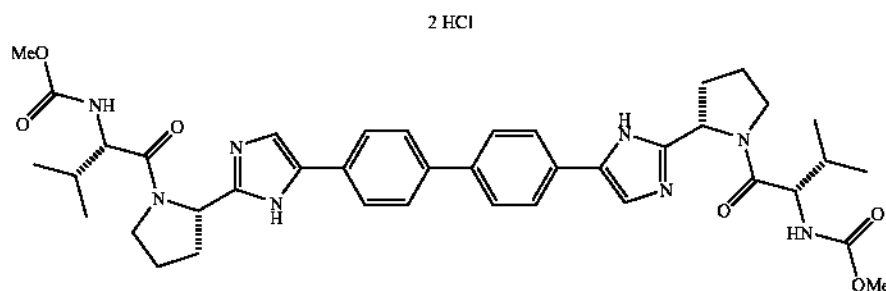
Flow Rate=4 mL/min

Wavelength=220 nm

[0452] Solvent A=0.1% TFA in 10% methanol/90% H₂OSolvent B=0.1% TFA in 90% methanol/10% H₂O

Example 24-23

[0453]



methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[0454] A 50 mL flask equipped with a stir bar was sequentially charged with 2.5 mL acetonitrile, 0.344 g (2.25 mmol, 2.5 equiv) hydroxy benzotriazole hydrate, 0.374 g (2.13 mmol, 2.4 equiv) N-(methoxycarbonyl)-L-valine, 0.400 g (2.09 mmol, 2.4 equiv) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and an additional 2.5 mL acetonitrile. The resulting solution was agitated at 20° C. for 1 hour and charged with 0.501 g (0.88 mmol, 1 equiv) Example A-1e-4. The slurry was cooled to about 0° C. and 0.45 g (3.48 mmol, 4 equiv) diisopropylethylamine was added over 30 minutes while maintaining a temperature below 10° C. The solution was slowly heated to 15° C. over 3 hours and held at 15° C. for 16 hours. The temperature was increased to 20° C. and stirred for 3.25 hours. The resulting solution was charged with 3.3 g of 13 wt % aqueous NaCl and heated to 50° C. for 1 hour. After cooling to 20° C., 2.5 mL of isopropyl acetate was added. The rich organic phase was washed with 2x6.9 g of a 0.5 N NaOH solution containing 13 wt % NaCl followed by 3.3 g of 13 wt % aqueous NaCl. The mixture was then

solvent exchanged into isopropyl acetate by vacuum distillation to a target volume of 10 mL. The resulting hazy solution was cooled to 20° C. and filtered through a 0.45 µm filter. The clear solution was then solvent exchanged into ethanol by vacuum distillation with a target volume of 3 mL. 1.67 mL (2.02 mmol, 2.3 equiv) of 1.21 M HCl in ethanol was added. The mixture was then stirred at 25° C. for 15 hours. The resulting slurry was filtered and the wet cake was washed with 2.5 mL of 2:1 acetone:ethanol. The solids were dried in a vacuum oven at 50° C. to give 0.550 g (0.68 mmol, 77%) of the desired product.

Recrystallization of Example 24-23

[0455] A solution of Example 24-23 prepared above was prepared by dissolving 0.520 g of the above product in 3.65

mL methanol. The solution was then charged with 0.078 g of type 3 Cuno Zeta loose carbon and allowed to stir for 0.25 hours. The mixture was then filtered and washed with 6 mL of methanol. The product rich solution was concentrated down to 2.6 mL by vacuum distillation. 7.8 mL acetone was added and allowed to stir at 25° C. for 15 h. The solids were filtered, washed with 2.5 mL 2:1 acetone:ethanol and dried in a vacuum oven at 70° C. to give 0.406 g (57.0%) of the desired product as white crystals: ¹H NMR (400 MHz, DMSO-d₆, 80° C.): 8.02 (d, J=8.34 Hz, 4H), 7.97 (s, 2H), 7.86 (d, J=8.34 Hz, 4H), 6.75 (s, 2H), 5.27 (t, J=6.44 Hz, 2H), 4.17 (t, J=6.95 Hz, 2H), 3.97-4.11 (m, 2H), 3.74-3.90 (m, 2H), 3.57 (s, 6H), 2.32-2.46 (m, 2H), 2.09-2.31 (m, 6H), 1.91-2.07 (m, 2H), 0.88 (d, J=6.57 Hz, 6H), 0.79 (d, J=6.32 Hz, 6H); ¹³C NMR (75 MHz, DMSO-d₆): δ 170.9, 156.9, 149.3, 139.1, 131.7, 127.1, 126.5, 125.9, 115.0, 57.9, 52.8, 51.5, 47.2, 31.1, 28.9, 24.9, 19.6, 17.7; IR (neat, cm⁻¹): 3385, 2971, 2873, 2669, 1731, 1650. Anal. Calcd for C₄₀H₅₂N₈O₆Cl₂: C, 59.18; H, 6.45; N, 13.80; Cl, 8.73. Found C, 59.98; H, 6.80; N, 13.68; Cl, 8.77. mp 267° C. (decomposed). Characteristic diffraction peak positions (degrees 2θ±0.1)@RT, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard are as follows: 10.3, 12.4, 12.8, 13.3, 13.6, 15.5, 20.3, 21.2, 22.4, 22.7, 23.7.

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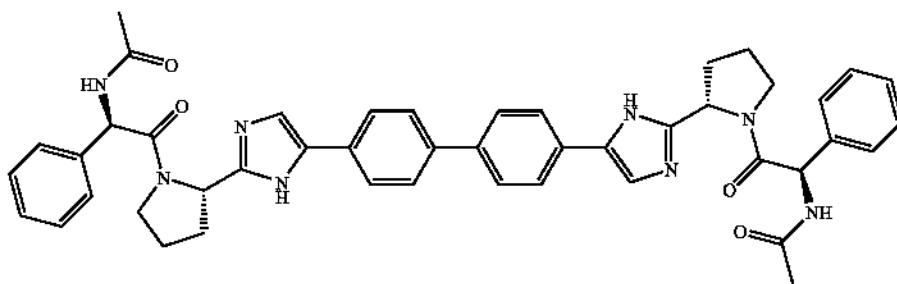
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Example 25

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl
(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-
ethanediyl)))diacetamide

[0456]

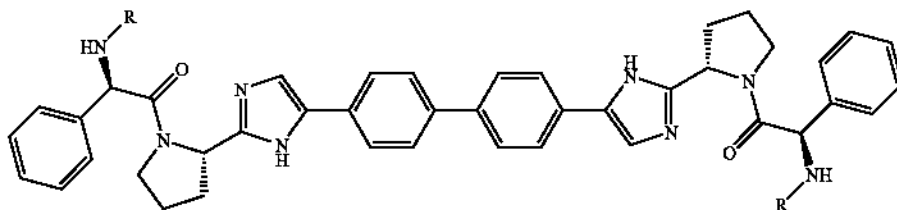


Example 25 Step a

di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-
diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,
1-ethanediyl)))biscarbamate and

Example 25 Step b

[0457]



25a: R = Boc
25b: R = H

[0458] HATU (96.2 mg, 0.253 mmol) was added to a mixture of pyrrolidine 1e (52.6 mg, 0.124 mmol), diisopropylethylamine (100 μ L, 0.57 mmol) and Boc-D-Phg-OH (69 mg, 0.275 mmol) in DMF (3.0 mL). The reaction mixture was stirred for 25 minutes, and then diluted with methanol and purified by a reverse phase HPLC system (H_2O /methanol/TFA). The HPLC elute was neutralized with excess 2.0 M/ NH_3 in CH_3OH and the volatile component was removed in vacuo. The residue was carefully partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was extracted with more CH_2Cl_2 (2 \times). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to provide 25a as a film of semisolid oil (78.8 mg). LC (Cond. 1): RT=1.99 min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{52}H_{59}N_8O_6$: 891.46; found 891.55.

[0459] Carbamate 25a was converted to amine 25b according to the procedure described for the preparation of 1e.

LC(Cond. 1): RT=1.44 min; 97% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{43}N_8O_2$: 691.35; found 691.32

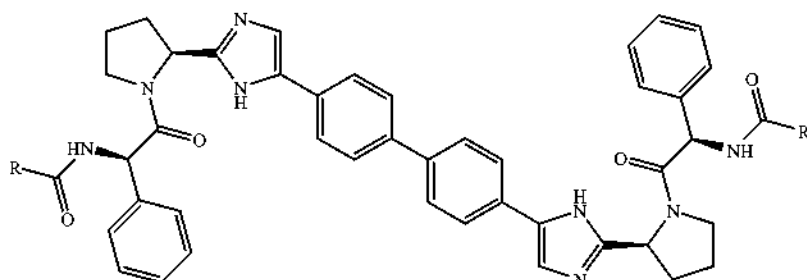
Example 25

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl
(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-
ethanediyl)))diacetamide

[0460] Acetic anhydride (20 μ L, 0.21 mmol) was added to a DMF (1.5 mL) solution of amine 25b (29 mg, 0.042 mmol) and triethylamine (30 μ L, 0.22 mmol) and stirred for 2.5 hours. The reaction mixture was then treated with NH_3 /methanol (1 mL of 2 M) and stirred for an additional 1.5 hours. The volatile component was removed in vacuo and the residue was purified by a reverse phase HPLC system (H_2O /methanol/TFA) to provide the TFA salt of Example 25 as a white foam (28.1 mg). LC (Cond. 1): RT=1.61 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_4$: 775.37; found 775.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_4$: 775.3720; found 775.3723

Example 25-1 to 25-5

[0461]

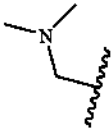
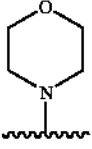
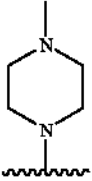
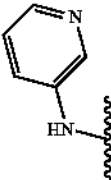


[0462] Examples 25-1 to 25-5 were prepared from 25b and the appropriate carboxylic acid using standard amide forming conditions similar to that described for the preparation of

example 1 from 1e. Examples 25-6 to 25-8 were prepared from 25b and the appropriate carbamoyl chloride or isocyanate.

Example Number	Compound Name	R	RT (LC-Cond.); % homogeneity index; MS data
25-1	(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyldiyl)))ditetrahydro-2-furancarboxamide		RT = 5.68 minutes; HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C ₅₂ H ₅₄ N ₈ O ₆ ; 887.06; Found: 887.58 (M + H) ⁺
25-2	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyldiyl)))bis(1-methyl-1H-imidazole-5-carboxamide)		RT = 3.54 minutes; HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C ₅₂ H ₅₀ N ₁₂ O ₄ ; 907.06; Found: 907.42 (M + H) ⁺
25-3	(2S,2'S)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyldiyl)))bis(1-methyl-2-pyrrolidinecarboxamide)		RT = 3.1 minutes; HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C ₅₄ H ₆₀ N ₁₀ O ₄ ; 913.14; Found: 913.54 (M + H) ⁺
25-4	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyldiyl)))bis(2-(3-pyridinyl)acetamide)		RT = 3.37 minutes; HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C ₅₆ H ₅₂ N ₁₀ O ₄ ; 929.10; Found: 929.42 (M + H) ⁺

-continued

Example Number	Compound Name	R	RT (LC-Cond.); % homogeneity index; MS data
25-5	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)))bis(2-dimethylamino)acetamide) (non-preferred name)		RT = 7.07 minutes; HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C ₅₀ H ₅₆ N ₁₀ O ₄ 861.07 Found: 859.69 (M + H) ⁺
25-6	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)))di(4-morpholinecarboxamide)		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.86-2.18 (m, 6 H), 2.23-2.39 (m, 2 H), 3.20-3.40 (m, 8 H), 3.40-3.61 (m, 8 H), 3.90-4.19 (m, 4 H), 5.27 (dd, J = 8.09, 3.51 Hz, 2 H), 5.37-5.63 (m, 2 H), 6.92-7.11 (m, 3 H), 7.30-7.45 (m, 5 H), 7.44-7.56 (m, 4 H), 7.83-8.04 (m, 8 H), 8.15 (s, 2 H), 14.29 (s, 2 H); HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 6.01 minutes; LCMS: Anal. Calcd. for: C ₅₂ H ₅₆ N ₁₀ O ₆ 917.09; Found: 917.72 (M + H) ⁺
25-7	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)))bis(4-methyl-1-piperazinecarboxamide)		RT = 3.74 minutes; HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C ₅₄ H ₆₂ N ₁₂ O ₄ 943.17; Found: 943.84 (M + H) ⁺
25-8	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)))bis(3-(3-pyridinyl)urea)		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.79-2.17 (m, 6 H), 2.29 (d, J = 9.77 Hz, 2 H), 3.06-3.39 (m, 2 H), 3.72-4.14 (m, 2 H), 5.27 (dd, J = 8.24, 2.75 Hz, 2 H), 5.66 (d, J = 7.02 Hz, 2 H), 7.26-7.65 (m, 12 H), 7.82-8.11 (m, 12 H), 8.17 (s, 2 H), 8.23-8.45 (m, 2 H), 8.61-8.97 (m, 2 H), 9.38 (s, 2 H), 14.51 (s, 2 H); HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 4.05 minutes; LCMS: Anal. Calcd. for: C ₅₄ H ₅₀ N ₁₂ O ₄ 931.08; Found: 931.78 (M + H) ⁺

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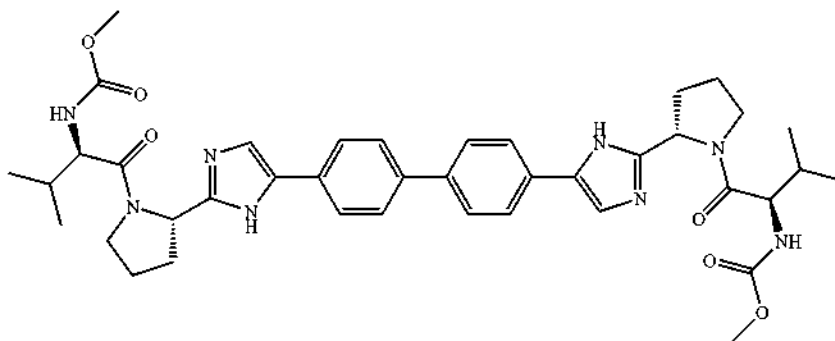
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Example 26

methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

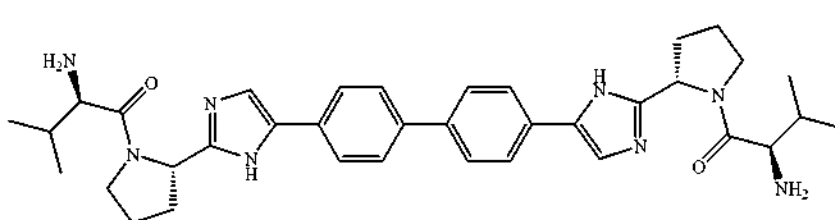
[0463]



Example 26, Step a

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanamine)

[0464]



26a

[0465] Diamine 26a was prepared starting from pyrrolidine 1e and BOC-D-Val-OH according to the procedure described for the synthesis of diamine 25b.

Example 26

methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

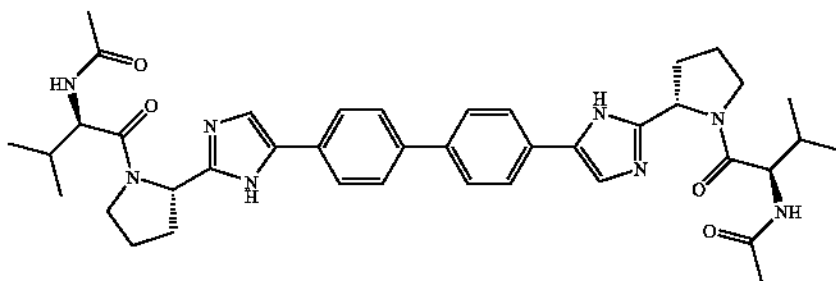
[0466] Methyl chloroformate (18 μ L, 0.23 mmol) was added to a THF (1.5 mL) solution of diamine 26a (30 mg,

0.048 mmol) and triethylamine (30 μ L, 0.22 mmol), and the reaction mixture was stirred at ambient condition for 3 hours. The volatile components was removed in vacuo, and the residue was treated with NH_3 /methanol (2 mL of 2 M) and stirred at ambient conditions for 15 minutes. All the volatile component was removed in vacuo, and the crude product was purified by reverse phase prep-HPLC (H_2O /methanol/TFA) to provide the TFA salt of Example 26 as a white solid (13.6 mg). LC (Cond. 2): RT=2.00 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{40}\text{H}_{51}\text{N}_8\text{O}_6$: 739.39; found 739.67; HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{40}\text{H}_{51}\text{N}_8\text{O}_6$: 739.3932; found 739.3966.

Example 27

N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide

[0467]

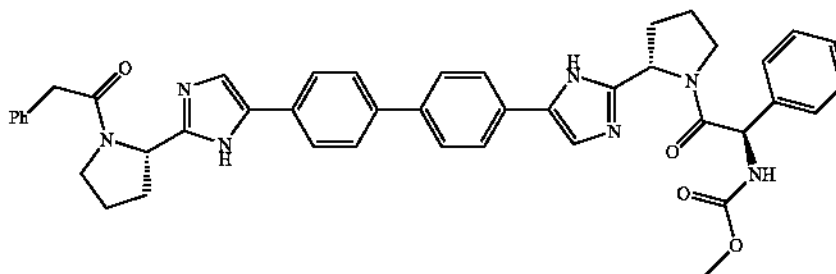


[0468] Diamine 26a was converted to Example 27 (TFA salt) according to a method described in the preparation of Example 25. LC (Cond. 2): RT=1.93 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_4$: 707.40; found 707.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_4$: 707.4033; found 707.4054.

Example 28

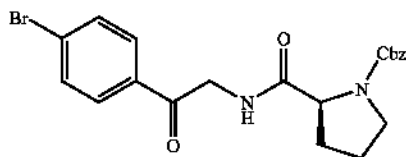
methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate

[0469]



Example 28, Step a

[0470]



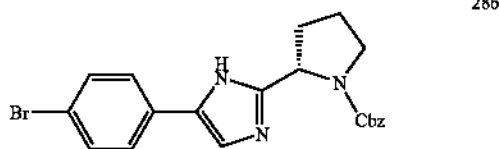
28a

[0471] HATU (19.868 g, 52.25 mmol) was added to a heterogeneous mixture of N-Cbz-L-proline (12.436 g, 49.89 mmol) and the HCl salt of 2-amino-1-(4-bromophenyl)etha-

none (12.157 g, 48.53 mmol) in DMF (156 mL). The mixture was lowered in an ice-water bath, and immediately afterward N,N-diisopropylethylamine (27 mL, 155 mmol) was added dropwise to it over 13 minutes. After the addition of the base was completed, the cooling bath was removed and the reaction mixture was stirred for an additional 50 minutes. The volatile component was removed in vacuo; water (125 mL) was added to the resulting crude solid and stirred for about 1 hour. The off-white solid was filtered and washed with copious water, and dried in vacuo to provide ketoamide 28a as a white solid (20.68 g). 1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): δ 8.30 (m, 1H), 7.91 (m, 2H), 7.75 (d, J =8.5, 2H), 7.38-7.25 (m, 5H), 5.11-5.03 (m, 2H), 4.57-4.48 (m, 2H), 4.33-4.26 (m, 1H), 3.53-3.36 (m, 2H), 2.23-2.05 (m, 1H), 1.94-1.78 (m, 3H); LC (Cond. 1): RT=1.65 min; 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; found 445.31.

Example 28, Step b

[0472]



[0473] Ketoamide 28a (10.723 g, 24.08 mmol) was converted to 28b according to the procedure described for the synthesis of carbamate 1b, with the exception that the crude material was purified by flash chromatography (sample was loaded with eluting solvent; 50% ethyl acetate/hexanes). Bromide 28b was retrieved as an off-white foam (7.622 g). ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): δ 12.23/12.04/11.97 (m, 1H), 7.73-6.96 (m, 10H), 5.11-4.85 (m, 3H), 3.61 (m, 1H), 3.45 (m, 1H), 2.33-1.84 (m, 4H). LC (Cond. 1): RT=1.42 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{21}\text{H}_{21}\text{BrN}_3\text{O}_2$: 426.08; found 426.31; HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{21}\text{H}_{21}\text{BrN}_3\text{O}_2$: 426.0817; found: 426.0829. The optical purity of 28b was assessed using the following chiral HPLC methods, and an ee of 99% was observed.

Column: Chiralpak AD, 10 μm , 4.6 \times 50 mm

[0474] Solvent: 20% ethanol/heptane (isocratic)
Flow rate: 1 mL/min

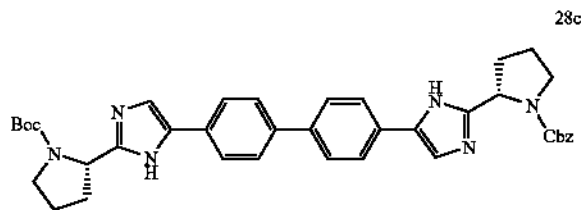
Wavelength: 254 nm

[0475] Relative retention time: 1.82 minutes (R), 5.23 minutes (S)

Example 28, Step c

benzyl tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)

[0476]



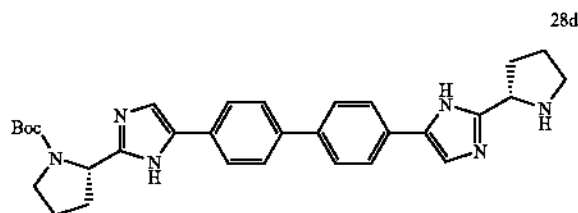
[0477] $\text{Pd}(\text{Ph}_3\text{P})_4$ (711.4 mg, 0.616 mmol) was added to a mixture of boronate ester 1c (7.582 g, ~17 mmol), bromide 28b (7.62 g, 17.87 mmol), NaHCO_3 (4.779 g, 56.89 mmol) in 1,2-dimethoxyethane (144 mL) and water (48 mL). The reaction mixture was purged with N_2 and heated with an oil bath at 80° C. for 15.5 hours, and then the volatile component was removed in vacuo. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The resulting material

was submitted to flash chromatography (sample was loaded as a silica gel mesh; ethyl acetate used as eluent) to provide biphenyl 28c as an off-white foam containing Ph_3PO impurity (7.5 g). ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): δ 12.24-12.19 (m, 0.36H), 12.00-11.82 (m, 1.64H), 7.85-6.98 (15H), 5.12-4.74 (4H), 3.68-3.34 (4H), 2.34-1.79 (8H), 1.41/1.17 (two br s, 9H); LC (Cond. 1): RT=1.41 minutes; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{39}\text{H}_{43}\text{N}_6\text{O}_4$: 659.34; found 659.52; HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{39}\text{H}_{43}\text{N}_6\text{O}_4$: 659.3346; found 659.3374.

Example 28, Step d

tert-butyl (2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

[0478]



[0479] K_2CO_3 (187.8 mg, 1.36 mmol) was added to a mixture of catalyst (10% Pd/C, 205.3 mg), carbamate 28c (1.018 g, ~1.5 mmol), methanol (20 mL) and 3 pipet-drops of water. A balloon of H_2 was attached and the mixture was stirred for 6 hours. Then, additional catalyst (10% Pd/C, 100.8 mg) and K_2CO_3 (101.8 mg, 0.738 mmol) were added and stirring continued for 3.5 hours. During the hydrogenation process, the balloon of H_2 was changed at intervals three times. The reaction mixture was filtered through a pad of diatomaceous earth (Celite® 521), and the filtrate was removed in vacuo. The resulting crude material was submitted to flash chromatography using a short column (sample was loaded as a silica gel mesh; 0-20% methanol/ CH_2Cl_2 used as eluent) to provide 28d as a light-yellow foam (605.6 mg). ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): δ 12.18/11.89/11.82 (three br s, 2H), 7.83-7.29 (m, 10H), 4.89-4.73 (m, 1H), 4.19 (app t, J=7.2, 1H), 3.55 (app br s, 1H), 3.40-3.35 (m, 1H), 3.02-2.96 (m, 1H), 2.91-2.84 (m, 1H), 2.30-1.69 (m, 8H), 1.41/1.16 (two br s, 9H). Note: the signal of pyrrolidine NH appears to have overlapped with signals in the 3.6-3.2 ppm region; LC (Cond. 1): RT=1.21 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{31}\text{H}_{37}\text{N}_6\text{O}_2$: 525.30; found 525.40.

Example 28, Step e-f

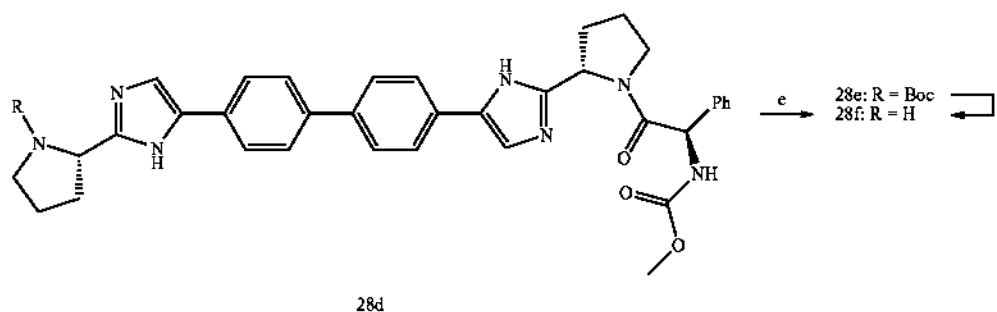
Example 28 Step e

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

Example 28 Step f

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)carbamate

[0480]



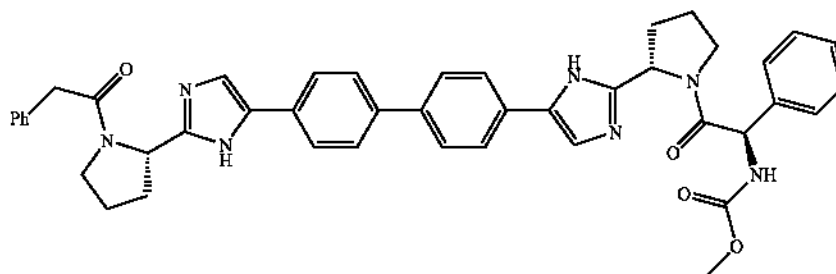
[0481] Step e: HATU (316.6 mg, 0.833 mmol) was added to a DMF (7.0 mL) solution of pyrrolidine 28d (427 mg, 0.813 mmol), Cap-4 (177.6 mg, 0.849 mmol) and diisopropylethylamine (0.32 mL, 1.84 mmol), and the reaction mixture was stirred for 45 minutes. The volatile component was removed in vacuo, and the residue was partitioned between CH_2Cl_2 (50 mL) and an aqueous medium (20 mL H_2O +1 mL saturated NaHCO_3 solution). The aqueous phase was re-extracted with CH_2Cl_2 , and the combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography (silica gel; ethyl acetate) to provide 28e as a yellow foam (336 mg). LC (Cond. 1): RT=1.68 min; 91% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{41}\text{H}_{46}\text{N}_7\text{O}_5$; 716.35; found 716.53.

[0482] Step f: Carbamate 28e was elaborated to amine 28f by employing the procedure described in the conversion of 1d to 1e. LC (Cond. 1): RT=1.49 min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{36}\text{H}_{38}\text{N}_7\text{O}_3$; 616.30; found 616.37; HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{36}\text{H}_{38}\text{N}_7\text{O}_3$; 616.3036; found 616.3046.

Example 28

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)carbamate

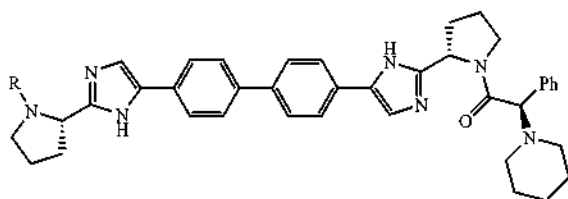
[0483]



[0484] Amine 28f was converted to the TFA salt of Example 28 by employing the last step of the synthesis of Example 1. ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 8.21-7.03 (m, 21H), 5.78-5.14 (3H), 3.98-3.13 (m, 9H; includes the signal for OCH₃ at 3.54 & 3.53), 2.45-1.72 (m, 8H). LC (Cond. 1): RT=1.66 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₄H₄₄N₇O₄: 734.35; found 734.48; HRMS: Anal. Calcd. for [M+H]⁺ C₄₄H₄₄N₇O₄: 734.3455; 734.3455.

Example 28-1 to 28-4

[0485]



[0486] Examples 28-1 through 28-4 (R groups shown in the table below) were prepared in similar fashion to example 28 via the intermediacy of intermediate 28d.

Example 28-1

(1R)—N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1-pyrrolidinyl)ethanamine

[0487] Cap-1 was appended, the Boc carbamate was removed with TFA or HCl, and Cap-14 was appended.

Example 28-2

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine

[0488] Tetrahydrofuroic acid was appended, the Boc carbamate was removed with TFA or HCl, and Cap-14 was appended.

Example 28-3

methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate

[0489] Cap-40 was appended, the Boc carbamate was removed with TFA or HCl, and Cap-14 was appended.

Example 28-4

(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

[0490] Cap-39 was appended, the Boc carbamate was removed with TFA or HCl, and Cap-14 was appended.

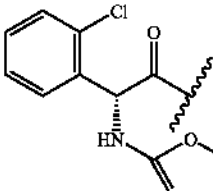
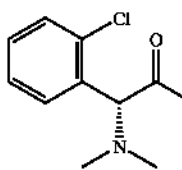
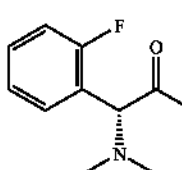
Example 28-5

(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

[0491] Cap-38 was appended, the Boc carbamate was removed with TFA or HCl, and Cap-14 was appended.

Example	Compound Name	R	Data
28-1	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for C ₄₉ H ₅₄ N ₈ O ₂ : 786; found: 787 (M+H) ⁺ .
28-2	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for C ₄₄ H ₄₉ N ₇ O ₃ : 723; found: 724 (M+H) ⁺ .

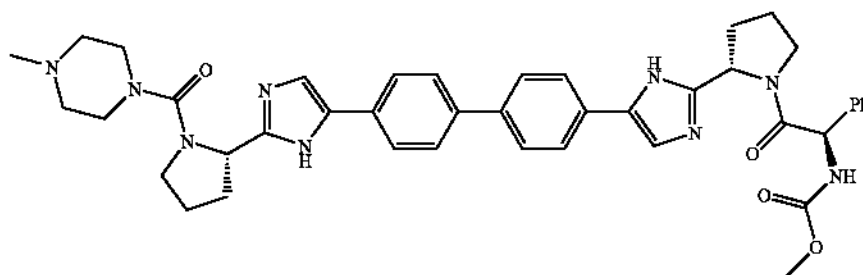
-continued

Example	Compound Name	R	Data
28-3	methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{51}ClN_8O_4$: 850; found: 851 (M + H) ⁺ .
28-4	(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{49}H_{53}ClN_8O_2$: 820; found: 821 (M + H) ⁺ .
28-5	(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{49}H_{53}FN_8O_2$: 804; found: 805 (M + H) ⁺ .

Example 29

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate

[0492]



[0493] 4-Methylpiperazine-1-carbonyl chloride/HCl (11.6 mg, 0.58 mmol) was added to a mixture of 28f (30 mg, 0.049 mmol), triethylamine (15 μ l, 0.11 mmol) and THF (1.0 mL), and stirred at ambient conditions for 1 hour. The volatile component was removed in vacuo, and the residue was puri-

fied by a reverse phase HPLC (H_2O /methanol/TFA) to provide the TFA salt of Example 29 as a light yellow foam (29.3 mg). LC (Cond. 2): RT=1.82 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.38; found 742.49.

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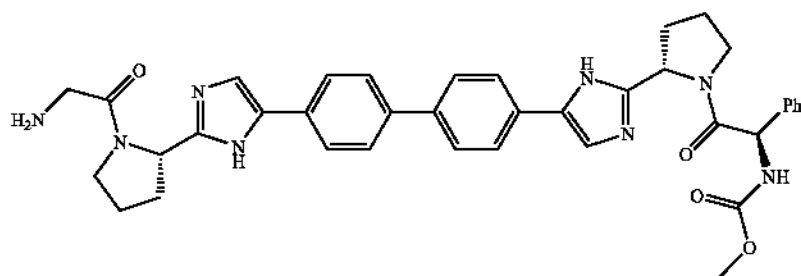
Mar. 12, 2009

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Example 30

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-glycyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) carbamate

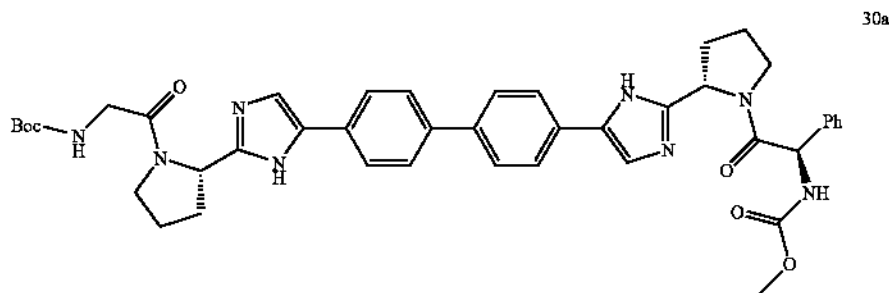
[0494]



Example 30, Step a

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(tert-butoxycarbonyl)glycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) carbamate

[0495] from 1d. LC (Cond. 2): RT=1.81 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₃₈H₄₁N₈O₄: 673.33; found 673.43



[0496] Carbamate 30a was prepared from pyrrolidine 28f and Boc-Glycine by using the procedure described for the preparation of 25a from 1e. LC (Cond. 2): RT=2.12 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₃H₄₉N₈O₆: 773.38; found 773.46

Example 30

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-glycyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) carbamate

[0497] Carbamate 30a was converted to Example 30 according to the procedure described for the preparation of 1e from 1d. LC (Cond. 2): RT=1.81 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₃₈H₄₁N₈O₄: 673.33; found 673.43

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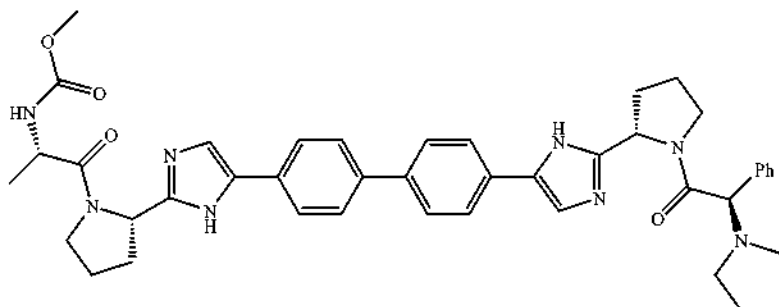
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[0498] HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{41}N_8O_4$: 673.3251; found 673.3262

Example 30-1

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-j-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate

[0499]



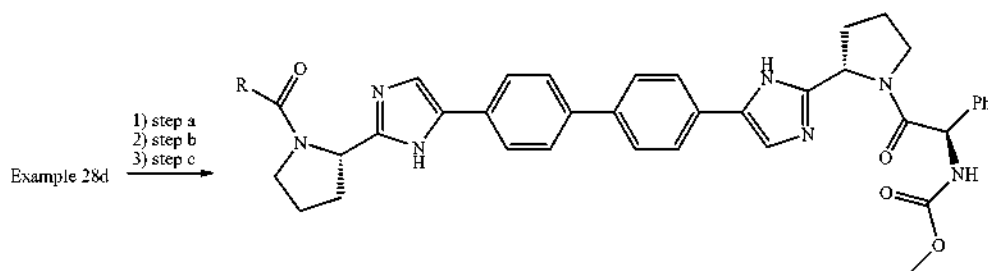
[0500] Example 30-1 was prepared in three steps from Example 28d. Step one: Append Cap-2 using the procedure describing the synthesis of 28e from 28d. Step two: Hydrolyze the Boc carbamate using the procedure describing the synthesis of 28f from 28e. Step three: Append Cap-52 using the procedure describing the synthesis of 28e from 28d. RT=1.70 min (Cond. 1b); >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; found, 743.

50. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; found, 743.4053

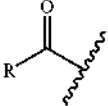
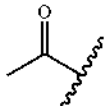
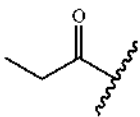
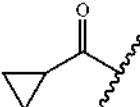
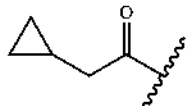
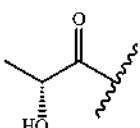
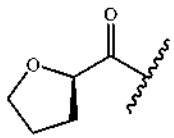
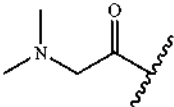
[0501] Substituting the appropriate acid chloride or carboxylic acid into Example 29 or 30, the following compounds (Example 31 to 84-87) were prepared as TFA salts.

Example 31 to 84-88

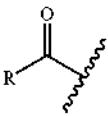
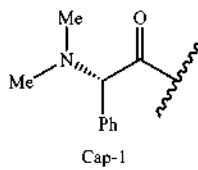
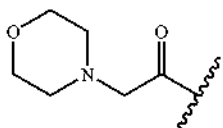
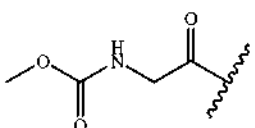
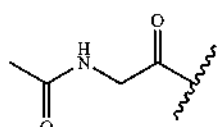
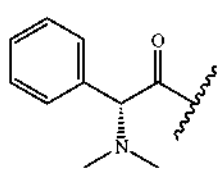
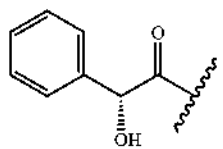
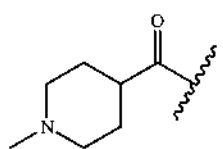
[0502]



step a: Cap with cap-4 as in Example 28
 step b: Same procedure as in conversion of Example 1d to 1e
 step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

Example	Compound Name		Retention time (LC-Condition): homogeneity index MS data
31	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.54 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₀ N ₇ O ₄ : 658.31; found 658.42; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₀ N ₇ O ₄ : 658.3142; found 658.3135
32	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-propionyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.57 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₂ N ₇ O ₄ : 672.33; found 672.46; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₂ N ₇ O ₄ : 672.3298; found 672.3299
33	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclopropylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.59 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₂ N ₇ O ₄ : 684.33; found 684.44; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₂ N ₇ O ₄ : 684.3298; found 684.3324
34	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.61 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₂ N ₇ O ₄ : 698.35; found 698.48; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₂ N ₇ O ₄ : 698.3455; found 698.3489
35	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.54 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₂ N ₇ O ₅ : 688.33; found 688.47
36	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.59 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₄ N ₇ O ₅ : 714.34; found 714.49; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₄ N ₇ O ₅ : 714.3404; found 714.3430
37	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.48 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₅ N ₈ O ₄ : 701.36; found 701.49; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₅ N ₈ O ₄ : 701.3564; found 701.3553

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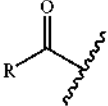
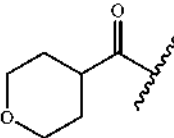
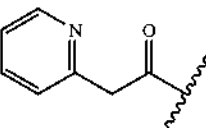
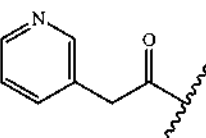
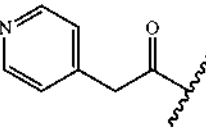
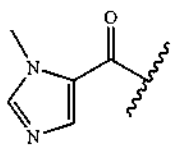
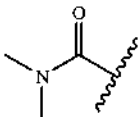
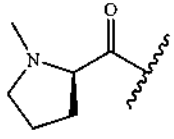
Example	Compound Name		Retention time (LC-Condition): homogeneity index MS data
38	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-1	1.20 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₄₉ N ₈ O ₄ : 777.39; found 777.61; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₄₉ N ₈ O ₄ : 777.3877; found 777.3909
39	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.79 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₅ : 743.37; found 743.49; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₅ : 743.3669; found 743.3672
40	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(methoxycarbonylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₃ N ₈ O ₆ : 731.33; found 731.42; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₃ N ₈ O ₆ : 731.3306; found 731.3333
41	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetylglucyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.86 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₃ N ₈ O ₅ : 715.34; found 715.49; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₃ N ₈ O ₅ : 715.3356; found 715.3369
42	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.85 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₄₉ N ₈ O ₄ : 777.39; found 777.56
43	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.96 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₃ N ₇ O ₅ : 750.34; found 750.51; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₃ N ₇ O ₅ : 750.3404; found 750.3437
44	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-4-piperidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.78 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₉ N ₈ O ₄ : 741.39; found 741.55; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₉ N ₈ O ₄ : 741.3877; found 741.3893

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Example	Compound Name		Retention time (LC-Condition): homogeneity index MS data
45	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)carbamate		1.87 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₆ N ₇ O ₅ : 728.36; found 728.52; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₆ N ₇ O ₅ : 728.3560; found 728.3587
46	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₃ N ₈ O ₄ : 735.34; found 735.51; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₃ N ₈ O ₄ : 735.3407; found 735.3416
47	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)carbamate		1.76 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₃ N ₈ O ₄ : 735.34; found 735.52
48	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)carbamate		1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₃ N ₈ O ₄ : 735.34; found 735.50; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₃ N ₈ O ₄ : 735.3407; found 735.3405
49	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₂ N ₉ O ₄ : 724.34; found 724.51; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₂ N ₉ O ₄ : 724.3360; found 724.3380
50	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(dimethylcarbamoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₃ N ₈ O ₄ : 687.34; found 687.49; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₃ N ₈ O ₄ : 687.3407; found 687.3414
51	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-methyl-D-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.79 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₄ : 727.37; found 727.34; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₄ : 727.3720; found 727.3719

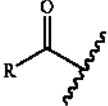
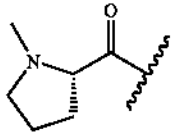
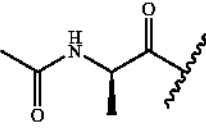
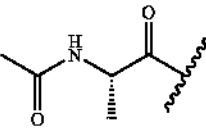
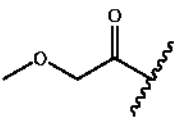
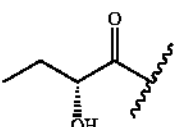
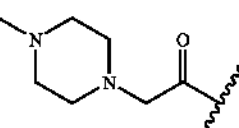
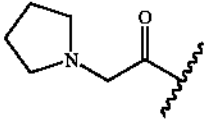
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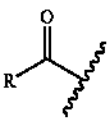
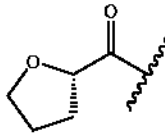
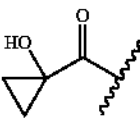
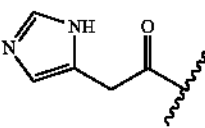
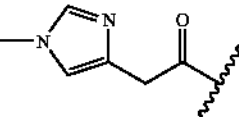
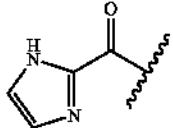
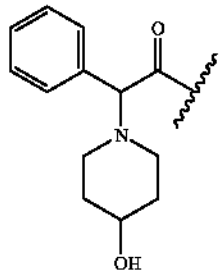
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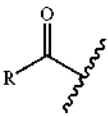
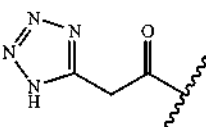
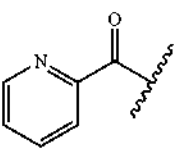
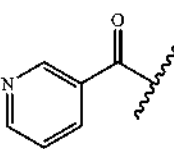
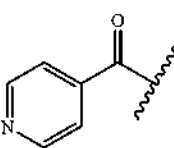
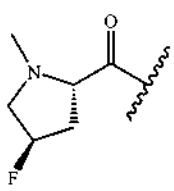
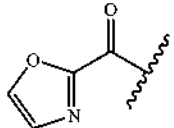
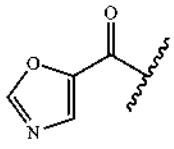
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
52	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-methyl-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 enantiomer of Cap-10	1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₄ : 727.37; found 727.33; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₄ : 727.3720; found 727.3738
53	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₅ N ₈ O ₅ : 729.35; found 729.33; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₅ N ₈ O ₅ : 729.3513; found 729.3530
54	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.87 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₅ N ₈ O ₅ : 729.35; found 729.33
55	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(methoxyacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.89 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₂ N ₇ O ₅ : 688.32; found 688.28; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₂ N ₇ O ₅ : 688.3247; found 688.3231
56	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxybutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₄ N ₇ O ₅ : 702.34; found 702.30; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₄ N ₇ O ₅ : 702.3404; found 702.3393
57	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₀ N ₉ O ₄ : 756.40; found 756.36; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₀ N ₉ O ₄ : 756.3986; found 756.3965
58	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pyrrolidinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.82 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₄ : 727.37; found 727.33; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₄ : 727.3720; found 727.3696

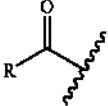
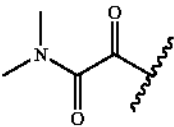
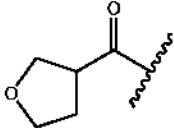
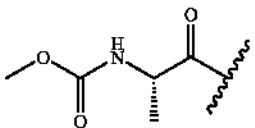
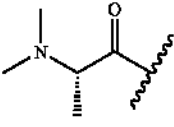
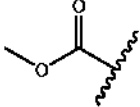
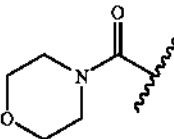
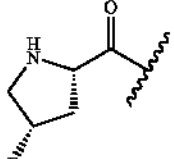
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
59	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.94 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₃ N ₇ O ₅ : 714.34; found 714.24
60	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-hydroxycyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.93 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₂ N ₇ O ₅ : 700.32; found 700.23; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₂ N ₇ O ₅ : 700.3247; found 700.3265
61	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₂ N ₉ O ₄ : 724.34; found 724.21; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₂ N ₉ O ₄ : 724.3360; found 724.3365
62	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.85 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₄ N ₉ O ₄ : 738.35; found 738.22; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₄ N ₉ O ₄ : 738.3516; found 738.3539
63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-2-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.95 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₁ N ₉ O ₄ : 710.32; found 710.17
64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-hydroxy-1-piperidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-8 A single diastereomer	1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₉ H ₅₃ N ₉ O ₅ : 833.41; found 833.32; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₉ H ₅₃ N ₉ O ₅ : 833.4139; found 833.4163

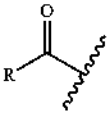
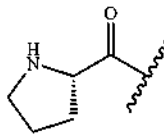
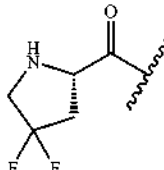
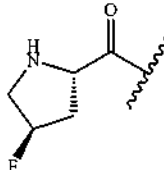
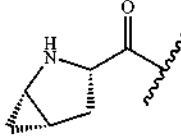
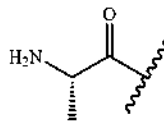
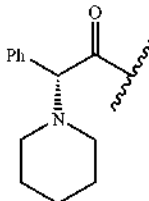
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Example	Compound Name		Retention time (LC-Condition): homogeneity index MS data
65	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-tetrazol-5-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₀ N ₁₁ O ₄ : 726.33; found 726.22; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₀ N ₁₁ O ₄ : 726.3265; found 726.3290
67	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-pyridinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		2.03 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₁ N ₈ O ₄ : 721.33; found 721.31; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₁ N ₈ O ₄ : 721.3251; found 721.3247
68	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₁ N ₈ O ₄ : 721.33; found 721.31; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₁ N ₈ O ₄ : 721.3251; found 721.3226
69	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-isonicotinoyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.89 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₁ N ₈ O ₄ : 721.33; found 721.29; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₁ N ₈ O ₄ : 721.3251; found 721.3251
70	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-1-methyl-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-11	1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₆ FN ₈ O ₄ : 745.36; found 745.27; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₆ FN ₈ O ₄ : 745.3626; found 745.3658
71	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.97 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₃₉ N ₈ O ₅ : 711.30; found 711.27
72	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-5-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.95 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₃₉ N ₈ O ₅ : 711.30; found 711.27; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₃₉ N ₈ O ₅ : 711.3043; found 711.3078

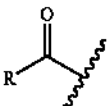
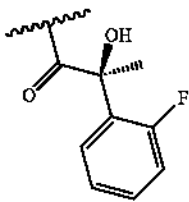
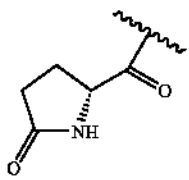
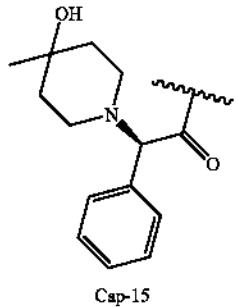
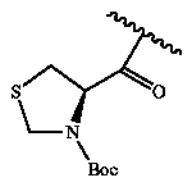
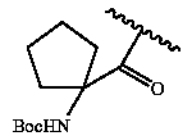
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
73	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(oxo)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₃ N ₈ O ₅ : 715.34; found 715.40
74	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahydro-3-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₄ N ₇ O ₅ : 714.34; found 714.39; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₄ N ₇ O ₅ : 714.3404; found 714.3433
75	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-12	1.94 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₅ N ₈ O ₆ : 745.35 found 745.34; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₅ N ₈ O ₆ : 745.3462; found 745.3486
76	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₄ : 715.37; found 715.35; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₄ : 715.3720; found 715.3737
77	methyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		1.97 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₀ N ₇ O ₅ : 674.31; found 674.66; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₀ N ₇ O ₅ : 674.3091; found 674.3110
78	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.95 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₅ N ₈ O ₅ : 729.35; found 729.40; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₅ N ₈ O ₅ : 729.3513; found 729.3502
79	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4S)-4-fluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₄ FN ₈ O ₄ : 731.84; found 731.26

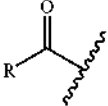
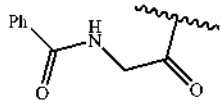
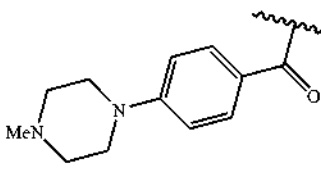
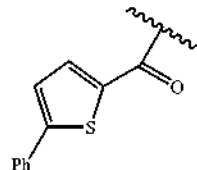
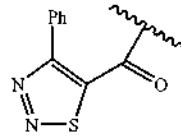
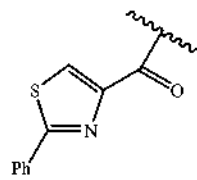
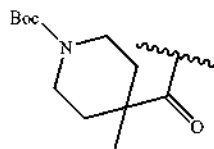
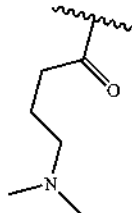
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Example	Compound Name		Retention time (LC-Condition): homogeneity index MS data
80	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-L-prolyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₅ N ₉ O ₄ : 713.36; found 713.36; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₅ N ₉ O ₄ : 713.3564; found 713.3563
81	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4,4-difluoro-L-prolyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.88 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₃ F ₂ N ₉ O ₄ : 749.34; found 749.31; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₃ F ₂ N ₉ O ₄ : 749.3375; found 749.3390
82	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.83 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₄ FN ₉ O ₄ : 731.35; found 731.37; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₄ FN ₉ O ₄ : 731.3470; found 731.3502
83	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1S,3S,5S)-2-azabicyclo[3.1.0]hex-3-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.82 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₅ N ₉ O ₄ : 725.36; found 725.39; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₅ N ₉ O ₄ : 725.3564; found 725.3574
84	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-L-alanyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.82 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₃ N ₉ O ₄ : 687.34; found 687.32; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₃ N ₉ O ₄ : 687.3407; found 687.3435
84-1	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 Cap-14	¹ HNMR (400 MHz, CD ₃ OD) δ 7.90-7.85 (m, 9 H), 7.81-7.79 (m, 1 H), 7.63-7.57 (m, 5 H), 7.45-7.32 (m, 6 H), 5.51 (s, 1 H), 5.45 (s, 1 H), 5.33-5.29 (m, 2 H), 4.06-4.01 (m, 2 H), 3.63 (d, J = 4.04 Hz, 3 H), 3.59-3.50 (m, 2 H), 3.19-3.12 (m, 1 H), 3.07-3.01 (m, 1 H), 2.93-2.76 (m, 2 H), 2.57-2.51 (m, 1 H), 2.40-2.31 (m, 2 H), 2.22-2.06 (m, 4 H), 2.00-1.90 (m, 3 H), 1.84-1.64 (m, 4 H), 1.52-1.43 (m, 2 H); LCMS: Anal. Calcd. for C ₄₉ H ₅₂ N ₉ O ₄ : 816; found: 817 (M + H) ⁺ .

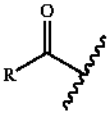
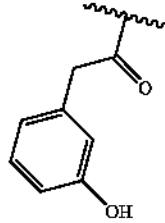
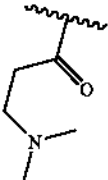
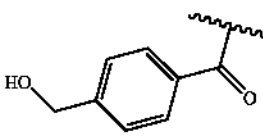
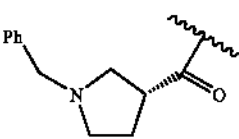
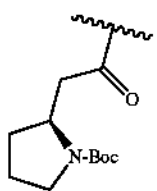
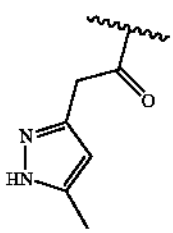
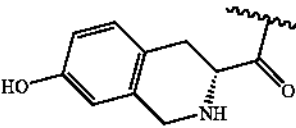
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-2	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(2-fluorophenyl)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		¹ HNMR (400 MHz, CD ₃ OD) δ 7.89-7.85 (m, 8 H), 7.81-7.73 (2 H), 7.67-7.65 (m, 1 H), 7.45-7.26 (m, 7H), 7.13-7.08 (m, 1 H), 6.94-6.89 (m, 0.5 H), 6.72-6.67 (0.5 H), 6.09-6.07 (m, 0.4 H), 5.51 (s, 1 H), 5.32-5.25 (m, 1.6 H), 4.08-3.95 (m, 2 H), 3.85-3.79 (1 H), 3.64-3.63 (m, 3 H), 3.56-3.49 (1 H), 3.09-3.03 (m, 1 H), 2.59-2.50 (m, 1 H), 2.42-2.33 (m, 2 H), 2.21-2.00 (m, 6 H), 1.82-1.74 (m, 1 H), 1.66 (d, J = 4.55 Hz, 3 H); LCMS: Anal. Calcd. for C ₄₉ H ₄₆ FN ₇ O ₈ : 781; found: 782 (M + H) ⁺ .
84-3	methyl ((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(5-oxo-D-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₄₂ N ₈ O ₈ : 726; found: 727 (M + H) ⁺ .
84-4	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-hydroxy-4-methyl-1-piperidinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-15	LCMS: Anal. Calcd. for C ₅₀ H ₅₄ N ₈ O ₈ : 846; found: 847 (M + H) ⁺ .
84-5	tert-butyl (4R)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-thiazolidine-3-carboxylate		LCMS: Anal. Calcd. for C ₄₅ H ₅₀ N ₈ O ₈ S: 830; found: 831 (M + H) ⁺ .
84-6	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-((tert-butoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 BocHN	LCMS: Anal. Calcd. for C ₄₇ H ₅₄ FN ₈ O ₈ : 826; found: 827 (M + H) ⁺ .

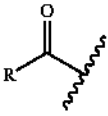
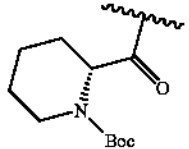
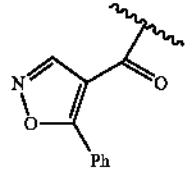
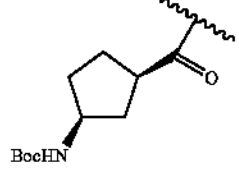
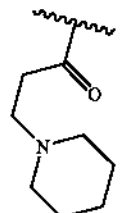
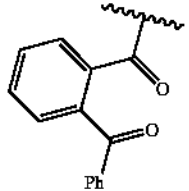
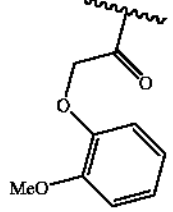
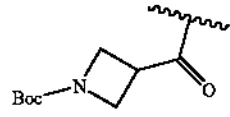
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Example	Compound Name		Retention time (LC-Condition): homogeneity index MS data
84-7	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-benzoylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₄ N ₈ O ₅ : 776; found: 777 (M + H) ⁺ .
84-8	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-methyl-1-piperazinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₁ N ₉ O ₅ : 817; found: 818 (M + H) ⁺ .
84-9	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-2-thienyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₄₃ N ₇ O ₄ S: 801; found: 802 (M + H) ⁺ .
84-10	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₁ N ₉ O ₄ S: 803; found: 804 (M + H) ⁺ .
84-11	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-phenyl-1,3-thiazol-4-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₄₃ N ₈ O ₄ S: 802; found: 803 (M + H) ⁺ .
84-12	tert-butyl 4-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-4-methyl-1-piperidinecarboxylate		LCMS: Anal. Calcd. for C ₄₈ H ₅₆ N ₈ O ₆ : 840; found: 841 (M + H) ⁺ .
84-13	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₄₈ N ₈ O ₄ : 728; found: 729 (M + H) ⁺ .

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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-14	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-hydroxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₃ N ₇ O ₅ : 749; found: 750 (M + H) ⁺ .
84-15	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethyl-beta-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₄₆ N ₈ O ₄ : 714; found: 715 (M + H) ⁺ .
84-16	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(hydroxymethyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₃ N ₇ O ₅ : 749; found: 750 (M + H) ⁺ .
84-17	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₀ N ₈ O ₄ : 802; found: 803 (M + H) ⁺ .
84-18	tert-butyl (2S)-2-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)-1-pyrrolidinecarboxylate		LCMS: Anal. Calcd. for C ₄₇ H ₅₄ N ₈ O ₆ : 826; found: 827 (M + H) ⁺ .
84-19	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₄₃ N ₉ O ₄ : 737; found: 738 (M + H) ⁺ .
84-20	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3S)-7-hydroxy-1,2,3,4-tetrahydro-3-isoquinoliny)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₄₆ N ₈ O ₅ : 790; found: 791 (M + H) ⁺ .

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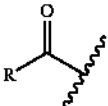
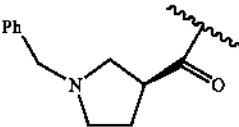
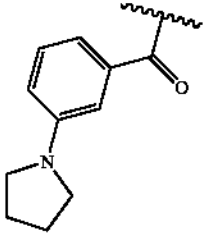
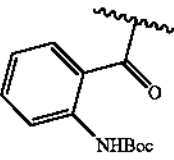
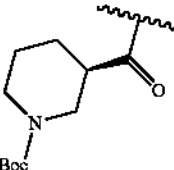
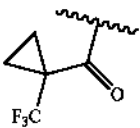
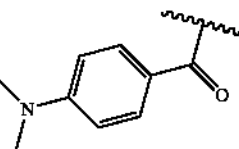
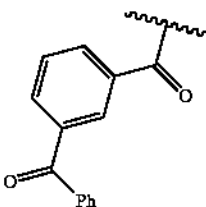
Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-21	tert-butyl (2R)-2-(2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for C ₄₇ H ₅₄ N ₈ O ₆ : 826; found: 827 (M + H) ⁺ .
84-22	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-4-isoxazolyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₄₂ N ₈ O ₅ : 786; found: 787 (M + H) ⁺ .
84-23	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1R,3S)-3-((tert-butoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₅₄ N ₈ O ₆ : 826; found: 827 (M + H) ⁺ .
84-24	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₅₀ N ₈ O ₄ : 754; found: 755 (M + H) ⁺ .
84-25	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzoylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₅₀ H ₄₅ N ₇ O ₅ : 823; found: 824 (M + H) ⁺ .
84-26	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₅ N ₇ O ₆ : 779; found: 780 (M + H) ⁺ .
84-27	tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		LCMS: Anal. Calcd. for C ₄₅ H ₅₀ N ₈ O ₆ : 798; found: 799 (M + H) ⁺ .

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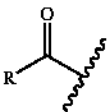
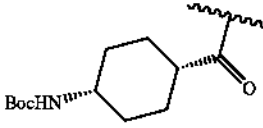
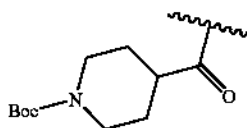
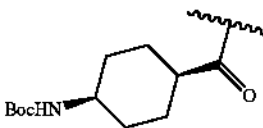
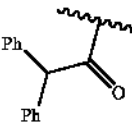
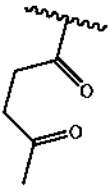
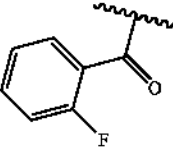
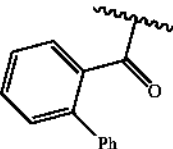
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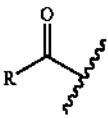
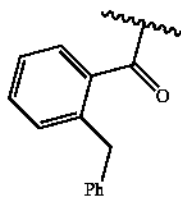
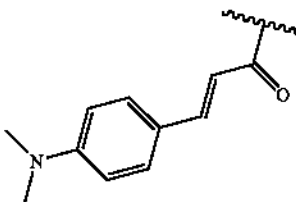
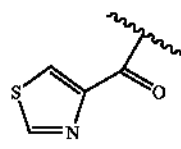
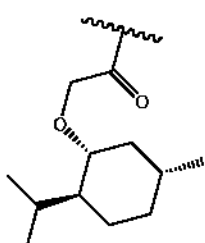
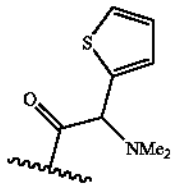
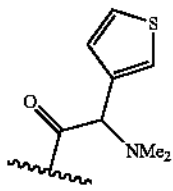
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-28	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₀ N ₈ O ₄ : 802; found: 803 (M + H) ⁺ .
84-29	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pyrrolidinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₄₈ N ₈ O ₄ : 788; found: 789 (M + H) ⁺ .
84-30	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-(tert-butoxycarbonyl)amino)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₉ H ₅₀ N ₈ O ₆ : 834; found: 835 (M + H) ⁺ .
84-31	tert-butyl (3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for C ₄₇ H ₅₄ N ₈ O ₆ : 826; found: 827 (M + H) ⁺ .
84-32	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₃₀ F ₃ N ₇ O ₄ : 751; found: 752 (M + H) ⁺ .
84-33	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimethylamino)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₆ N ₈ O ₄ : 762; found: 763 (M + H) ⁺ .
84-34	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-benzoylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₅₀ H ₄₅ N ₇ O ₅ : 823; found: 824 (M + H) ⁺ .

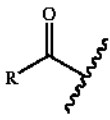
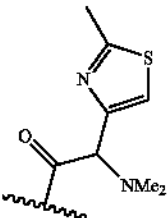
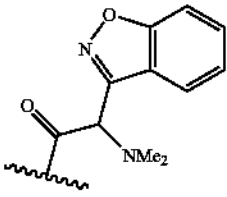
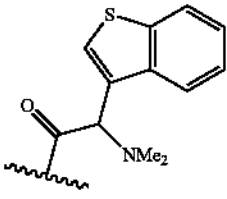
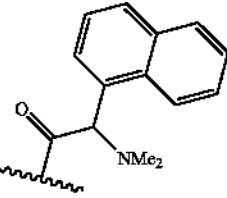
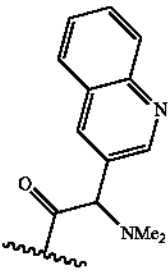
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-35	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(tert-butoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₆ N ₈ O ₆ : 840; found: 841 (M + H) ⁺ .
84-36	tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for C ₄₇ H ₅₄ N ₈ O ₆ : 826; found: 827 (M + H) ⁺ .
84-37	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(tert-butoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₆ N ₈ O ₆ : 840; found: 841 (M + H) ⁺ .
84-38	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₅₀ H ₄₇ N ₇ O ₄ : 809; found: 810 (M + H) ⁺ .
84-39	methyl ((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-oxopentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₄₃ N ₇ O ₅ : 713; found: 714 (M + H) ⁺ .
84-40	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₃ H ₄₀ FN ₇ O ₄ : 737; found: 738 (M + H) ⁺ .
84-41	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-biphenylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₉ H ₄₅ N ₇ O ₄ : 795; found: 796 (M + H) ⁺ .

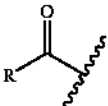
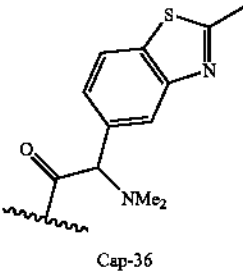
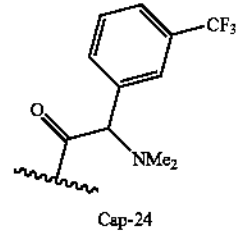
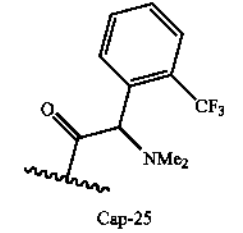
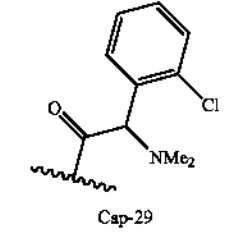
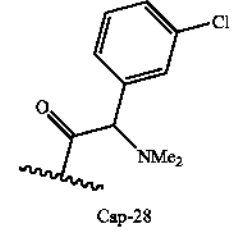
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-42	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₅₀ H ₄₇ N ₇ O ₄ : 809; found: 810 (M + H) ⁺ .
84-43	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2E)-3-(4-(dimethylamino)phenyl)-2-propenoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₄₈ N ₈ O ₄ : 788; found: 789 (M + H) ⁺ .
84-44	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₀ H ₃₈ N ₈ O ₄ S: 726; found: 727 (M + H) ⁺ .
84-45	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₇ N ₇ O ₅ : 811; found: 812 (M + H) ⁺ .
84-46	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-32	LCMS: Anal. Calcd. for C ₄₄ H ₄₆ N ₈ O ₄ S: 782; found: 782 (M + H) ⁺ .
84-47	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-33	LCMS: Anal. Calcd. for C ₄₄ H ₄₆ N ₈ O ₄ S: 782; found: 782 (M + H) ⁺ .

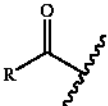
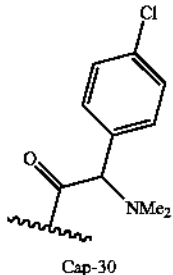
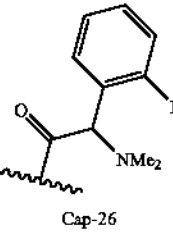
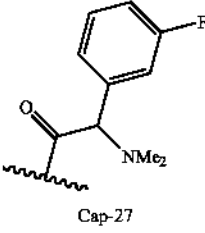
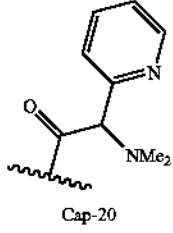
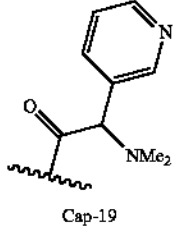
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-48	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₇ N ₉ O ₄ S: 797; found: 798 (M + H) ⁺ .
84-49	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-yl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₄₇ N ₉ O ₅ : 817; found: 818 (M + H) ⁺ .
84-50	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzothiophen-3-yl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₄₈ N ₉ O ₄ S: 832; found: 833 (M + H) ⁺ .
84-51	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-naphthyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₅₀ H ₅₀ N ₈ O ₄ : 826; found: 827 (M + H) ⁺ .
84-52	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-quinoliny)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₉ H ₄₉ N ₉ O ₄ : 827; found: 828 (M + H) ⁺ .

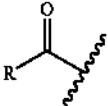
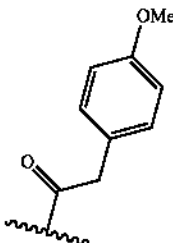
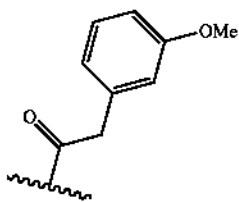
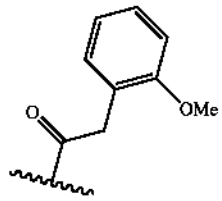
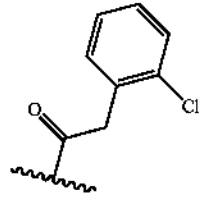
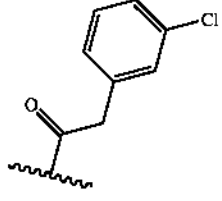
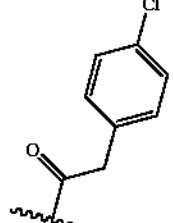
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-53	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-methyl-1,3-benzothiazol-5-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-36	LCMS: Anal. Calcd. for C ₄₈ H ₄₈ N ₆ O ₄ S: 847; found: 848 (M + H) ⁺ .
84-54	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-(trifluoromethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-24	LCMS: Anal. Calcd. for C ₄₇ H ₄₇ F ₃ N ₆ O ₄ : 844; found: 845 (M + H) ⁺ .
84-55	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-(trifluoromethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-25	LCMS: Anal. Calcd. for C ₄₇ H ₄₇ F ₃ N ₆ O ₄ : 844; found: 845 (M + H) ⁺ .
84-56	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-29	LCMS: Anal. Calcd. for C ₄₆ H ₄₇ ClN ₆ O ₄ : 810; found: 811 (M + H) ⁺ .
84-57	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Cap-28	LCMS: Anal. Calcd. for C ₄₆ H ₄₇ ClN ₆ O ₄ : 810; found: 811 (M + H) ⁺ .

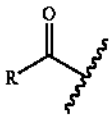
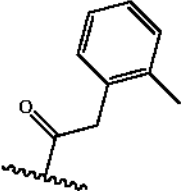
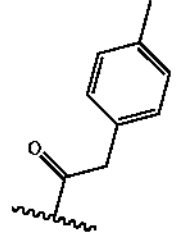
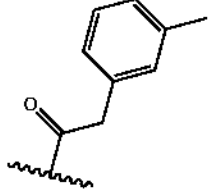
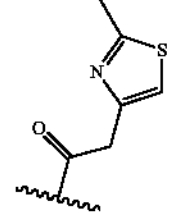
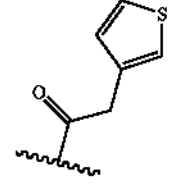
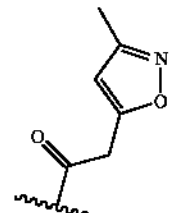
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-58	methyl ((1R)-2-((2S)-2-(5-(4'-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 <p data-bbox="743 787 801 808">Cap-30</p>	LCMS: Anal. Calcd. for C ₄₆ H ₄₇ ClN ₉ O ₄ : 810; found: 811 (M + H) ⁺ .
84-59	methyl ((1R)-2-((2S)-2-(5-(4'-fluorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 <p data-bbox="743 1060 801 1081">Cap-26</p>	LCMS: Anal. Calcd. for C ₄₆ H ₄₇ FN ₉ O ₄ : 794; found: 795 (M + H) ⁺ .
84-60	methyl ((1R)-2-((2S)-2-(5-(3'-fluorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 <p data-bbox="743 1333 801 1354">Cap-27</p>	LCMS: Anal. Calcd. for C ₄₆ H ₄₇ FN ₉ O ₄ : 794; found: 795 (M + H) ⁺ .
84-61	methyl ((1R)-2-((2S)-2-(5-(4'-pyridinyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 <p data-bbox="743 1606 801 1627">Cap-20</p>	LCMS: Anal. Calcd. for C ₄₅ H ₄₇ N ₉ O ₄ : 777; found: 778 (M + H) ⁺ .
84-62	methyl ((1R)-2-((2S)-2-(5-(3'-pyridinyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 <p data-bbox="743 1879 801 1900">Cap-19</p>	LCMS: Anal. Calcd. for C ₄₅ H ₄₇ N ₉ O ₄ : 777; found: 778 (M + H) ⁺ .

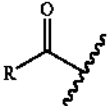
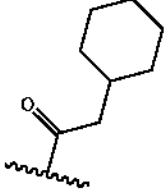
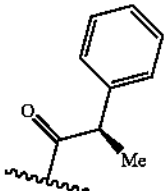
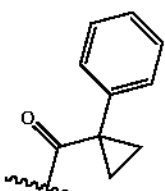
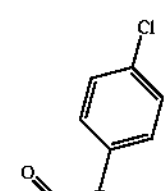
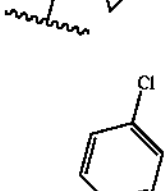
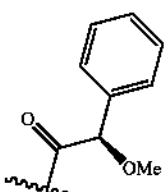
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₅ N ₇ O ₅ : 763; found: 764 (M + H) ⁺ .
84-64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₅ N ₇ O ₅ : 763; found: 764 (M + H) ⁺ .
84-65	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₅ N ₇ O ₅ : 763; found: 764 (M + H) ⁺ .
84-66	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₂ ClN ₇ O ₄ : 767; found: 768 (M + H) ⁺ .
84-67	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₂ ClN ₇ O ₄ : 767; found: 768 (M + H) ⁺ .
84-68	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₂ ClN ₇ O ₄ : 767; found: 768 (M + H) ⁺ .

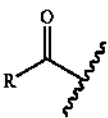
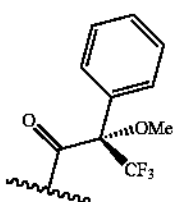
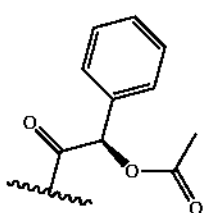
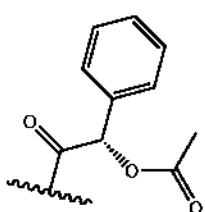
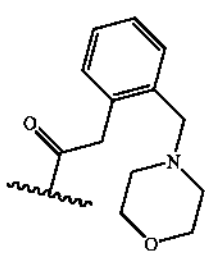
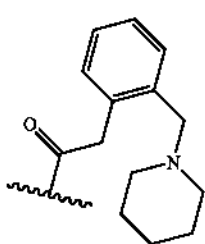
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-69	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₅ N ₇ O ₄ : 747; found: 748 (M + H) ⁺ .
84-70	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₅ N ₇ O ₄ : 747; found: 748 (M + H) ⁺ .
84-71	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₅ N ₇ O ₄ : 747; found: 748 (M + H) ⁺ .
84-72	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₄₂ N ₈ O ₄ S: 754; found: 755 (M + H) ⁺ .
84-73	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₄₁ N ₇ O ₄ S: 739; found: 740 (M + H) ⁺ .
84-74	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-methyl-5-isoxazolyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₄₂ N ₈ O ₅ : 738; found: 739 (M + H) ⁺ .

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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-75	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclohexylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₉ N ₇ O ₄ : 739; found: 740 (M + H) ⁺ .
84-76	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₅ N ₇ O ₄ : 747; found: 748 (M + H) ⁺ .
84-77	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₄₅ N ₇ O ₄ : 759; found: 760 (M + H) ⁺ .
84-78	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-(4-chlorophenyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₄₄ ClN ₇ O ₄ : 793; found: 794 (M + H) ⁺ .
84-79	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-(4-chlorophenyl)-2-methylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₄₆ ClN ₇ O ₄ : 795; found: 796 (M + H) ⁺ .
84-80	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₄₅ N ₇ O ₅ : 763; found: 764 (M + H) ⁺ .

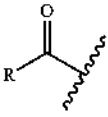
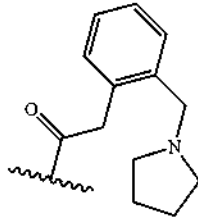
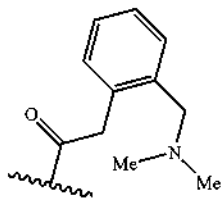
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-81	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{44}F_3N_7O_5$: 831; found: 832 (M + H) ⁺ .
84-82	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_6$: 791; found: 792 (M + H) ⁺ .
84-83	(1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_6$: 791; found: 792 (M + H) ⁺ .
84-84	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-1-((2-((4-morpholinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_5$: 832; found: 833 (M + H) ⁺ .
84-85	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-1-((2-((4-morpholinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_4$: 830; found: 831 (M + H) ⁺ .

Cap-41

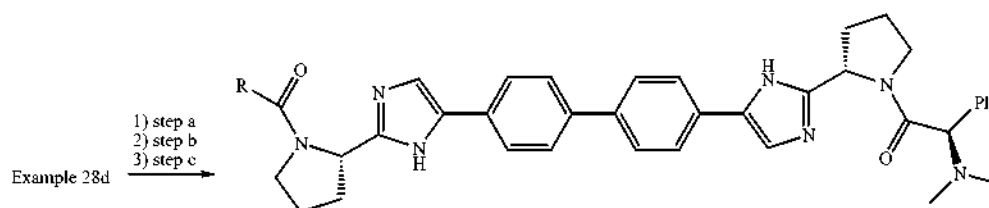
Cap-42

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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
84-86	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-((1-pyrrolidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₉ H ₅₂ N ₈ O ₄ : 816; found: 816 (M + H) ⁺ .
84-87	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-((dimethylamino)methyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₅₀ N ₈ O ₄ : 790; found: 791 (M + H) ⁺ .

Examples 85-94

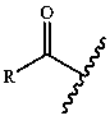
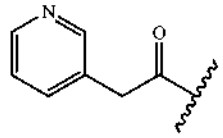
[0503]



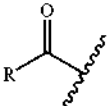
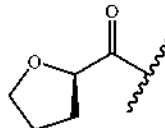
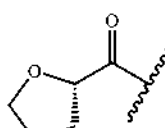
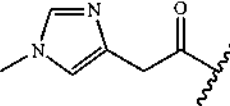
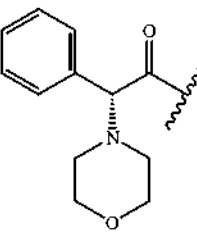
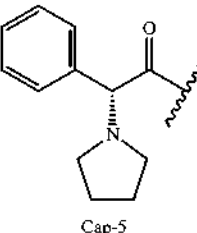
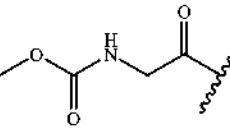
step a: Cap with cap-1 as in Example 28

step b: Same procedure as in conversion of Example 1d to 1e

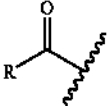
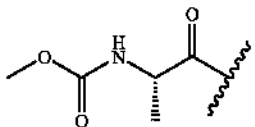
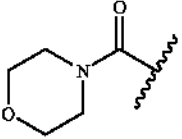
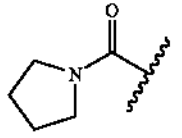
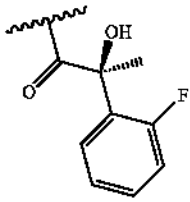
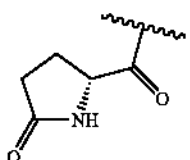
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
85	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.64 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₅ N ₈ O ₂ : 705.37; found 705.43; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₅ N ₈ O ₂ : 705.3665; found 705.3675

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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
86	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.73 minutes (Cond. 2); >98% LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₆ N ₇ O ₃ : 684.37; found 684.44; HRMS Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₆ N ₇ O ₃ : 684.3662; found 684.3671
87	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.12 minutes (Cond. 2); >98% LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₆ N ₇ O ₃ : 684.37; found 684.68; HRMS Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₆ N ₇ O ₃ : 684.3662; found 684.3692
88	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.66 minutes (Cond. 2); >98% LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₆ N ₉ O ₂ : 708.38; found 708.36
89	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morpholinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	 Cap-6	1.70 minutes (Cond. 2); >98% LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₅ N ₈ O ₄ : 701.36; found 701.34; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₅ N ₈ O ₄ : 701.3564; found 701.3576
90	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 Cap-5	1.80 minutes (Cond. 2); >98% LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₅₃ N ₈ O ₂ : 773.43; found 773.42; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₅₃ N ₈ O ₂ : 773.4291; found 773.4309
91	methyl 2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.66 minutes (Cond. 2); >98% LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₆ N ₉ O ₂ : 708.38; found 708.36; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₆ N ₉ O ₂ : 708.3774; found 708.3770

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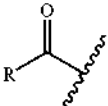
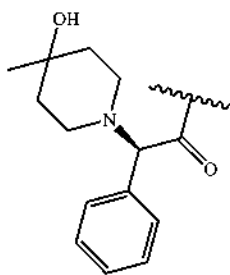
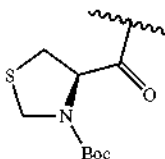
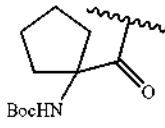
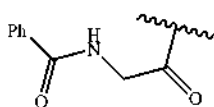
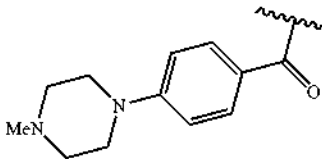
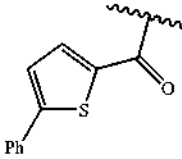
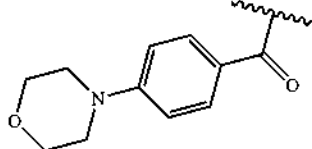
Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
92	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Cap-12	1.73 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₄ : 715.37; found 715.41; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₄ : 715.3720; found 715.3729
93	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.76 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₃ : 699.38; found 699.45; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₃ : 699.3771; found 699.3803
94	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pyrrolidinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.86 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₂ : 683.38; found 683.46; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₂ : 683.3822; found 683.3835
94-1	(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-(2-fluorophenyl)-1-oxo-2-propanol		¹ HNMR (400 MHz, CD ₃ OD) δ 7.90-7.84 (m, 9 H), 7.79-7.73 (m, 2 H), 7.67-7.65 (m, 1 H), 7.63-7.52 (m, 5 H), 7.39-7.36 (m, 1 H), 7.30-7.26 (m, 1 H), 7.13-7.08 (m, 1 H), 6.93-6.88 (m, 0.5 H), 6.72-6.67 (m, 0.5 H), 5.51 (s, 0.2 H), 5.46 (s, 0.8 H), 5.33-5.30 (m, 1 H), 5.28-5.24 (m, 1 H), 4.05-3.94 (m, 2 H), 3.84-3.73 (m, 1 H), 3.69-3.55 (m, 1 H), 3.21-3.04 (m, 2 H), 2.79 (br s, 6 H), 2.39-2.33 (m, 2 H), 2.21-1.93 (m, 5 H), 1.65 (d, J = 4.55 Hz, 3 H); LCMS: Anal. Calcd. for C ₄₅ H ₄₆ FN ₇ O ₃ : 751; found: 752 (M + H) ⁺ .
94-2	(5R)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-pyrrolidinone		LCMS: Anal. Calcd. for C ₄₁ H ₄₄ N ₈ O ₃ : 696; found: 697 (M + H) ⁺ .

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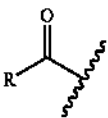
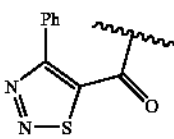
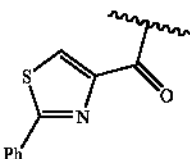
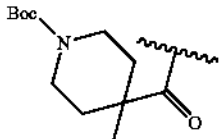
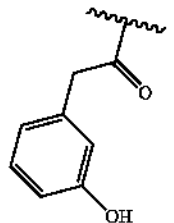
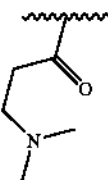
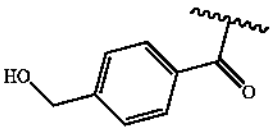
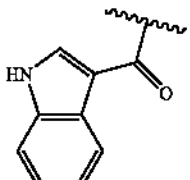
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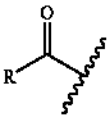
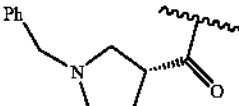
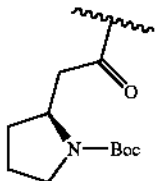
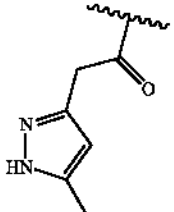
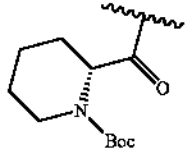
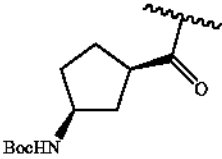
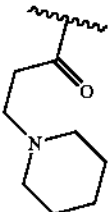
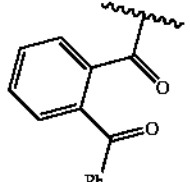
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
94-3	1-((1R)-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-4-methyl-4-piperidinol		LCMS: Anal. Calcd. for C ₅₀ H ₅₆ N ₈ O ₃ : 816; found: 817 (M + H) ⁺ .
94-4	tert-butyl (4R)-4-((1S)-2-(5-(4'-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-thiazolidine-3-carboxylate		LCMS: Anal. Calcd. for C ₄₅ H ₅₂ N ₈ O ₄ S: 800; found: 801 (M + H) ⁺ .
94-5	tert-butyl (1-((1S)-2-(5-(4'-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl) carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₅₆ N ₈ O ₄ : 796; found: 797 (M + H) ⁺ .
94-6	N-(2-((2S)-2-(5-(4'-((2R)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)benzamide		LCMS: Anal. Calcd. for C ₄₅ H ₄₆ N ₈ O ₃ : 746; found: 747 (M + H) ⁺ .
94-7	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-((2S)-1-((4-(4-methyl-1-piperazinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)ethanamine		LCMS: Anal. Calcd. for C ₄₈ H ₅₃ N ₉ O ₂ : 787; found: 788 (M + H) ⁺ .
94-8	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((5-phenyl-2-thienyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for C ₄₇ H ₄₅ N ₇ O ₂ S: 771; found: 772 (M + H) ⁺ .
94-9	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-((2S)-1-((4-(4-morpholinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)ethanamine		LCMS: Anal. Calcd. for C ₄₇ H ₅₀ N ₈ O ₃ : 774; found: 775 (M + H) ⁺ .

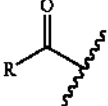
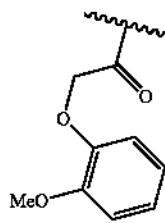
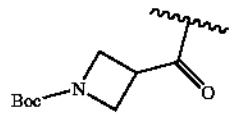
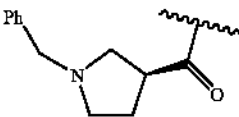
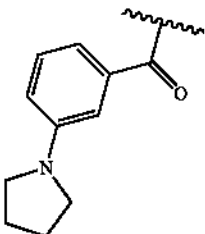
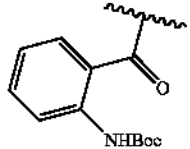
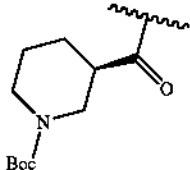
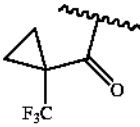
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
94-10	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for C ₄₅ H ₄₃ N ₉ O ₂ S: 773; found: 774 (M + H) ⁺ .
94-11	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-phenyl-1,3-thiazol-4-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for C ₄₆ H ₄₄ N ₈ O ₂ S: 772; found: 773 (M + H) ⁺ .
94-12	tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-4-methyl-1-piperidinecarboxylate		LCMS: Anal. Calcd. for C ₄₈ H ₅₈ N ₈ O ₄ : 810; found: 811 (M + H) ⁺ .
94-13	3-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)phenol		LCMS: Anal. Calcd. for C ₄₄ H ₄₅ N ₇ O ₃ : 719; found: 720 (M + H) ⁺ .
94-14	3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-3-oxo-1-propanamine		LCMS: Anal. Calcd. for C ₄₁ H ₄₈ N ₈ O ₂ : 684; found: 685 (M + H) ⁺ .
94-15	4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)methanol		LCMS: Anal. Calcd. for C ₄₄ H ₄₅ N ₇ O ₃ : 719; found: 720 (M + H) ⁺ .
94-16	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1H-indol-3-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₅ H ₄₄ N ₈ O ₂ : 728; found: 729 (M + H) ⁺ .

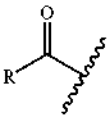
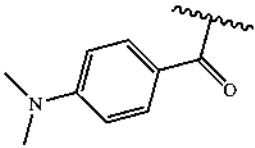
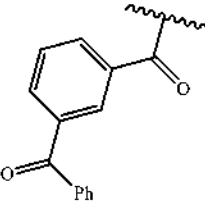
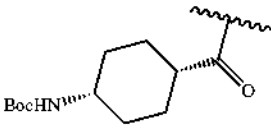
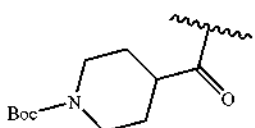
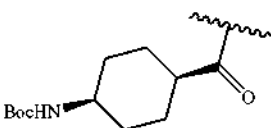
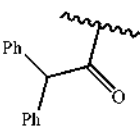
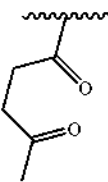
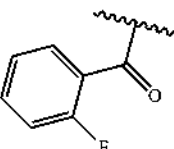
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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
94-17	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₈ H ₅₂ N ₈ O ₂ : 772; found: 773 (M + H) ⁺ .
94-18	tert-butyl (2S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)-1-pyrrolidinecarboxylate		LCMS: Anal. Calcd. for C ₄₇ H ₅₆ N ₈ O ₄ : 796; found: 797 (M + H) ⁺ .
94-19	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₂ H ₄₅ N ₉ O ₂ : 707; found: 708 (M + H) ⁺ .
94-20	tert-butyl (2R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for C ₄₇ H ₅₆ N ₈ O ₄ : 796; found: 797 (M + H) ⁺ .
94-21	tert-butyl ((1S,3R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₅₆ N ₈ O ₄ : 796; found: 797 (M + H) ⁺ .
94-22	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for C ₄₄ H ₅₂ N ₈ O ₂ : 724; found: 725 (M + H) ⁺ .
94-23	(2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-1-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)phenyl)methanone		LCMS: Anal. Calcd. for C ₅₀ H ₄₇ N ₇ O ₃ : 793; found: 794 (M + H) ⁺ .

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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
94-24	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₅ H ₄₇ N ₇ O ₄ : 749; found: 750 (M + H) ⁺ .
94-25	tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		LCMS: Anal. Calcd. for C ₄₅ H ₅₂ N ₈ O ₄ : 768; found: 769 (M + H) ⁺ .
94-26	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₈ H ₅₂ N ₈ O ₂ : 772; found: 773 (M + H) ⁺ .
94-27	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pyrrolidinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for C ₄₇ H ₅₀ N ₈ O ₂ : 758; found: 759 (M + H) ⁺ .
94-28	tert-butyl 2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₂ N ₈ O ₄ : 804; found: 805 (M + H) ⁺ .
94-29	tert-butyl 3(R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for C ₄₇ H ₅₆ N ₈ O ₄ : 796; found: 797 (M + H) ⁺ .
94-30	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for C ₄₁ H ₄₃ F ₃ N ₇ O ₂ : 721; found: 722 (M + H) ⁺ .

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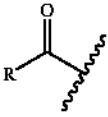
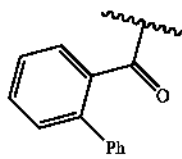
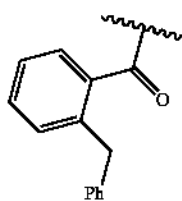
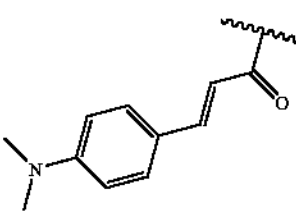
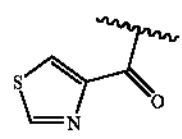
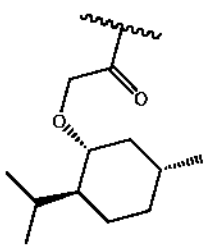
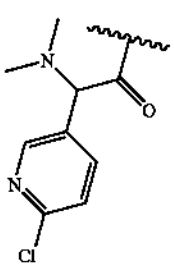
Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
94-31	4-(((2S)-2-(5-(4'-(2-(2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-N,N-dimethylamine		LCMS: Anal. Calcd. for C ₄₅ H ₄₈ N ₈ O ₂ : 732; found: 733 (M + H) ⁺ .
94-32	(3-(((2S)-2-(5-(4'-(2-(2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)phenyl)methanone		LCMS: Anal. Calcd. for C ₅₀ H ₄₇ N ₇ O ₃ : 793; found: 794 (M + H) ⁺ .
94-33	tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-(2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₈ N ₈ O ₄ : 810; found: 811 (M + H) ⁺ .
94-34	tert-butyl 4-(((2S)-2-(5-(4'-(2-(2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for C ₄₇ H ₅₆ N ₈ O ₄ : 796; found: 797 (M + H) ⁺ .
94-35	tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-(2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₈ N ₈ O ₄ : 810; found: 811 (M + H) ⁺ .
94-36	(1R)-2-(2-(2S)-2-(5-(4'-(2-(2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₅₀ H ₄₆ N ₇ O ₂ : 779; found: 780 (M + H) ⁺ .
94-37	5-((2S)-2-(5-(4'-(2-(2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-5-oxo-2-pentanone		LCMS: Anal. Calcd. for C ₄₁ H ₄₅ N ₇ O ₃ : 683; found: 684 (M + H) ⁺ .
94-38	(1R)-2-(2-(2S)-2-(5-(4'-(2-(2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₃ H ₄₃ FN ₇ O ₂ : 707; found: 708 (M + H) ⁺ .

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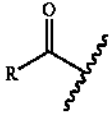
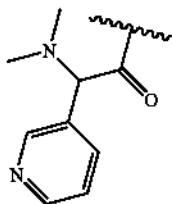
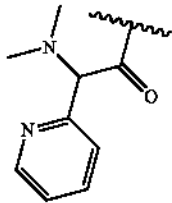
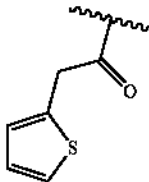
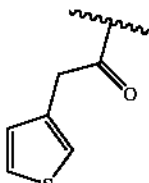
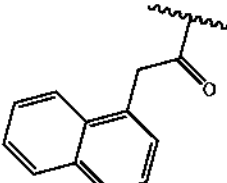
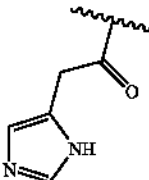
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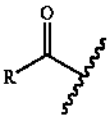
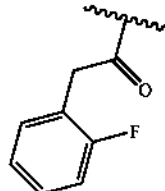
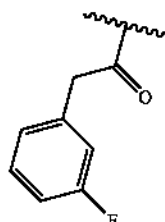
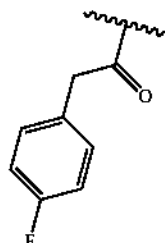
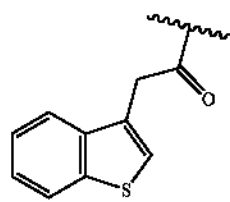
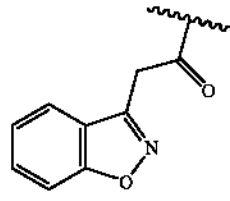
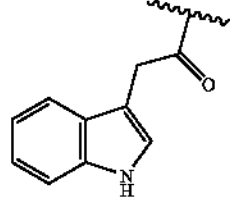
Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
94-39	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-biphenylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₉ H ₄₇ N ₇ O ₂ : 765; found: 766 (M + H) ⁺ .
94-40	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₅₀ H ₄₉ N ₇ O ₂ : 779; found: 780 (M + H) ⁺ .
94-41	4-((1E)-3-((2S)-2-(5-(4'-(2-((2S)-1-(2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-propen-1-yl)-N,N-dimethylaniline		LCMS: Anal. Calcd. for C ₄₇ H ₅₀ N ₈ O ₂ : 758; found: 759 (M + H) ⁺ .
94-42	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for C ₄₀ H ₄₀ N ₈ O ₂ S: 696; found: 697 (M + H) ⁺ .
94-43	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₈ H ₅₉ N ₇ O ₅ : 781; found: 782 (M + H) ⁺ .
94-44	1-(6-chloro-3-pyridinyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine		LCMS: Anal. Calcd. for C ₄₅ H ₄₈ ClN ₉ O ₂ : 781; found: 782 (M + H) ⁺ .

Cap-21

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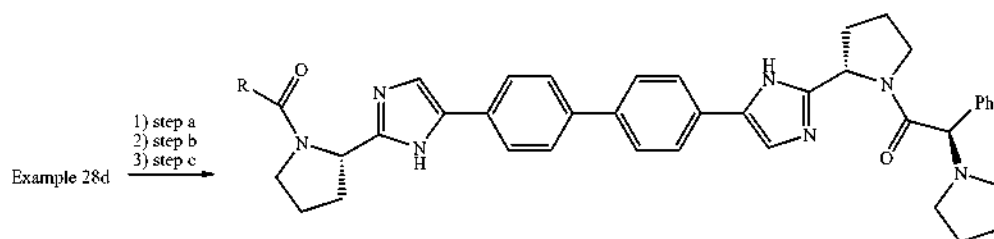
Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
94-45	2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-1-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-(3-pyridinyl)ethanamine	 <p data-bbox="741 737 797 758">Cap-19</p>	LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 (M + H) ⁺ .
94-46	2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-1-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-(2-pyridinyl)ethanamine	 <p data-bbox="741 1010 797 1031">Cap-20</p>	LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 (M + H) ⁺ .
94-47	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{42}H_{43}N_7O_2S$: 709; found: 710 (M + H) ⁺ .
94-48	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{42}H_{43}N_7O_2S$: 709; found: 710 (M + H) ⁺ .
94-49	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-naphthylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{48}H_{47}N_7O_2$: 753; found: 754 (M + H) ⁺ .
94-50	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{41}H_{43}N_9O_2$: 693; found: 694 (M + H) ⁺ .

-continued

Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
94-51	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₄ H ₄₄ FN ₇ O ₂ : 721; found: 722 (M + H) ⁺ .
94-52	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₄ H ₄₄ FN ₇ O ₂ : 721; found: 722 (M + H) ⁺ .
94-53	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₄ H ₄₄ FN ₇ O ₂ : 721; found: 722 (M + H) ⁺ .
94-54	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzothiophen-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₆ H ₄₅ N ₇ O ₂ S: 759; found: 760 (M + H) ⁺ .
94-55	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₅ H ₄₄ N ₈ O ₃ : 744; found: 745 (M + H) ⁺ .
94-56	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for C ₄₆ H ₄₆ N ₈ O ₂ : 742; found: 743 (M + H) ⁺ .

Examples 95-103

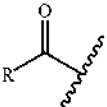
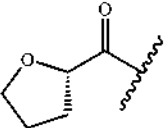
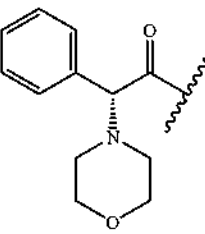
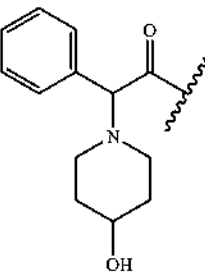
[0504]



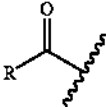
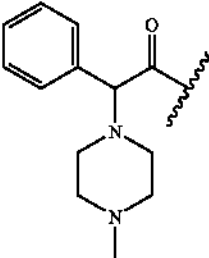
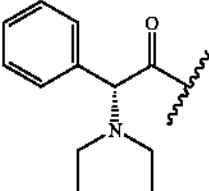
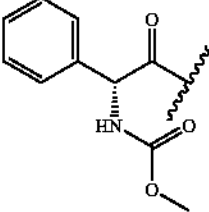
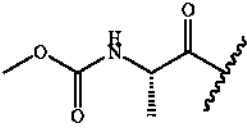
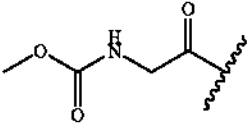
step a: Cap w/cap-5 as in Example 28

step b: Same procedure as in conversion of Example 1d to 1e

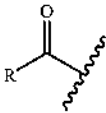
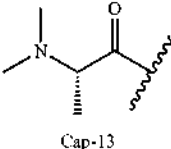
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
95	2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol		1.16 minutes (Cond. 1); >98%; LC/MS Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₈ N ₇ O ₃ : 710.38; found 710.60
96	4-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)morpholine	 Cap-6	1.82 minutes (Cond. 1); >98%; LC/MS Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₅ N ₈ O ₃ : 815.44; found 815.45; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₅ N ₈ O ₃ : 815.4397; found 815.4395
97	1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinol	 A single diastereomer Cap-8	1.79 minutes (Cond. 2); >98%; LC/MS Anal. Calcd. for [M + H] ⁺ C ₅₁ H ₅₇ N ₈ O ₃ : 829.46; found 829.43; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₁ H ₅₇ N ₈ O ₃ : 829.4554; found 829.4585

-continued

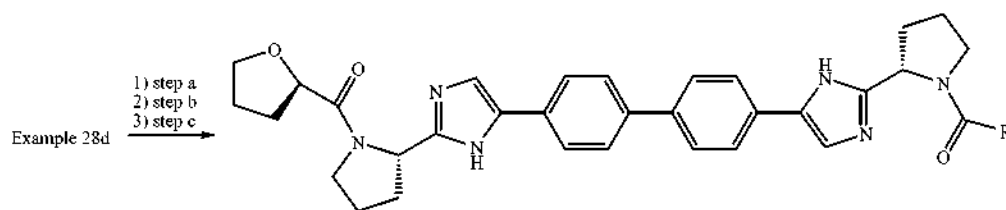
Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
98	1-methyl-4-((2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-2-phenyl-2-(1-pyrrolidinyl)scetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine		1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₁ H ₅₈ N ₉ O ₂ : 828.47; found 828.45; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₁ H ₅₈ N ₉ O ₂ : 828.4713; found 828.4722
	A single diastereomer Cap-17c		
99	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)scetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.86 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₇ N ₈ O ₂ : 801.46; found 801.44; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₇ N ₈ O ₂ : 801.4604; found 801.4595
	Cap-2		
100	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)scetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.93 minutes (Cond. 2); LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₅₁ N ₈ O ₄ : 803.40; found 803.47; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₅₁ N ₈ O ₄ : 803.4033; found 803.4058
	Cap-4		
101	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)scetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.80 minutes (Cond. 2); LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₉ N ₈ O ₄ : 741.39; found 741.33; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₉ N ₈ O ₄ : 741.3877; found 741.3900
	Cap-12		
102	methyl (2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)scetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.80 minutes (Cond. 2); LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₄ : 727.37; found 727.24; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₄ : 727.3720; found 727.3743

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Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
103	(2S)-N,N-dimethyl-1-oxo-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-propanamine	 Cap-13	1.69 minutes (Cond. 2); LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₁ N ₈ O ₂ : 711.41; found 711.37; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₁ N ₈ O ₂ : 711.4135; found 711.4154

Examples 103-1 to 103-12

[0505]

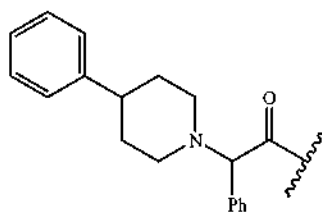


step a: Cap with (R)-2-tetrahydrofuroic acid as in Example 28

step b: Same procedure as in the conversion of Example 1d to 1e

step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

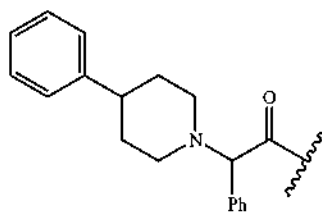
103-1 1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-phenylpiperidine



Diastereomer 1
Cap-17d

RT = 4.80 minutes;
HPLC Xterra 4.6 × 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid; B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C₅₀H₅₃N₇O₃ 800.03
Found: 800.49
(M + H)⁺

103-2 1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-phenylpiperidine

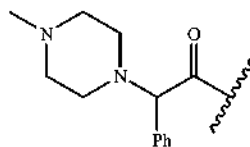


Diastereomer 2
Cap-17d

RT = 4.59 minutes;
HPLC Xterra 4.6 × 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid; B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C₅₀H₅₃N₇O₃ 800.03
Found: 800.48
(M + H)⁺

-continued

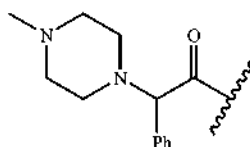
- 103-3 1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)piperazine



Diastereomer 1
Cap-17c

RT = 3.36;
HPLC Xterra 4.6 × 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C₄₄H₅₀N₈O₃ 738.94
Found: 739.49
(M + H)⁺

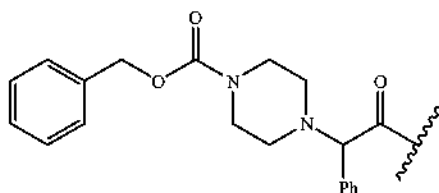
- 103-4 1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)piperazine



Diastereomer 2
Cap-17c

RT = 3.47 minutes;
HPLC Xterra 4.6 × 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C₄₄H₅₀N₈O₃ 738.94
Found: 739.51
(M + H)⁺

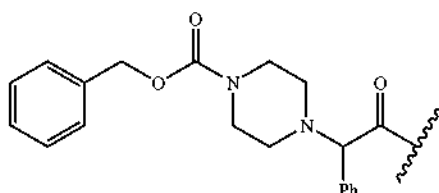
- 103-5 benzyl 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-1-piperazinecarboxylate



Diastereomer 1
Cap-17a

RT = 5.00 minutes;
HPLC Xterra 4.6 × 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C₅₁H₅₄N₈O₅ 859.05
Found: 859.51
(M + H)⁺

- 103-6 benzyl 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-1-piperazinecarboxylate

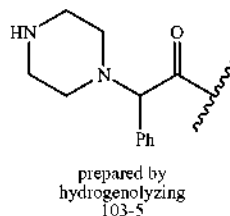


Diastereomer 2
Cap-17a

RT = 5.10 minutes;
HPLC Xterra 4.6 × 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: C₅₁H₅₄N₈O₅ 859.05
Found: 859.49
(M + H)⁺

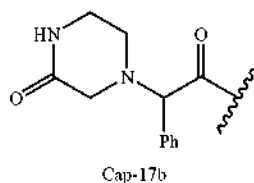
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- 103-7 1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)piperazine



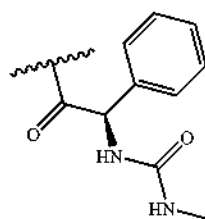
RT = 3.61 minutes;
HPLC Xterra 4.6 ×
50 mm,
0 to 100% B over 10
minutes, one
minute hold time,
A = 90% water, 10%
methanol, 0.2%
phosphoric acid, B =
10% water, 90%
methanol, 0.2%
phosphoric acid;
LCMS: Anal. Calcd.
for: C₄₃H₄₈N₈O₃
724.91
Found: 725.47
(M + H)⁺

- 103-8 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-2-piperazinone



RT = 3.97;
HPLC Xterra 4.6 ×
50 mm, 0 to 100% B
over 10 minutes, one
minute hold time,
A = 90% water, 10%
methanol, 0.2%
phosphoric acid, B =
10% water, 90%
methanol, 0.2%
phosphoric acid;
LCMS: Anal. Calcd.
for: C₄₃H₄₆N₈O₄
738.90
Found: 739.56
(M + H)⁺

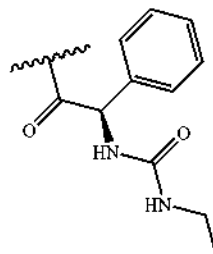
- 103-9 1-methyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)urea



HPLC XTERRA C-18
4.6 ×
30 mm, 0 to 100% B
over 4 minutes, 1
minute hold time,
A = 90% water, 10%
methanol, 0.2%
H₃PO₄, B =
10% water, 90%
methanol, 0.2%
H₃PO₄, RT = 1.81
minutes, 96%
homogeneity index.;
LCMS: Anal. Calcd.
for C₄₁H₄₄N₈O₄:
712.84; found:
713.37 (M + H)⁺;
HRMS: Anal. Calcd.
for C₄₁H₄₅N₈O₄
713.3564; found:
713.3564 (M + H)⁺.

-continued

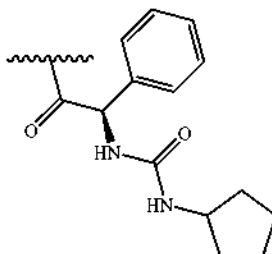
103-10 1-ethyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea



employed Cap-46

HPLC XTERRA C-18
4.6 ×
30 mm, 0 to 100% B
over 2 minutes, 1
minute hold time,
A = 90% water, 10%
methanol, 0.2%
H₃PO₄, B =
10% water, 90%
methanol, 0.2%
H₃PO₄, RT = 1.88
minutes, 95%
homogeneity index;
LCMS: Anal. Calcd.
for C₄₂H₄₆N₈O₄:
726.87; found:
727.71 (M + H)⁺;
HRMS: Anal. Calcd.
for C₄₂H₄₇N₈O₄
727.3720; found:
727.3695 (M + H)⁺.

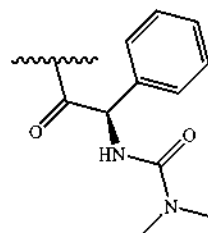
103-11 1-cyclopentyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea



employed Cap-48

HPLC XTERRA C-18
4.6 ×
30 mm, 0 to 100% B
over 2 minutes, 1
minute hold time,
A = 90% water, 10%
methanol, 0.2%
H₃PO₄, B =
10% water, 90%
methanol, 0.2%
H₃PO₄, RT = 2.11
minutes, 96%
homogeneity index;
LCMS: Anal. Calcd.
for C₄₅H₅₀N₈O₄:
766.93; found:
767.45 (M + H)⁺;
HRMS: Anal. Calcd.
for C₄₅H₅₁N₈O₄
767.4033; found:
767.4032 (M + H)⁺.

103-12 1,1-dimethyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea

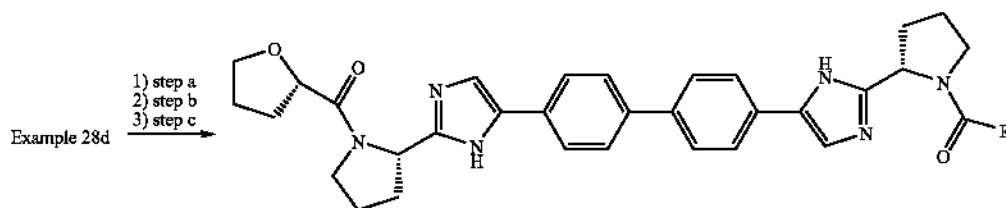


employed Cap-47

HPLC XTERRA C-18
4.6 ×
30 mm, 0 to 100% B
over 2 minutes, 1
minute hold time,
A = 90% water, 10%
methanol, 0.2%
H₃PO₄, B =
10% water, 90%
methanol, 0.2%
H₃PO₄, RT = 1.87
minutes, 97%
homogeneity index;
LCMS: Anal. Calcd.
for C₄₂H₄₆N₈O₄:
726.87; found:
727.38 (M + H)⁺;
HRMS: Anal. Calcd.
for C₄₂H₄₇N₈O₄
727.3720; found:
727.3723 (M + H)⁺.

Examples 104-107

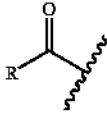
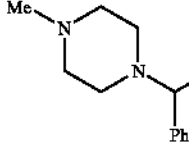
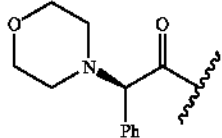
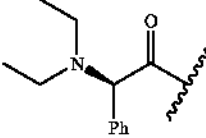
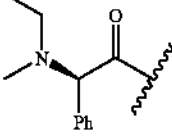
[0506]



step a: Cap with (S)-2-tetrahydrofuroic acid as in Example 28

step b: Same procedure as in conversion of Example 1d to Example 1e

step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
104	1-methyl-4-((2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 A single diastereomer Cap-17c	1.12 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₁ N ₈ O ₃ : 739.41; found 739.63; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₁ N ₈ O ₃ : 739.4084; found 739.4054
105	4-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)morpholine	 Cap-6	1.13 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₈ N ₇ O ₄ : 726.38; found 726.63; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₈ N ₇ O ₄ : 726.3768; found 726.3803
106	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 Cap-2	1.12 minutes (Cond. 1); >97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₀ N ₇ O ₃ : 712.40; found 712.45; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₀ N ₇ O ₃ : 712.3975; found 712.3998
107	(1R)-N-ethyl-N-methyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 Cap-3	1.10 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₈ N ₇ O ₃ : 698.38; found 698.45; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₈ N ₇ O ₃ : 698.3819; found 698.3823

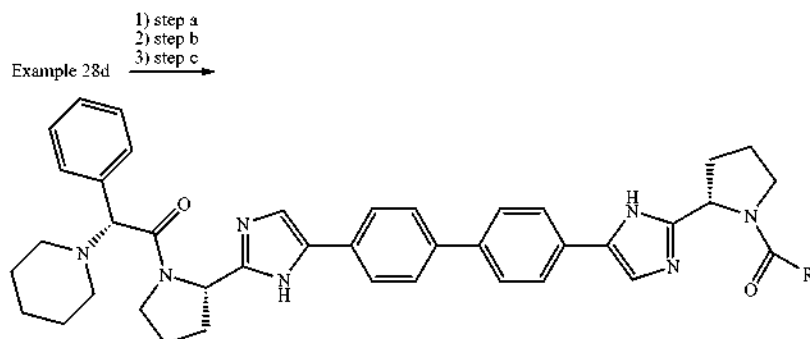
US 2009/0068140 A1

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Mar. 12, 2009

Examples 107-1 to 107-30

[0507]



step a: Cap with cap-14 as in Example 28

step b: Same procedure as in the conversion of Example 1d to 1e

step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

Example

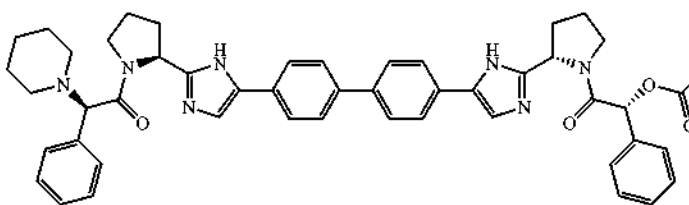
Number Compound Name

Structure

Data

Example
107-1

(1S)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl acetate



¹HNMR (400 MHz, CDCl₃) δ 7.63-7.85 (m, 8H), 7.48-7.54 (m, 2H), 7.26-7.46 (m, 7H), 6.94-7.17 (m, 3H), 6.22 and 6.18 (s, 1H, rotamers, 1:1), 5.99 and 5.68 (s, 1H, rotamers, 1:1), 5.61 and 5.54 (d, J = 7.8 Hz, 1H, rotamers, 1:1), 5.20-5.23 and 5.10-5.13 (m, 1H, rotamers, 1:1), 4.46 and 4.43 (s, 1H, rotamers, 1:1), 3.97-4.06 (m, 1H), 3.89-3.93 and 3.78-3.84 (m, 1H, rotamers, 1:1), 3.63-3.72 and 3.46-3.60 (m, 1H, rotamers, 1:1), 3.23-3.32 (m, 2H), 2.41-2.59 (m, 4H), 2.13-2.26 (m, 2H), 2.11 and 2.10 (s, 3H, rotamers, 1:1), 2.05-2.09 (m, 2H), 1.97-1.98 (m, 1H), 1.82-1.90 (m, 1H), 1.58 (br s, 4H), 1.45 (br s, 2H); LCMS: Anal. Calcd. for C₄₉H₅₁N₇O₄: 801; found: 802 (M + H)⁺.

-continued

Example Number	Compound Name	Structure	Data
Example 107-2	4-methyl-1-((1R)-2-oxo-1-phenyl-2-((2S)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinol		LCMS: Anal. Calcd. for $C_{53}H_{60}N_8O_3$; 856; found: 857 (M + H) ⁺ .
Example 107-3	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{46}H_{36}FN_7O_2$; 747; found: 748 (M + H) ⁺ .
Example 107-4	N,N-dimethyl-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)aniline		LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_2$; 772; found: 773 (M + H) ⁺ .
Example 107-5	5-oxo-5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-pentanone		LCMS: Anal. Calcd. for $C_{44}H_{40}N_7O_3$; 723; found: 724 (M + H) ⁺ .
Example 107-6	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{53}H_{53}N_7O_2$; 819; found: 820 (M + H) ⁺ .

-continued

Example Number	Compound Name	Structure	Data
Example 107-7	1-(3-oxo-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)propyl)piperidine		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_2$: 764; found: 765 ($M + H$) ⁺ .
Example 107-8	1-((1R)-2-((2S)-2-(5-(4'-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_2$: 789; found: 790 ($M + H$) ⁺ .
Example 107-9	tert-butyl 4-(((2S)-2-(5-(4'-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidine-carboxylate		LCMS: Anal. Calcd. for $C_{50}H_{60}N_8O_4$: 836; found: 837 ($M + H$) ⁺ .
Example 107-10	4-(4-(((2S)-2-(5-(4'-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)morpholine		LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_3$: 814; found: 815 ($M + H$) ⁺ .
Example 107-11	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((1,3-triazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{43}H_{44}N_8O_2S$: 736; found: 737 ($M + H$) ⁺ .

-continued

Example Number	Compound Name	Structure	Data
Example 107-12	tert-butyl 3-(((2S)-2-(5-(4'-(2-(2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_4$: 808; found: 809 (M + H) ⁺ .
Example 107-13	tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-(2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{51}H_{62}N_8O_4$: 850; found: 851 (M + H) ⁺ .
Example 107-14	tert-butyl 4-methyl-4-(((2S)-2-(5-(4'-(2-(2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{51}H_{62}N_8O_4$: 850; found: 851 (M + H) ⁺ .
Example 107-15	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-(2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{44}H_{46}F_3N_7O_2$: 761; found: 762 (M + H) ⁺ .
Example 107-16	1-((1R)-2-(2S)-2-(5-(4'-(2-(2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 (M + H) ⁺ .

-continued

Example Number	Compound Name	Structure	Data
Example 107-17	1-((1R)-2-((2S)-2-(5-(4'-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)-carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) piperidine		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_2$: 812; found: 813 (M + H) ⁺ .
Example 107-18	1-((1R)-2-((2S)-2-(5-(4'-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)-carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) piperidine		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_2$: 812; found: 813 (M + H) ⁺ .
Example 107-19	1-((1R)-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) piperidine		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_3$: 773; found: 774 (M + H) ⁺ .
Example 107-20	1-((1R)-2-((2S)-2-(5-(4'-((2S)-1-((2S)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) piperidine		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_3$: 773; found: 774 (M + H) ⁺ .

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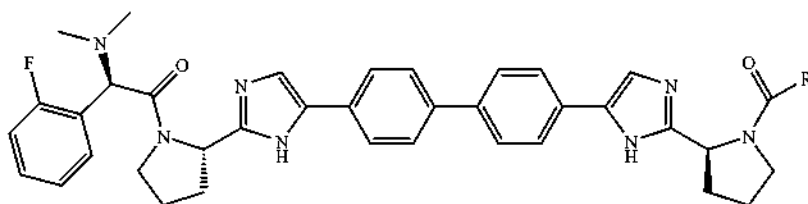
Example Number	Compound Name	Structure	Data
Example 107-21	(1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl acetate		LCMS: Ansl. Calcd. for $C_{49}H_{51}N_7O_4$: 801; found: 802 (M + H) ⁺ .
Example 107-22	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl) piperidine		LCMS: Ansl. Calcd. for $C_{49}H_{51}N_7O_2$: 769; found: 770 (M + H) ⁺ .
Example 107-23	N,N-dimethyl-1-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)phenyl) methanamine		LCMS: Ansl. Calcd. for $C_{50}H_{56}N_8O_2$: 800; found: 801 (M + H) ⁺ .
Example 107-24	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-methyl-5-isoxazolyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) piperidine		LCMS: Ansl. Calcd. for $C_{45}H_{48}N_8O_3$: 748; found: 749 (M + H) ⁺ .
Example 107-25	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) piperidine		LCMS: Ansl. Calcd. for $C_{45}H_{48}N_8O_2S$: 764; found: 765 (M + H) ⁺ .

-continued

Example Number	Compound Name	Structure	Data
Example 107-26	4-(2-(2-oxo-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)benzyl)morpholine		LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_3$: 842; found: 843 (M + H) ⁺ .
Example 107-27	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((2-((1-pyrrolidinyl)methyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_3$: 826; found: 827 (M + H) ⁺ .
Example 107-28	1-((1R)-2-((2S)-2-(5-(4'-((2S)-1-((2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{47}H_{48}FN_7O_2$: 800; found: 801 (M + H) ⁺ .
Example 107-29	1-((1R)-2-((2S)-2-(5-(4'-((2S)-1-((2-(2-acetyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{41}H_{45}FN_7O_2$: 667; found: 668 (M + H) ⁺ .
Example 107-30	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((2-(2-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{45}H_{47}N_7O_2$: 749; found: 750 (M + H) ⁺ .

Example 107-31 to 107-34

[0508]



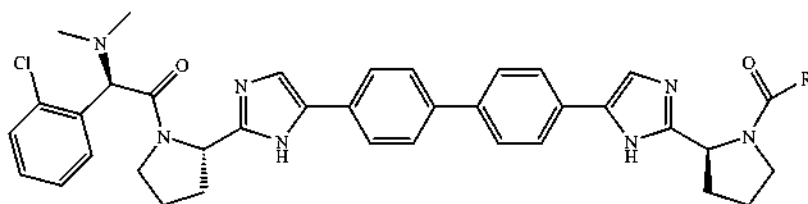
[0509] Examples 107-31 through 107-34 were prepared in similar fashion to example 28. Cap-38 was appended to inter-

mediate 28d, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

Example	Compound Name	Structure	Data
Example 107-31	(1R)-2-((2S)-2-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{46}H_{49}FN_8O_2$: 764; found: 765 (M + H) ⁺ .
Example 107-32	(1R)-1-(2-fluorophenyl)-2-((2S)-2-(5-(4-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine		LCMS: Anal. Calcd. for $C_{45}H_{46}FN_8O_3$: 751; found: 752 (M + H) ⁺ .
Example 107-33	(1R)-2-((2S)-2-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate		LCMS: Anal. Calcd. for $C_{46}H_{46}FN_8O_4$: 779; found: 780 (M + H) ⁺ .
Example 107-34	(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4-(2-((2S)-1-(1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{46}H_{46}FN_7O_2$: 747; found: 748 (M + H) ⁺ .

Example 107-35 to 107-38

[0510]



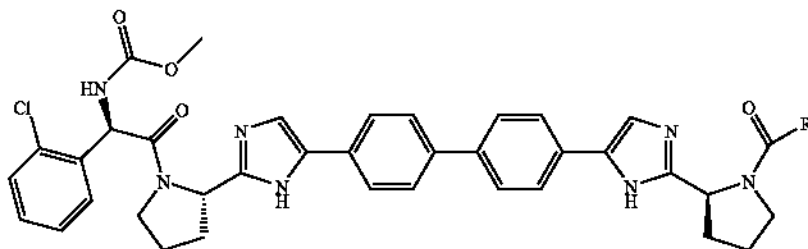
[0511] Examples 107-35 through 107-38 were prepared in similar fashion to example 28. Cap-39 was appended to inter-

mediate 28d, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

Example	Compound Name	Structure	Data
Example 107-35	(1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine		LCMS: Anal. Calcd. for $C_{46}H_{49}ClN_8O_2$: 780; found: 781 ($M + H$) ⁺ .
Example 107-36	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 ($M + H$) ⁺ .
Example 107-37	(1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine		LCMS: Anal. Calcd. for $C_{44}H_{46}ClN_7O_3$: 767; found: 768 ($M + H$) ⁺ .
Example 107-38	(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{41}H_{44}ClN_7O_3$: 717; found: 718 ($M + H$) ⁺ .

Example 107-39 to 107-43

[0512]



[0513] Examples 107-39 through 107-44 were prepared in similar fashion to example 28. Cap-40 was appended to inter-

mediate 28d, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

Example	Compound Name	Structure	Data
Example 107-39	methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl) carbamate		¹ H NMR (400 MHz, CD ₃ OD) δ 7.58-7.77 (m, 8 H), 7.42-7.55 (m, 2 H), 7.19-7.39 (m, 4 H), 5.94 and 5.89 (s, 1 H, rotamers, 1:1), 5.80 and 5.61 (s, 1 H, rotamers, 1:1), 5.43-5.47 and 5.35-5.38 (m, 1 H, rotamers, 1:1), 5.20-5.24 (m, 1 H), 5.15-5.18 (m, 1 H), 4.67-4.70 and 4.39-4.42 (m, 1 H, rotamers, 1:1), 3.92-3.98 (m, 1 H), 3.85-3.90 (m, 1 H), 3.69-3.84 (m, 2 H), 3.64 and 3.63 (s, 3 H, rotamers, 1:1), 3.53-3.59 (m, 1 H), 2.35-2.46 (m, 1 H), 2.21-2.29 (m, 2 H), 2.06-2.17 (m, 3 H), 1.84-2.01 (m, 4 H), 1.66-1.76 and 1.41-1.47 (m, 1 H, rotamers, 1:1); LCMS: Anal. Calcd. for C ₄₁ H ₄₂ ClN ₇ O ₅ : 747; found 748 (M + H) ⁺ .

-continued

Example	Compound Name	Structure	Data
Example 107-40	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 (M + H) ⁺ .
Example 107-41	methyl ((1R)-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(2-chlorophenyl)-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{45}ClN_8O_6$: 840; found: 841 (M + H) ⁺ .
Example 107-42	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(4-hydroxy-4-methyl-1-piperidinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{53}ClN_8O_5$: 880; found: 881 (M + H) ⁺ .
Example 107-43	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{44}ClN_7O_5$: 797; found: 798 (M + H) ⁺ .
Example 107-44	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(2-chlorophenyl)-2-((dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{46}Cl_2N_8O_4$: 844; found: 845 (M + H) ⁺ .

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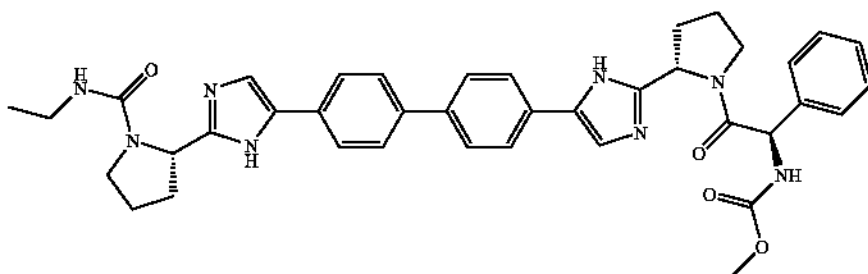
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Example 108

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(ethylcarbamoyl)-2-pyrrolidiny)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidiny)-2-oxo-1-phenylethyl)carbamate

[0514]

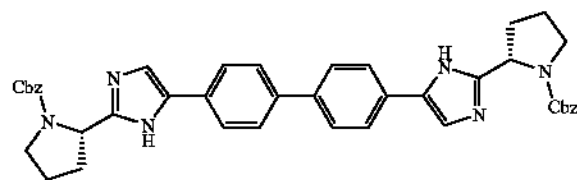


[0515] Ethyl isocyanate (5 μ L, 0.063 mmol) was added to a methanol (1.0 mL) solution of 28f (30 mg, 0.049 mmol) and stirred at ambient condition for 1.8 hours. The residue was treated with 2.0 M NH_3 /methanol (2 mL) and stirred for an additional 30 minutes, and all the volatile components were removed in vacuo. The resulting material was purified by a reverse phase HPLC (H_2O /methanol/TFA) to provide the TFA salt of Example 108 as a light yellow foam (16.7 mg) LC: 1.95 minutes (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{39}\text{H}_{43}\text{N}_8\text{O}_4$: 687.34; found 687.53; HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{39}\text{H}_{43}\text{N}_8\text{O}_4$: 687.3407; found 687.3417.

Example 109

dibenzyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)

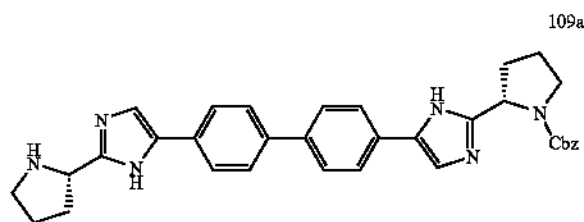
[0516]



Example 109, Step a

benzyl (2S)-2-(5-(4'-(2-((2S)-2-pyrrolidiny)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

[0517]

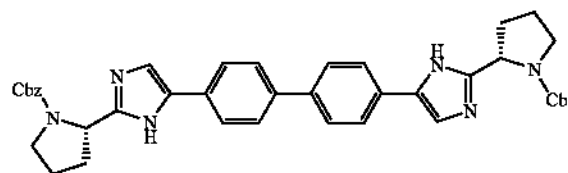


[0518] The Boc-deprotection of 28c using the procedure described for the synthesis of pyrrolidine 1e from carbamate 1d provided 109a. RT=1.92 minutes (Cond 2); >98% homogeneity index; LC/MS: Anal. Calcd. $\text{C}_{34}\text{H}_{35}\text{N}_6\text{O}_2$: 559.28; found 559.44

Example 109

dibenzyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)

[0519]



[0520] Benzyl chloroformate (10.5 μ L, 0.0736 mmol) was added to a THF (2.0 mL) solution of 109a (37.1 mg, 0.664 mmol) and triethylamine (15 μ L, 0.107 mmol), and stirred under ambient conditions for 6 hours. The volatile component was removed in vacuo, and the residue was treated with 2N NH_3 /methanol (2 mL) and stirred for 15 minutes. The volatile component was removed in vacuo, and the residue purified by a reverse phase HPLC (H_2O /methanol/TFA) to provide the TFA salt of Example 109 as an off-white foam (37.9 mg). LC (Cond. 2): RT=2.25 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{42}\text{H}_{41}\text{N}_6\text{O}_4$: 693.32; found 693.59; HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{42}\text{H}_{41}\text{N}_6\text{O}_4$: 693.3189; found 693.3220.

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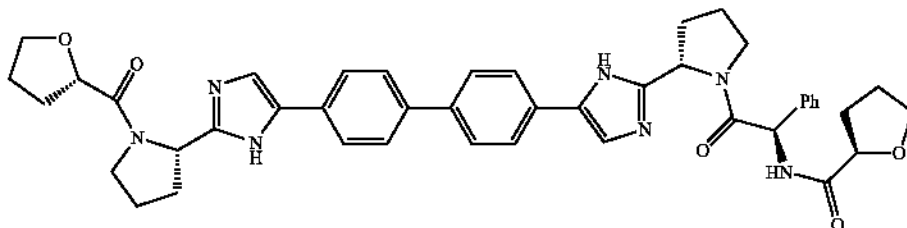
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Example 110

(2R)—N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-(2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide

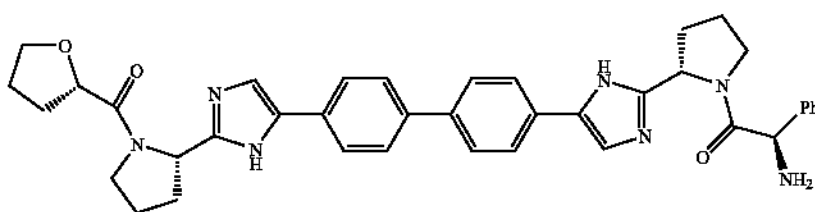
[0521]



Example 110, Step a

(1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-(2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

[0522]



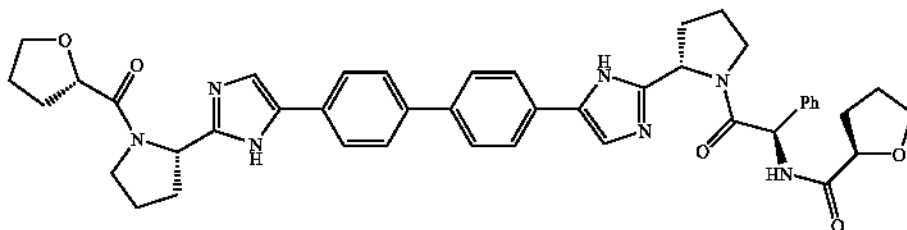
110a

[0523] Amine 110a was synthesized starting from 28d and (S)-tetrahydrofuran-2-carboxylic by sequentially employing procedures described in the preparation of 28f (from 28d) and 25b (from 1e). LC (Cond. 1): RT=1.13 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_3$: 656.34; found 656.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_3$: 656.3349; found 656.3377.

Example 110

(2R)—N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-(2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide

[0524]



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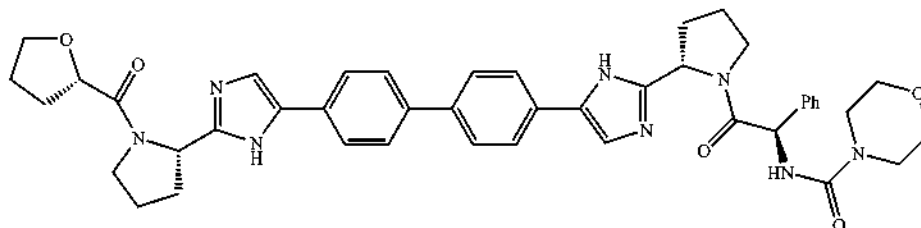
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[0525] Example 110 (TFA salt) was prepared from Example 110a and (S)-tetrahydrofuran-2-carboxylic acid using the conditions described for the synthesis Example 1 from amine 1e. LC (Cond. 1): RT=1.28 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.60; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3690.

Example 111

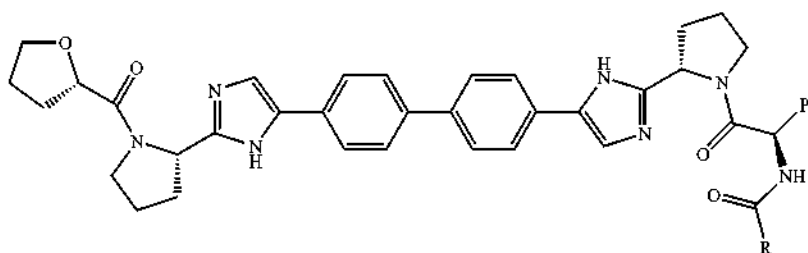
N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-morpholinecarboxamide

[0526]

[0527] Example 111 (TFA salt) was prepared from amine 110a and morpholine 4-carbonyl chloride using the procedure described for the synthesis of Example 29 from amine 28f. LC (Cond. 1): RT=1.28 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{49}N_8O_5$: 769.38; found 769.60.

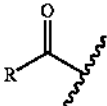
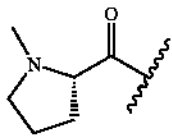
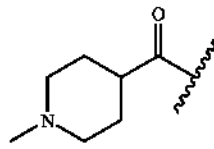
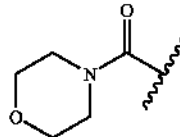
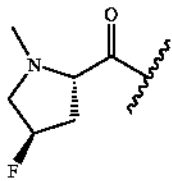
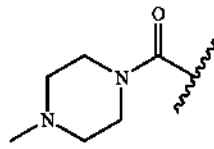
[0528] Using similar methods described for the preparation of Example 111, the following compounds (Example 112-120) were synthesized as TFA salts.

Example 112-117

[0529]

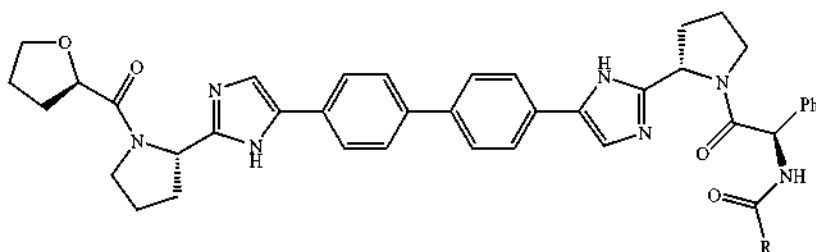
Example	Compound Name	Retention time (LC-Condition); homogeneity index MS data
112	(2S)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-morpholinecarboxamide	1.28 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3731

-continued

Example	Compound Name		Retention time (LC-Condition); homogeneity index MS data
113	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-L-prolinamide		1.14 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₁ N ₉ O ₄ ; 767.40; found 767.68; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₁ N ₉ O ₄ ; 767.4033; found 767.4035
114	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-4-piperidinecarboxamide		1.12 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₃ N ₉ O ₄ ; 781.42; found 781.67; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₃ N ₉ O ₄ ; 781.4190; found 781.4195
115	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-tetrahydro-2H-pyran-4-carboxamide		1.24 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₀ N ₇ O ₅ ; 768.39; found 768.66; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₀ N ₇ O ₅ ; 768.3873; found 768.3897
116	(4R)-4-fluoro-1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-L-prolinamide	 Cap-11	1.16 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₀ FN ₉ O ₄ ; 785.39; found 785.63; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₀ FN ₉ O ₄ ; 785.3939; found 785.3940
117	4-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-1-piperazinecarboxamide		1.15 minutes (Cond. 1); 97.6%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₂ N ₉ O ₄ ; 782.41; found 782.64; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₂ N ₉ O ₄ ; 782.4142; found 782.4161

Examples 118 to 120-9

[0530]

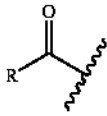
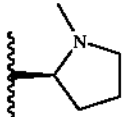
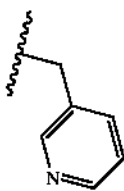
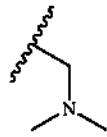


[0531] Examples 118 to 120-9 were prepared as described in the preparation of Example 110a substituting (R)-tetrahy-

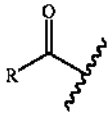
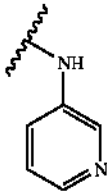
drofuryl carboxylic acid and the appropriate carboxylic acid, carboxylic acid chloride, carbamoyl chloride, or isocyanate.

Example	Compound Name		Retention time (LC-Condition); homogeneity index; MS data
118	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)acetamide		1.89 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₄ N ₇ O ₅ : 698.35; found 698.25; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₄ N ₇ O ₅ : 698.3455; found 698.3474
119	(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)tetrahydro-2-furancarboxamide		1.99 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₈ N ₇ O ₅ : 754.37; found 754.28; [M + H] ⁺ C ₄₄ H ₄₈ N ₇ O ₅ : 754.3717; found 754.3705
120	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-4-morpholinecarboxamide		2.00 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₉ N ₈ O ₅ : 769.38; found 769.32
120-5	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-1H-imidazole-5-carboxamide		RT = 4.02 (97%); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H ₃ PO ₄ , B = 10% water, 90% methanol, 0.2% H ₃ PO ₄ , RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: C ₄₄ H ₄₅ N ₉ O ₄ 763.91; Found: 764.52 (M + H) ⁺

-continued

Example	Compound Name		Retention time (LC-Condition); homogeneity index; MS data
120-6	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide		RT = 3.68 (99%); HPLC XTERRA C-18 4.6 x 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H ₃ PO ₄ , B = 10% water, 90% methanol, 0.2% H ₃ PO ₄ , RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: C ₄₅ H ₅₀ N ₈ O ₄ 766.95; Found: 767.47 (M + H) ⁺
120-7	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-2-(3-pyridinyl)acetamide		RT = 3.81 (99%); HPLC XTERRA C-18 4.6 x 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H ₃ PO ₄ , B = 10% water, 90% methanol, 0.2% H ₃ PO ₄ , RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: C ₄₆ H ₄₆ N ₈ O ₄ 774.93; Found: 775.47 (M + H) ⁺
120-8	N ² ,N ² -dimethyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)glycinamide		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.71-2.44 (m, 12 H), 2.65-2.89 (m, 6 H), 3.04-3.21 (m, J = 8.55 Hz, 1 H), 3.46-3.68 (m, 1 H), 3.64-4.07 (m, 6 H), 4.64 (dd, J = 8.09, 5.34 Hz, 1 H), 5.09-5.30 (m, 2 H), 5.66-5.86 (m, 1 H), 7.32-7.49 (m, 4 H), 7.82-8.22 (m, 10 H), 9.15-9.38 (m, 1 H), 9.68 (s, 1 H), 14.60 (s, 2 H); HPLC Xterra 4.6 x 50 mm, 0 to 100% B over 10 minutes, one minute hold time A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 3.61 min; LCMS: Anal. Calcd. for: C ₅₂ H ₅₆ N ₁₀ O ₆ 740.91; Found: 741.48 (M + H) ⁺

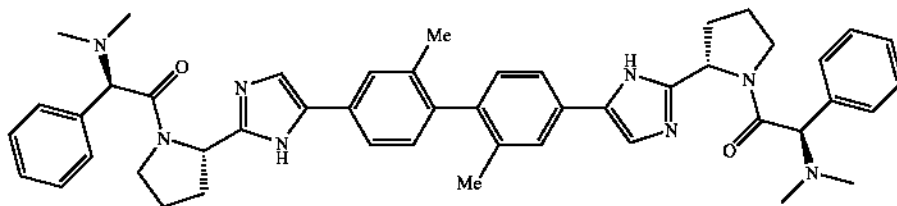
-continued

Example	Compound Name		Retention time (LC-Condition); homogeneity index; MS data
120-9	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinylethyl)-3-(3-pyridinyl)urea		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.64-2.40 (m, 12 H), 3.11-3.27 (m, 1 H), 3.51-3.65 (m, 1 H), 3.80 (dd, J = 18.46, 6.87 Hz, 3 H), 3.96-4.11 (m, 1 H), 4.64 (dd, J = 7.78, 5.34 Hz, 1 H), 5.13-5.23 (m, 1 H), 5.21-5.35 (m, 1 H), 5.66 (d, J = 7.02 Hz, 1 H), 7.29-7.57 (m, 7 H), 7.82-8.07 (m, 10 H), 8.14 (s, 1 H), 8.22 (d, J = 4.58 Hz, 1 H), 8.68 (s, 1 H), 9.32 (s, 1 H), 14.46 (s, 2 H); HPLC Xterra 4.6 × 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 3.83 min; LCMS: Anal. Calcd. for: C ₄₅ H ₄₅ N ₉ O ₄ 775.92; Found: 776.53 (M + H) ⁺ .

Example 121

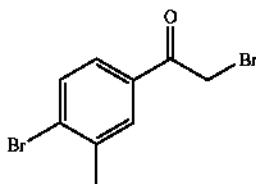
(1R,1'R)-2,2'-((2,2'-dimethyl-4,4'-biphenyldiyl)bis
(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis
(N,N-dimethyl-2-oxo-1-phenylethanamine)

[0532]



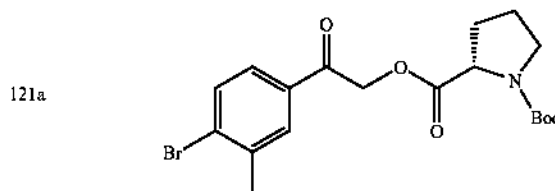
Example 121, Step a-b

[0533]



-continued

121b



[0534] PdCl₂(Ph₃P)₂ (257 mg, 0.367 mmol) was added to a dioxane (45 mL) solution of 1-bromo-4-iodo-2-methylbenzene (3.01 g, 10.13 mmol) and tri-n-butyl(1-ethoxyvinyl) stannane (3.826 g, 10.59 mmol) and heated at 80° C. for 17 hours. The reaction mixture was treated with water (15 mL), cooled to -0° C. (ice/water), and then NBS (1.839 g, 10.3

mmol) was added in batches over 7 minutes. After about 25 minutes of stirring, the volatile component was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 , and the combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The resulting crude material was purified by a gravity chromatography (silica gel; 4% ethyl acetate/hexanes) to provide bromide 121a as a brownish-yellow solid (2.699 g); the sample is impure and contains stannane-derived impurities, among others. ^1H NMR (CDCl_3 , δ =7.24, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

[0535] A CH_3CN (15 mL) solution of 121a (2.69 g, <9.21 mmol) was added dropwise over 3 minutes to a CH_3CN (30 mL) solution of (S)-Boc-proline (2.215 g, 10.3 mmol) and triethylamine (1.40 mL, 10.04 mmol), and stirred for 90 minutes. The volatile component was removed in vacuo, and the residue was partitioned between water and CH_2Cl_2 , and the organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The resulting crude material was purified by a flash chromatography (silica gel; 15-20% ethyl acetate/hexanes) to provide 121b as a colorless viscous oil (2.74 g). ^1H NMR ($\text{DMSO}-d_6$, δ =2.50, 400 MHz): δ 7.98 (m, 1H), 7.78 (d, J =8.3, 1H), 7.72-7.69 (m, 1H), 5.61-5.41 (m, 2H), 4.35-4.30 (m, 1H), 3.41-3.30 (m, 2H), 2.43 (s, 3H), 2.33-2.08 (m, 2H), 1.93-1.83 (m, 2H), 1.40/1.36 (s, 9H); LC (Cond. 1): RT=1.91 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{Na}]^+$ $\text{C}_{19}\text{H}_{24}\text{BrNNaO}_5$ 448.07; found 448.10.

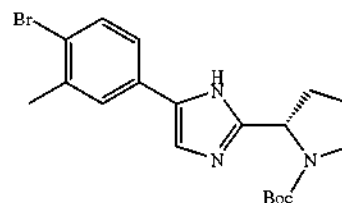
[0536] Additional keto-esters can be prepared in analogous fashion.

[0537] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

[0538] Condition 2: Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

Example 121, Step c

[0539]



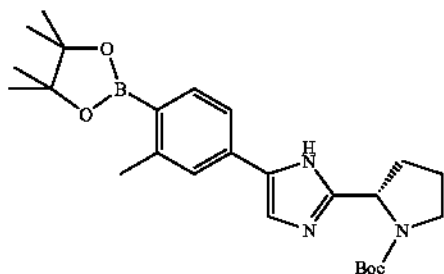
121c

[0540] A mixture of ketoester 121b (1.445 g, 3.39 mmol) and NH_4OAc (2.93 g, 38.0 mmol) in xylenes (18 mL) was heated with a microwave at 140° C. for 80 minutes. The volatile component was removed in vacuo, and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated NaHCO_3 solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2 , and the combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The crude product was purified by a flash chromatography (silica gel, 40% ethyl acetate/hexanes) to provide imidazole 121c as an off-white solid (1.087 g). ^1H NMR ($\text{DMSO}-d_6$, δ =2.50, 400 MHz): 12.15/11.91/11.84 (br s, 1H), 7.72-7.24 (m, 4H), 4.78 (m, 1H), 3.52 (m, 1H), 3.38-3.32 (m, 1H), 2.35 (s, 3H), 2.28-1.77 (m, 4H), 1.40/1.14 (s, 9H); LC (Cond. 1): RT=1.91 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{19}\text{H}_{25}\text{BrN}_3\text{O}_2$ 405.96; found 406.11.

Example	Structure	Data
121b-1		RT = 2.15 minutes (condition 2, 98%); LRMS: Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{NO}_5$ 399.07; found: 400.10 ($\text{M} + \text{H}$) ⁺ .
121b-2		RT = 2.78 minutes (condition 1, 90%); LRMS: Anal. Calcd. for $\text{C}_{20}\text{H}_{20}^{37}\text{BrNO}_5$ 435.05 found: 458.02 ($\text{M} + \text{Na}$) ⁺ .

Example 121, Step d

[0541]



121d

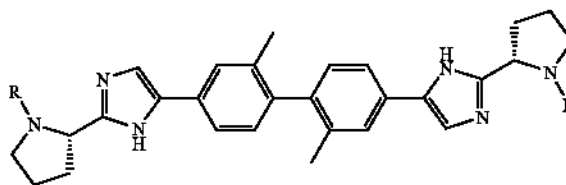
[0542] $\text{PdCl}_2\text{dppf} \cdot \text{CH}_2\text{Cl}_2$ (50.1 mg, 0.061 mmol) was added to a pressure tube containing a mixture of bromide 121c (538.3 mg, 1.325 mmol), bis(pinacolato)diboron (666.6 mg, 2.625 mmol), potassium acetate (365.8 mg, 3.727 mmol) and DMF (10 mL). The reaction mixture was flushed with N_2 and heated at 80°C . for 24.5 hours. The volatile component was removed in vacuo and the residue was partitioned between CH_2Cl_2 and water, where enough saturated NaHCO_3 solution was added to make the pH of the aqueous medium neutral. The aqueous phase was extracted with CH_2Cl_2 , and the combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The resulting material was purified by a Biotage system (silica gel, 40-50% ethyl acetate/hexanes) to provide boronate 121d as a white foam (580 mg). According to ^1H NMR the sample contains residual pinacol in a product/pinacol ratio of ~3. ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz): δ 12.16/11.91/11.83 (br s, 1H), 7.63-7.25 (m, 4H), 4.78 (m, 1H), 3.53 (m, 1H), 3.39-3.32 (m, 1H), 2.48/2.47 (s, 3H), 2.28-1.78 (m, 4H), 1.40/1.14/1.12 (br s, 9H), 1.30 (s, 12H);

LC (Cond. 1): $\text{RT}=1.62$ min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{25}\text{H}_{37}\text{BN}_3\text{O}_4$ 454.29; found 454.15

Example 121, Step e and

Example 121, Step f

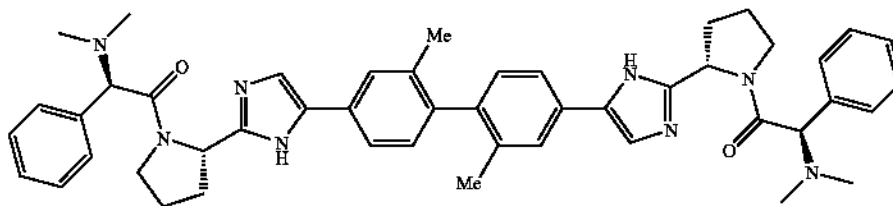
[0543]



121e: R = Boc
121f: R = H

[0544] Carbamate 121e was prepared from bromide 121c and boronate 121d according to the preparation of dimer 1d; LC (Cond. 1): $\text{RT}=1.43$ min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{38}\text{H}_{49}\text{N}_6\text{O}_4$ 653.38; found 653.65.

[0545] The deprotection of carbamate 121e, according to the preparation of pyrrolidine 1e, provided 121f as an off-white foam. ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz): 11.79 (br s, 2H), 7.66 (s, 2H), 7.57 (d, $J=7.8$, 2H), 7.41 (br s, 2H), 7.02 (d, $J=7.8$, 2H), 4.15 (app t, $J=7.2$, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.09-2.01 (m, 2H), 2.04 (s, 6H), 1.93-1.85 (m, 2H), 1.82-1.66 (m, 4H). Note: although broad signals corresponding to the pyrrolidine NH appear in the 2.8-3.2 ppm region, the actual range for their chemical shift could not be determined. LC (Cond. 1): $\text{RT}=1.03$ min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{28}\text{H}_{33}\text{N}_6$ 453.28; found 453.53



Example 121

(1R,1'R)-2,2'-(2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

[0546] Example 121 (TFA salt) was synthesized from 121f according to the preparation of Example 1 from 1e; LC (Cond. 1): $\text{RT}=1.14$ min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{48}\text{H}_{55}\text{N}_8\text{O}_2$ 775.45; 775.75; HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{48}\text{H}_{55}\text{N}_8\text{O}_2$ 775.4448; found 775.4473

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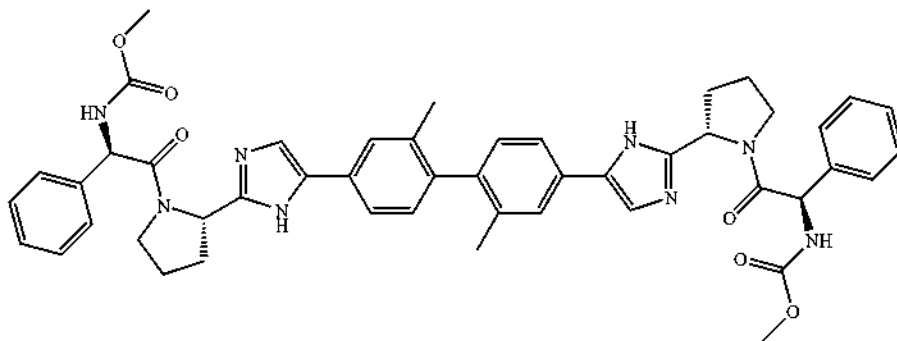
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Example 122

dimethyl ((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate

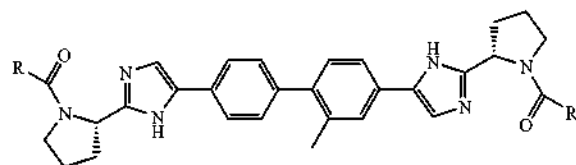
[0547]



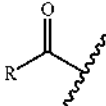
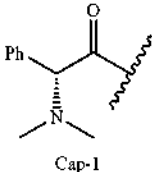
[0548] Example 122 (TFA salt) was prepared from pyrrolidine 121f and Cap-4 by using the procedure described for the preparation of Example 1 from pyrrolidine 1e. LC (Cond. 1): RT=1.35 min; >98% homogeneity index; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{51}N_8O_6$ 835.3932; found 835.3954

Example 123-125

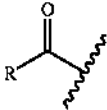
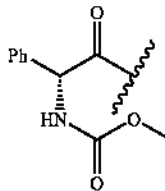
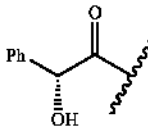
[0549]



[0550] Example 123-125 were prepared starting from boronate 1c and bromide 121c by using the methods described in Example 1, step d, Example 1, step e, and in the step describing the final preparation of Example 1.

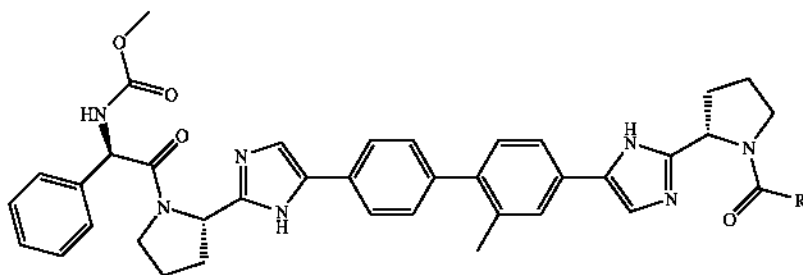
Example	Compound Name		RT (LC-Cond.); % homogeneity index; MS data
123	(1R,1'R)-2,2'-((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)		1.12 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{53}N_8O_2$: 761.43; found 761.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{53}N_8O_2$: 761.4291; found 761.4311

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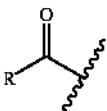
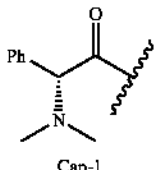
Example	Compound Name		RT (LC-Cond.); % homogeneity index; MS data
124	dimethyl ((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate		1.34 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₇ H ₄₉ N ₈ O ₆ : 821.38; found 821.45; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₇ H ₄₉ N ₈ O ₆ : 821.3775; found 821.3785
125	((1R,1'R)-2,2'-((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol))		1.23 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₃ N ₈ O ₄ : 707.34; found 707.38; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₃ N ₈ O ₄ : 707.3346; found 707.3356

Examples 126-128

[0551]



[0552] Example 126-128 were prepared starting from bromide 28b and boronate 121d by using the methods described in Example 28 starting with step c.

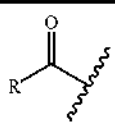
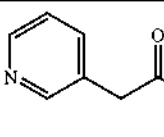
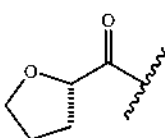
Example	Compound Name		RT (LC-Cond.); % homogeneity index; MS data
126	methyl ((1R)-2-((2S)-2-(5-(4'-((2-(2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidiny)-1H-imidazol-5-yl)-2'-methyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidiny)-2-oxo-1-phenylethyl)carbamate		1.22 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₇ H ₅₁ N ₈ O ₄ : 791.40; found 791.70; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₇ H ₅₁ N ₈ O ₄ : 791.4033; found 791.4061

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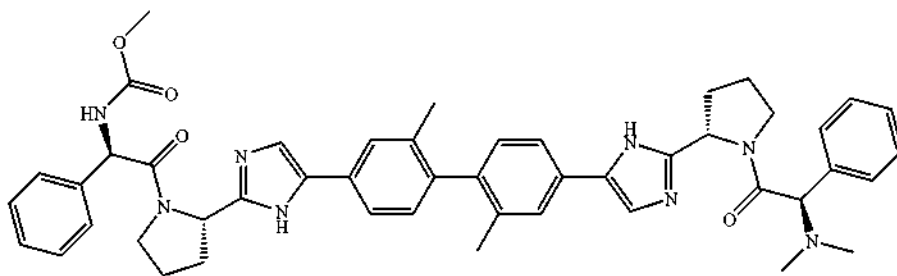
-continued

Example	Compound Name		RT (LC-Cond.); % homogeneity index; MS data
127	methyl ((1R)-2-((2S)-2-(5-(2'-methyl-4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.19 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₅ N ₈ O ₄ ; 749.36; found 749.62; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₅ N ₈ O ₄ ; 749.3564; found 749.3592
128	methyl ((1R)-2-((2S)-2-(5-(2'-methyl-4'-(2-((2S)-1-(2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.27 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₆ N ₇ O ₅ ; 728.36; found 728.59; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₆ N ₇ O ₅ ; 728.3560; found 728.3593

Example 129

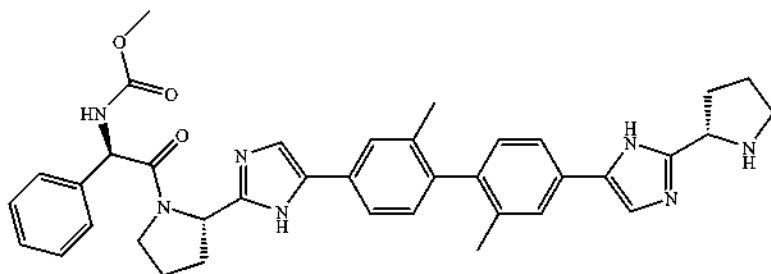
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,2'-dimethyl-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate

[0553]



Example 129, Step a

[0554]



129a

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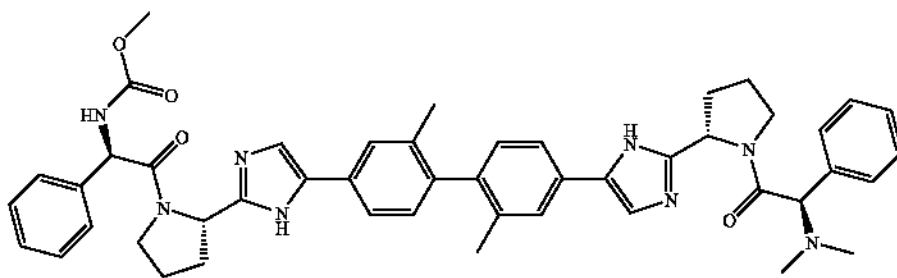
168

[0555] HATU (104.3 mg, 0.274 mmol) was added to a mixture of 121f, Cap-4 (58.8 mg, 0.281 mmol) and diisopropylethylamine (110 μ L, 0.631 mmol) in DMF (6.0 mL), and stirred for 90 minutes. The volatile component was removed in vacuo and the resulting crude material was purified by reverse phase HPLC (H_2O /methanol/TFA), and free-based by MCX column (methanol wash; 2.0 M NH_3 /methanol) to provide 129a (89.9 mg). LC (Cond. 1): RT=1.22 min; 95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}N_7O_3$ 644.34; found 644.55.

Example 129

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,2'-dimethyl-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) carbamate

[0556]

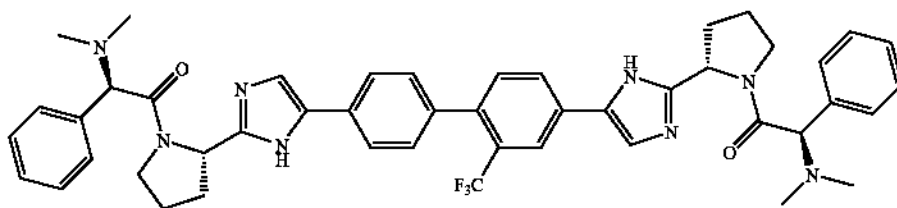


[0557] Example 129 (TFA salt) was prepared from 129a by the method used to convert Example 1e to Example 1. LC (Cond. 1): RT=1.27 min; 97% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_8O_4$ 805.42; found 805.61.

Example 130

(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl) bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)) bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

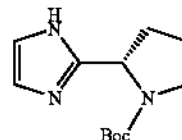
[0558]



Example 130, Step a

[0559]

130a



[0560] Glyoxal (2.0 mL of 40% in water) was added dropwise over 11 minutes to a methanol solution of NH_4OH (32 mL) and (S)-Boc-prolinal (8.564 g, 42.98 mmol) and stirred at ambient temperature for 19 hours. The volatile component was removed in vacuo and the residue was purified by a flash chromatography (silica gel, ethyl acetate) followed by a recrystallization (ethyl acetate, room temperature) to provide imidazole 130a as a white fluffy solid (4.43 g). 1H NMR ($DMSO-d_6$, δ =2.50, 400 MHz): 11.68/11.59 (br s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 4.76 (m, 1H), 3.48 (m, 1H), 3.35-3.29 (m, 1H), 2.23-1.73 (m, 4H), 1.39/1.15 (s, 9H). LC (Cond. 1):

RT=0.87 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{20}N_3O_2$ 238.16; found 238.22. Imidazole 130a had an ee of 98.9% when analyzed under chiral HPLC condition noted below.

Column: Chiralpak AD, 10 μ m, 4.6 \times 50 mm

[0561] Solvent: 1.7% ethanol/heptane (isocratic)

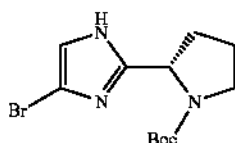
Flow rate: 1 mL/min

Wavelength: either 220 or 256 nm

Relative retention time: 3.25 min (R), 5.78 minutes (S)

Example 130, Step b

[0562]

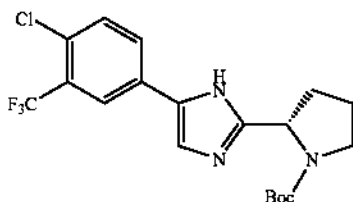


130b

[0563] N-Bromosuccinimide (838.4 mg, 4.71 mmol) was added in batches, over 15 minutes, to a cooled (ice/water) CH_2Cl_2 (20 mL) solution of imidazole 130a (1.0689 g, 4.504 mmol), and stirred at similar temperature for 75 minutes. The volatile component was removed in vacuo. The crude material was purified by a reverse phase HPLC system (H_2O /methanol/TFA) to separate bromide 130b from its dibromo-analog and the non-consumed starting material. The HPLC elute was neutralized with excess NH_3 /methanol and the volatile component was removed in vacuo. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with water. The combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo to provide 130b as a white solid (374 mg). ^1H NMR ($\text{DMSO}-d_6$, δ =2.50, 400 MHz): 12.12 (br s, 1H), 7.10 (m, 1H), 4.70 (m, 1H), 3.31 (m, 1H; overlapped with water signal), 2.25-1.73 (m, 4H), 1.39/1.17 (s, 3.8H+5.2H). LC (Cond. 1): RT=1.10 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{12}\text{H}_{19}\text{BrN}_3\text{O}_2$ 316.07; found 316.10.

Example 130, Step c

[0564]



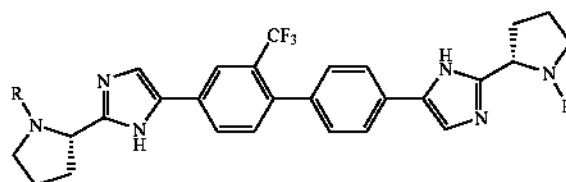
130c

[0565] $\text{Pd}(\text{Ph}_3\text{P})_4$ (78.5 mg, 0.0679 mmol) was added to a mixture of bromide 130b (545 mg, 1.724 mmol), 2-(4-chloro-3-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (542.8 mg, 1.771 mmol) (commercially available), NaHCO_3 (477 mg, 5.678 mmol) in 1,2-dimethoxyethane (12.5 mL) and water (4.2 mL). The reaction mixture was purged with nitrogen, heated with an oil bath at 80°C . for 27 hours, and then the volatile component was removed in vacuo. The residue was partitioned between CH_2Cl_2 and water, and the organic layer was dried (MgSO_4), filtered, and concentrated in vacuo. The resulting crude material was puri-

fied by a Biotage system (silica gel, 40-50% ethyl acetate/hexanes) followed by a reverse phase HPLC (water/methanol/TFA). The HPLC elute was treated with excess NH_3 /methanol and concentrated. The residue was partitioned between water and CH_2Cl_2 , and the organic layer was dried (MgSO_4), filtered, and concentrated in vacuo to provide 130c as a white foam (317.4 mg). ^1H NMR ($\text{DMSO}-d_6$, δ =2.50, 400 MHz): 12.36/12.09/12.03 (br s, 1H), 8.15 (d, J =1.8, 0.93H), 8.09 (br s, 0.07H), 8.01 (dd, J =8.3/1.3, 0.93H), 7.93 (m, 0.07H), 7.74 (m, 1H), 7.66 (d, J =8.3, 0.93H), 7.46 (m, 0.07H), 4.80 (m, 1H), 3.53 (m, 1H), 3.36 (m, 1H), 2.30-1.77 (m, 4 h), 1.40/1.15 (s, 3.8H+5.2H). LC (Cond. 1): RT=1.52 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{19}\text{H}_{22}\text{ClF}_3\text{N}_3\text{O}_2$ 416.14; found 416.17.

Example 130, Step d-e

[0566]



130d: R = Boc
130e: R = H

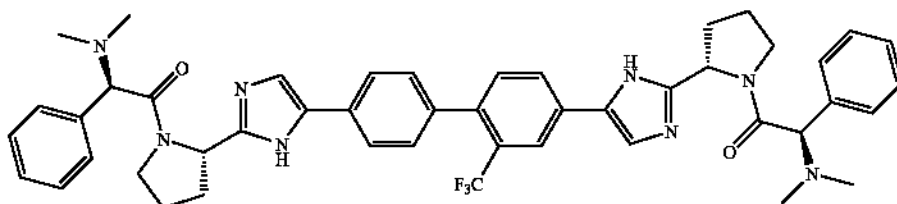
[0567] $\text{Pd}[\text{P}(\text{t-Bu})_3]_2$ (48 mg, 0.094 mmol) was added to a mixture of chloride 130c (245 mg, 0.589 mmol), boronate 1c (277.1 mg, 0.631 mmol), KF (106.7 mg, 1.836 mmol) in DMF (6 mL), and heated at 110°C . for ~30 hours. The volatile component was removed in vacuo, and the residue was partitioned between CH_2Cl_2 (50 mL), water (20 mL) and saturated NaHCO_3 (1 mL). The aqueous layer was extracted with CH_2Cl_2 (2x), and the combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The resulting material was purified by a Biotage system (silica gel, ethyl acetate) to provide carbamate 130d as an off-white foam (297 mg). LC (Cond. 1): RT=1.44 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{37}\text{H}_{44}\text{F}_3\text{N}_6\text{O}_4$ 693.34; found 693.34.

[0568] The deprotection of 130d, which was conducted according to the preparation of pyrrolidine 1e, provided 130e as a light yellow foam. ^1H NMR ($\text{DMSO}-d_6$, δ =2.50, 400 MHz): 11.88 (br s, 2H), 8.16 (d, J =1.5, 1H), 8.02 (d, J =7.8, 1H), 7.78 (d, J =8.1, 2H), 7.66 (br s, 1H), 7.48 (br s, 1H), 7.37 (d, J =8.1, 1H), 7.28 (d, J =8.3, 2H), 4.18 (m, 2H), 2.99-2.93 (m, 2H), 2.89-2.83 (m, 2H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.67 (m, 4H). Note: although broad signals corresponding to the pyrrolidine NH appear in the 2.8-3.2 ppm region, the actual range for their chemical shift could not be determined. LC (Cond. 1): RT=1.12 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_6$ 493.23; found 493.14.

Example 130

(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)
bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))
bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

[0569]

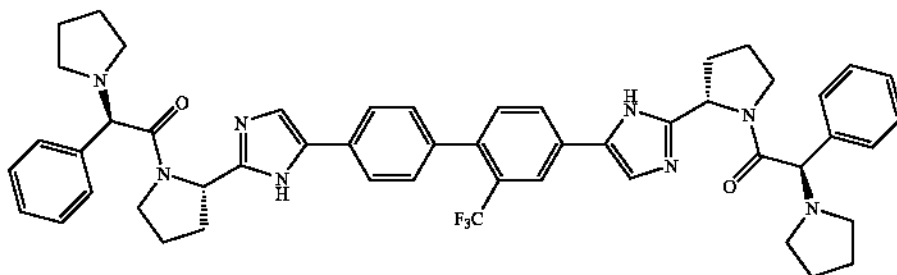


[0570] Example 130 (TFA salt) was prepared from 130e and Cap-1 according to the preparation of Example 1 from pyrrolidine 1e. LC (Cond. 1): RT=1.17 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{50}F_3N_8O_2$ 815.40; found 815.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{50}F_3N_8O_2$ 815.4009; found 815.4013

Example 131

5,5'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(2-
(2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-
pyrrolidinyl)-1H-imidazole)

[0571]



[0572] Example 131 (TFA salt) was synthesized from 130e and Cap-5 according to the preparation of Example 130.

[0573] LC (Cond. 1): RT=1.19 min; >98% homogeneity index

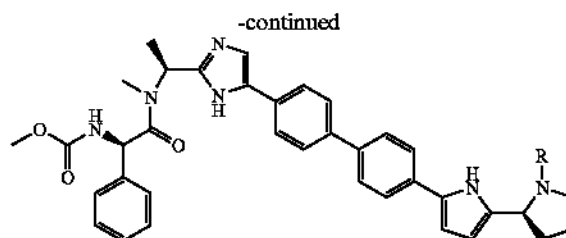
[0574] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{54}F_3N_8O_2$ 867.43; found 867.51

[0575] HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{54}F_3N_8O_2$ 867.4322; found 867.4315

Example 131.1-1 to 131.1-2

[0576]

Example 1-6e $\xrightarrow{\begin{matrix} 1) \text{ step a} \\ 2) \text{ step b} \\ 3) \text{ step c} \end{matrix}}$



step a: Couple cap-4 with HATU as in Example 28 step c
step b: Remove Chz group with H_2 , Pd/C
step c: Append appropriate cap

[0577] Examples 131.1-1 through 131.1-2 were prepared in similar fashion to example 28 via the intermediacy of intermediate 1-6e after appending Cap-4.

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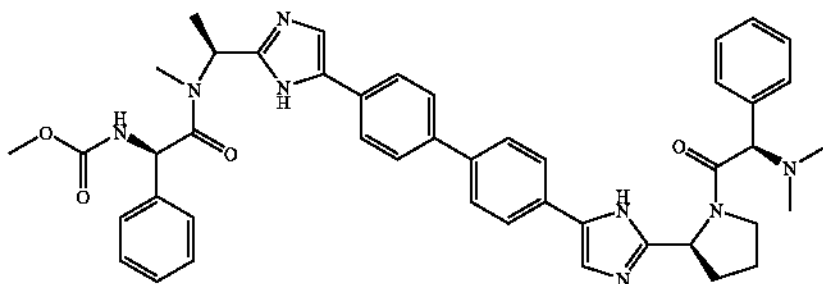
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Example 131.1-1

methyl ((1R)-2-(((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)ethyl)(methyl)amino)-2-oxo-1-phenylethyl)carbamate

[0578]



[0579] Cap-1 was appended after the CBz carbamate was removed from 1-6e with Pd/C/H₂.

[0580] LCMS conditions: Phenomenex LUNA C-18 4.6x 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 µL injection volume. t_R=1.42 min

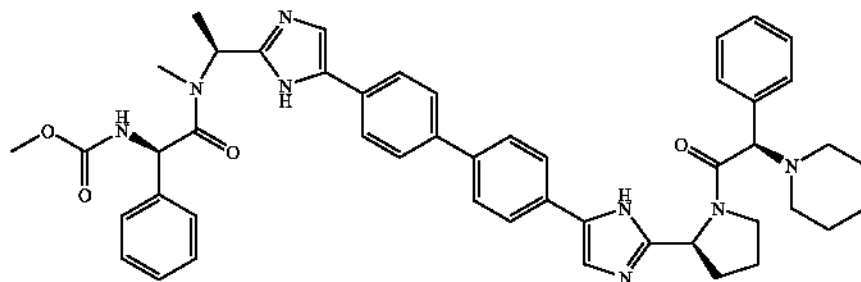
[0581] LRMS: Anal. Calcd. for C₄₅H₄₉N₈O₄ 765.39; found: 765.38 (M+H)⁺.

[0582] HRMS: Anal. Calcd. for C₄₅H₄₉N₈O₄ Calcd 765.3877 found: 765.3905 (M+H)⁺.

Example 131.1-2

methyl ((1R)-2-(methyl((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-phenylethyl)carbamate

[0583]



[0584] Cap-14 was appended after the CBz carbamate was removed from 1-6e with Pd/C/H₂.

[0585] LCMS conditions: Phenomenex LUNA C-18 4.6x 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time,

A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume. t_R =1.45 min (>95%)

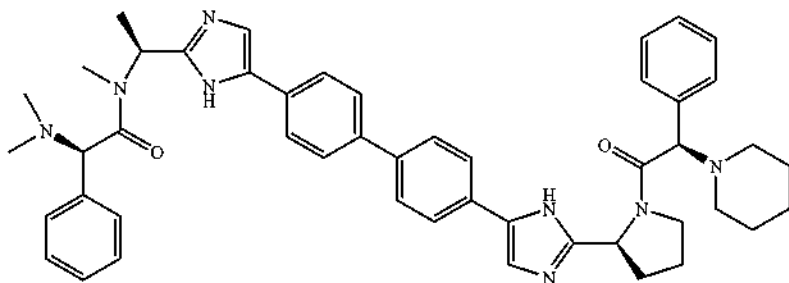
[0586] LRMS: Anal. Calcd. for $C_{48}H_{52}N_8O_4$ 805.42; found: 805.41 (M+H)⁺.

[0587] HRMS: Anal. Calcd. $C_{48}H_{52}N_8O_4$ Calcd 805.4190 found: 805.4214 (M+H)⁺.

Example 131.2

(2R)-2-(dimethylamino)-N-methyl-2-phenyl-N-((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)ethyl)acetamide

[0588]



[0589] Example 131. 2 was prepared in similar fashion to example 131.1-1 and example 131.1-2 via the intermediacy of intermediate 1-6e after appending Cap-1. Cap-14 was appended after the CBz carbamate was removed with Pd/C/H₂. LCMS conditions: Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume. t_R =1.28 min

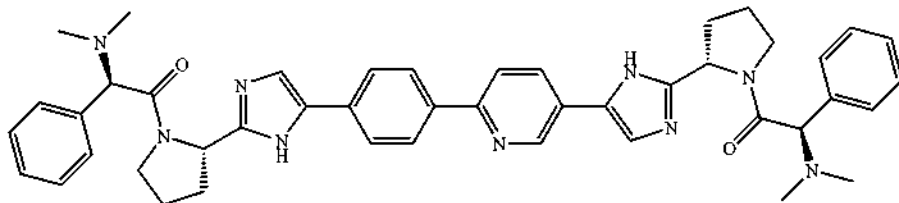
[0590] LRMS: Anal. Calcd. for $C_{48}H_{54}N_8O_2$ 775.44; found: 775.45 (M+H)⁺.

[0591] HRMS: Anal. Calcd. $C_{48}H_{54}N_8O_2$ Calcd 775.4448 found: 775.4460 (M+H)⁺.

Example 132

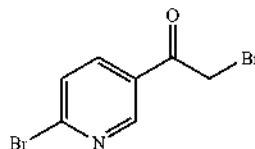
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine

[0592]



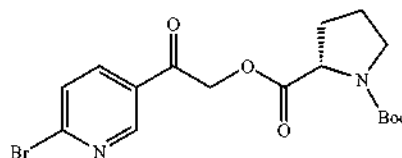
Example 132, Step a-b

[0593]



132a

-continued



132b

[0594] A CH_2Cl_2 (10 mL) solution of Br_2 (7.63 g, 47.74 mmol) was added-drop wise over 5 min to a cooled (ice/water) CH_2Cl_2 (105 mL) solution of 1-(6-bromopyridine-3-yl)ethanone (9.496 g, 47.47 mmol) and 48% HBr (0.4 mL). The cooling bath was removed 40 min later, and stirring was continued at ambient temperature for about 66 hr. The cake of solid that formed was filtered, washed with CH_2Cl_2 and dried in vacuo to afford impure 132a as an off-white solid (15.94 g).

[0595] Boc-L-proline (9.70 g, 45.06 mmol) was added in one batch to a heterogeneous mixture of crude 132a (15.4 g) and CH_3CN (150 mL), and immediately afterward Et_3N (13.0

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mL, 93.2 mmol) was added drop-wise over 6 min. The reaction mixture was stirred for 50 min, the volatile component was removed in vacuo and the residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was dried (MgSO_4), filtered and concentrated in vacuo, and the resultant material was purified by flash chromatography (silica gel; sample was loaded with eluting solvent; 25% EtOAc/hexanes) to afford 132b as a highly viscous yellow oil (11.44 g). ^1H NMR (DMSO, $\delta=2.5$ ppm; 400 MHz): 8.95 (m, 1H), 8.25-8.21 (m, 1H), 7.88 (d, $J=8.3$, 1H), 5.65-5.46 (m, 2H), 4.36-4.31 (m, 1H), 3.41-3.29 (m, 2H), 2.36-2.22 (m, 1H), 2.14-2.07 (m, 1H), 1.93-1.83 (m, 2H), 1.40 & 1.36 (two s, 9H).

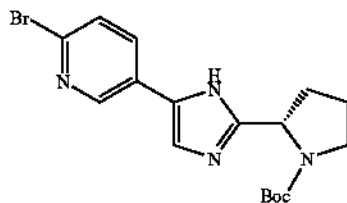
[0596] LC (Cond. 1): RT=2.01 min; >90% homogeneity index

[0597] LC/MS: Anal. Calcd. for $[\text{M}+\text{Na}]^+$ $\text{C}_{17}\text{H}_{21}\text{NaBrN}_2\text{O}_5$: 435.05; found 435.15

[0598] HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{22}\text{BrN}_2\text{O}_5$: 413.0712; found 413.0717

Example 132, Step c

[0599]



[0600] A mixture of ketoester 132b (1.318 g, 3.19 mmol) and NH_4OAc (2.729 g, 35.4 mmol) in xylenes (18 mL) was heated with a microwave at 140°C . for 90 min. The volatile component was removed in vacuo and the residue was partitioned between CH_2Cl_2 and water, where enough saturated NaHCO_3 solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2 , and the combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The resulting crude material was purified by a Biotage system (silica gel; 50% EtOAc/hexanes) to afford imidazole 132c as an off-white foam (1.025 g). ^1H NMR (DMSO, $\delta=2.5$ ppm, 400 MHz): 12.33/12.09/12.02 (br m, 1H), 8.74 (d, $J=2.3$, 0.93H), 8.70 (app br s, 0.07H), 8.03/7.98 (dd for the first peak, $J=8.3$, 1H), 7.69/7.67 (br m, 1H), 7.58/7.43 (d for the first peak, $J=8.3$, 1H), 4.80 (m, 1H), 3.53 (m, 1H), 3.36 (m, 1H), 2.33-2.11 (m, 1H), 2.04-1.79 (m, 3H), 1.39/1.15 (app br s, 3.9H+5.1H).

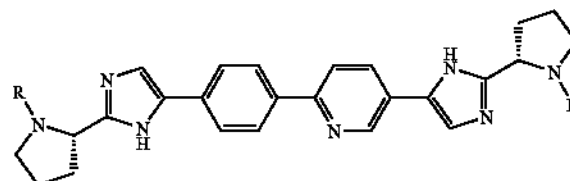
[0601] LC (Cond. 1): RT=1.52 min; >98% homogeneity index

[0602] LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{22}\text{BrN}_4\text{O}_2$: 393.09; found 393.19

[0603] HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{22}\text{BrN}_4\text{O}_2$: 393.0926; found 393.0909

Example 132, Step d-e

[0604]



132d: R = Boc
132e: R = H

[0605] $\text{Pd}(\text{Ph}_3\text{P})_4$ (115.1 mg, 0.10 mmol) was added to a mixture of bromide 132c (992 mg, 2.52 mmol), boronate 1c (1.207 g, 2.747 mmol), NaHCO_3 (698.8 mg, 8.318 mmol) in 1,2-dimethoxyethane (18 mL) and water (4 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 90°C . for 37 hr and allowed to cool to ambient temperature. The suspension that formed was filtered and washed with water followed by 1,2-dimethoxyethane, and dried in vacuo. A silica gel mesh was prepared from the crude solid and submitted to flash chromatography (silica gel; EtOAc) to afford carbamate 132d as a white solid, which yellowed slightly upon standing at ambient conditions (1.124 g). ^1H NMR indicated that the sample contains residual MeOH in a product/MeOH mole ratio of 1.3.

[0606] LC (Cond. 1): RT=1.71 min; >98% homogeneity index

[0607] LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{35}\text{H}_{44}\text{N}_7\text{O}_4$: 626.35; found 626.64

[0608] HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{35}\text{H}_{44}\text{N}_7\text{O}_4$: 626.3455; 626.3479

[0609] Carbamate 132d (217 mg) was treated with 25% TFA/ CH_2Cl_2 (3.6 mL) and stirred at ambient condition for 6 hr. The volatile component was removed in vacuo, and the resultant material was free based by MCX column (MeOH wash; 2.0 M NH_3 /MeOH elution) to afford 132e as a dull yellow foam that solidified gradually upon standing (150.5 mg; mass is above theoretical yield). ^1H NMR (DMSO, $\delta=2.5$ ppm; 400 MHz): 11.89 (very broad, 2H), 9.01 (d, $J=1.8$, 1H), 8.13 (dd, $J=8.3$, 2.2, 1H), 8.07 (d, $J=8.6$, 2H), 7.92 (d, $J=8.3$, 1H), 7.83 (d, $J=8.5$, 2H), 7.61 (br s, 1H), 7.50 (br s, 1H), 4.18 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.11-2.02 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). [Note: the exchangeable pyrrolidine hydrogens were not observed]

[0610] LC (Cond. 1): RT=1.21 min; >98% homogeneity index

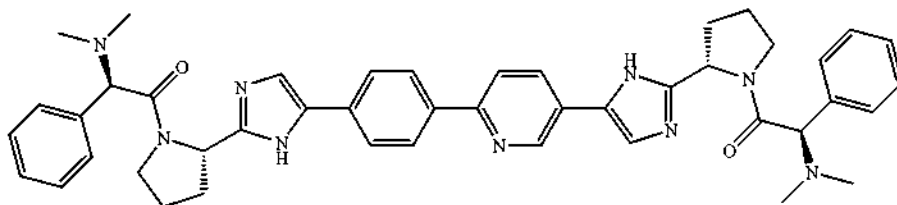
[0611] LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{25}\text{H}_{28}\text{N}_7$: 426.24; found 426.40

[0612] HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{25}\text{H}_{28}\text{N}_7$: 426.2406; found 426.2425

Example 132

(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine

[0613]



[0614] HATU (41.4 mg, 0.109 mmol) was added to a mixture of pyrrolidine 132e (23.1 mg, 0.054 mmol), (i-Pr)₂EtN (40 μ L, 0.23 mmol) and Cap-1 (25.3 mg, 0.117 mmol) in DMF (1.5 mL), and the mixture was stirred at ambient for 1 hr. The volatile component was removed in vacuo, and the residue was purified first by MCX (MeOH wash; 2.0 M NH₃/MeOH elution) and then by a reverse phase HPLC (H₂O/MeOH/TFA) to afford the TFA salt of Example 132 as a yellow foam (39.2 mg).

[0615] LC (Cond. 1): RT=1.37 min; >98% homogeneity index

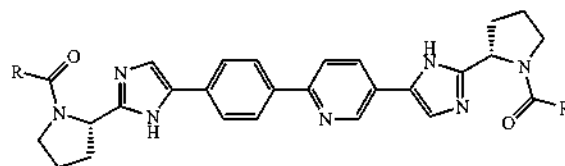
[0616] LC/MS: Anal. Calcd. for [M+H]⁺ C₄₅H₅₀N₉O₂: 748.41; found 748.53

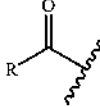
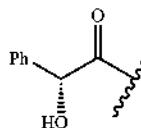
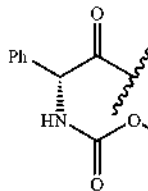
[0617] HRMS: Anal. Calcd. for [M+H]⁺ C₄₅H₅₀N₉O₂: 748.4087; found 748.4090

[0618] Example 133-135 were prepared as TFA salts from 132e by using the same method of preparations as Example 132 and appropriate reagents.

Example 133-135

[0619]



Example	Compound Name		RT (LC-Cond. 1); % homogeneity index; MS data
133	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol		1.49 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₀ N ₇ O ₄ : 694.31; found 694.42 HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₀ N ₇ O ₄ : 694.3142; found: 694.3164
134	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.60 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₄₆ N ₉ O ₆ : 808.36; found 808.51 HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₄₆ N ₉ O ₆ : 808.3571; found 808.3576

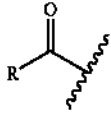
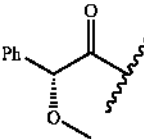
Cap-4

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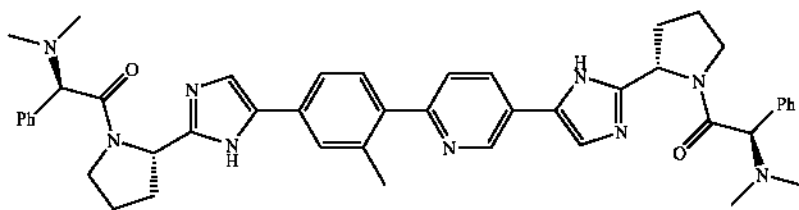
-continued

Example	Compound Name		RT (LC-Cond.); % homogeneity index; MS data
135	5-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-(4-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)pyridine		1.60 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M + H]^+$ $C_{43}H_{44}N_7O_4$: 722.35; found 722.40 HRMS: Anal. Calcd. for $[M + H]^+$ $C_{43}H_{44}N_7O_4$: 722.3455; found 722.3464

Example 136

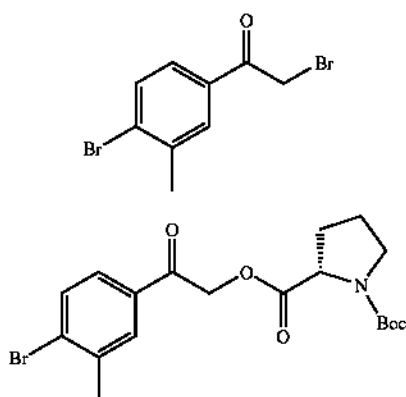
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-methylphenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine

[0620]



Example 136, Step a and b

[0621]



[0622] $PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmol) was added to a dioxane (45 mL) solution of 1-bromo-4-iodo-2-methylbenzene (3.01 g, 10.13 mmol) and tri-*n*-butyl(1-ethoxyvinyl) stannane (3.826 g, 10.59 mmol) and heated at 80° C. for 17 hr. The reaction mixture was treated with water (15 mL), cooled to -0° C. (ice/water), and then NBS (1.839 g, 10.3 mmol) was added in batches over 7 min. About 25 min of stirring, the

volatile component was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 , and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude material was purified by a gravity chromatography (silica gel; 4% EtOAc/hexanes) to afford bromide 136a as a brownish-yellow solid (2.699 g); the sample is impure and contains stannane-derived impurities, among others. 1H NMR ($CDCl_3$, δ =7.24, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

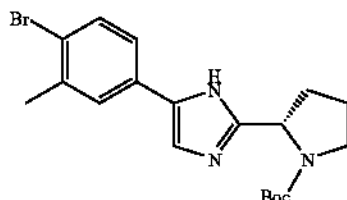
[0623] An CH_3CN (15 mL) solution of 136a (2.69 g, <9.21 mmol) was added drop wise over 3 min to a CH_3CN (30 mL) solution of (S)-Boc-proline (2.215 g, 10.3 mmol) and Et_3N (1.40 mL, 10.04 mmol), and stirred for 90 min. The volatile component was removed in vacuo, and the residue was partitioned between water and CH_2Cl_2 , and the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The resultant crude material was purified by a flash chromatography (silica gel; 15-20% EtOAc/hexanes) to afford 136b as a colorless viscous oil (2.74 g). 1H NMR ($DMSO-d_6$, δ =2.50, 400 MHz): 7.98 (m, 1H), 7.78 (d, J =8.3, 1H), 7.72-7.69 (m, 1H), 5.61-5.41 (m, 2H), 4.35-4.30 (m, 1H), 3.41-3.30 (m, 2H), 2.43 (s, 3H), 2.33-2.08 (m, 2H), 1.93-1.83 (m, 2H), 1.40/1.36 (s, 9H).

[0624] LC (Cond. 1): RT=1.91 min; >95% homogeneity index

[0625] LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{24}BrNNaO_5$ 448.07; found 448.10

Example 136, Step c

[0626]



136c

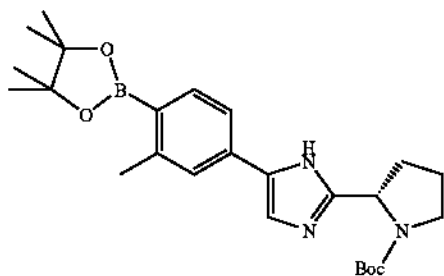
[0627] A mixture of ketoester 136b (1.445 g, 3.39 mmol) and NH_4OAc (2.93 g, 38.0 mmol) in xylenes (18 mL) was heated with a microwave at 140° C. for 80 min. The volatile component was removed in vacuo, and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated NaHCO_3 solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2 , and the combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The crude was purified by a flash chromatography (silica gel, 40% EtOAc/hexanes) to afford imidazole 136c as an off-white solid (1.087 g). ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz): 12.15/11.91/11.84 (br s, 1H), 7.72-7.24 (m, 4H), 4.78 (m, 1H), 3.52 (m, 1H), 3.38-3.32 (m, 1H), 2.35 (s, 3H), 2.28-1.77 (m, 4H), 1.40/1.14 (s, 9H).

[0628] LC (Cond. 1): RT=1.91 min; >98% homogeneity index

[0629] LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{19}\text{H}_{25}\text{BrN}_3\text{O}_2$ 405.96; found 406.11

Example 136, Step d

[0630]



136d

[0631] $\text{PdCl}_2\text{dppf}\cdot\text{CH}_2\text{Cl}_2$ (50.1 mg, 0.061 mmol) was added to a pressure tube containing a mixture of bromide 136c (538.3 mg, 1.325 mmol), bis(pinacolato)diboron (666.6 mg, 2.625 mmol), KOAc (365.8 mg, 3.727 mmol) and DMF (10 mL). The reaction mixture was flushed with N_2 and

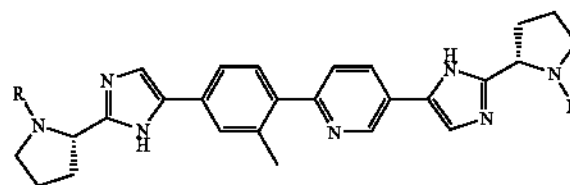
heated at 80° C. for 24.5 hr. The volatile component was removed in vacuo and the residue was partitioned between CH_2Cl_2 and water, where enough saturated NaHCO_3 solution was added to make the pH of the aqueous medium neutral. The aqueous phase was extracted with CH_2Cl_2 , and the combined organic phase was dried (MgSO_4), filtered, and concentrated in vacuo. The resulting material was purified by a Biotage system (silica gel, 40-50% EtOAc/hexanes) to afford boronate 136d as a white foam (580 mg). According to ^1H NMR the sample contains residual pinacol in a product/pinacol ratio of ~3. ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz): 12.16/11.91/11.83 (br s, 1H), 7.63-7.25 (m, 4H), 4.78 (m, 1H), 3.53 (m, 1H), 3.39-3.32 (m, 1H), 2.48/2.47 (s, 3H), 2.28-1.78 (m, 4H), 1.40/1.14/1.12 (br s, 9H), 1.30 (s, 12H).

[0632] LC (Cond. 1): RT=1.62 min

[0633] LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{25}\text{H}_{37}\text{BN}_3\text{O}_4$ 454.29; found 454.15

Example 136, Step e-f

[0634]



136e: R = Boc
136f: R = H

[0635] Biaryl 136e was prepared from bromide 132c and boronate 136d according to the coupling condition described for the preparation of biaryl 132d.

[0636] LC (Cond. 1a): RT=1.32 min; >90% homogeneity index

[0637] LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{36}\text{H}_{45}\text{N}_7\text{O}_4$ 640.36; found 640.66

[0638] The deprotection of biaryl 136e was done according to the preparation of pyrrolidine 132e to afford 136f as a light yellow foam. ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz): 11.88 (br s, 2H), 9.02 (d, J=2, 1H), 8.12 (dd, J=8.4, 2.3, 1H), 7.67 (s, 1H), 7.64-7.62 (m, 2H), 7.50 (d, J=8.3, 1H), 7.46 (br s, 1H), 7.40 (d, J=7.8, 1H), 4.21-4.14 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.40 (s, 3H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Note: the signal for the pyrrolidine NH appears in the region 3.22-2.80 and is too broad to make a chemical shift assignment.]

[0639] LC (Cond. 1): RT=0.84 min

[0640] LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{26}\text{H}_{30}\text{N}_7$ 440.26; found 440.50

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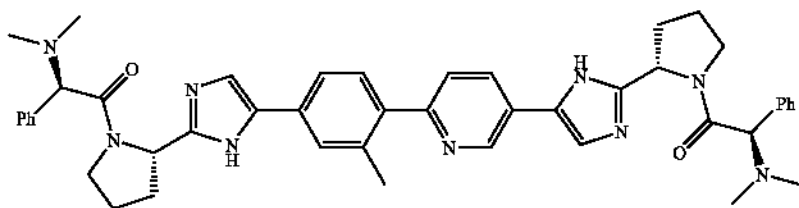
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Example 136

(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-methylphenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine

[0641]



[0642] Example 136 (TFA salt) was synthesized from 136f according to the preparation of Example 132 from 132e.

[0643] 1.05 min (Cond. 1); >98%

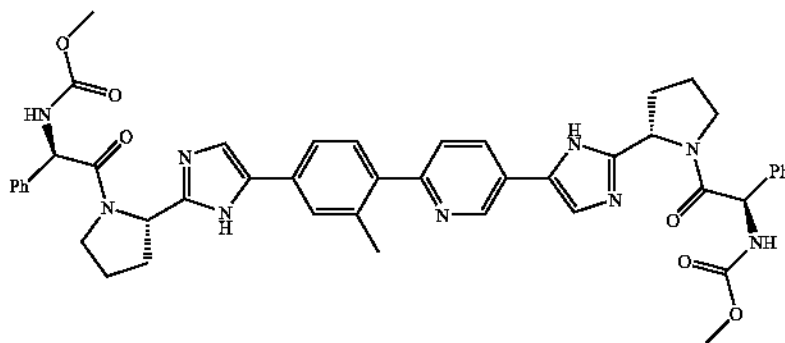
[0644] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{52}N_9O_2$: 762.42, found: 762.77

[0645] HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{52}N_9O_2$: 762.4244; found 762.4243

Example 138

methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-methylphenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate

[0646]



[0647] Example 138 was prepared similarly from pyrrolidine 136f and Cap-4.

[0648] 1.60 min (Cond. 1); >98%

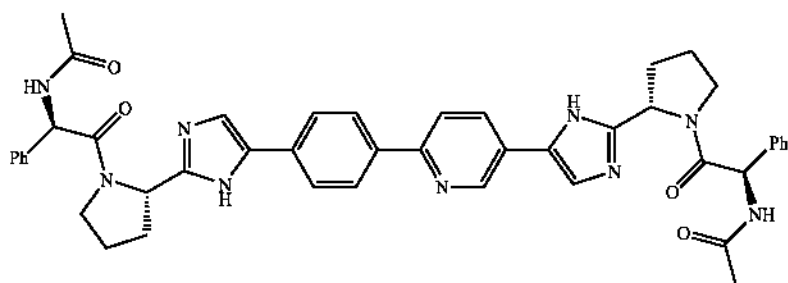
[0649] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.37; found 822.74

[0650] HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.3728; found 822.3760

Example 139

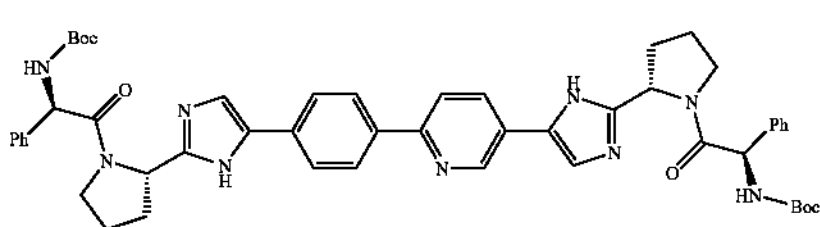
N-((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)acetamide

[0651]



Example 139, Step a

[0652]



139a

[0653] HATU (99.8 mg, 0.262 mmol) was added to a mixture of 132e (54.1 mg, 0.127 mmol), (R)-2-(t-butoxycarbonylamino)-2-phenylacetic acid (98.5 mg, 0.392 mmol) and *i*-Pr₂EtN (100 μ L, 0.574 mol), and the reaction mixture was stirred for 70 min. The volatile component was removed in vacuo, and the residue was purified by a reverse phase HPLC (H₂O/MeOH/TFA), where the HPLC elute was treated with excess 2.0 N NH₃/MeOH before the removal of the volatile component in vacuo. The resulting material was partitioned between CH₂Cl₂ and water, and the aqueous phase was

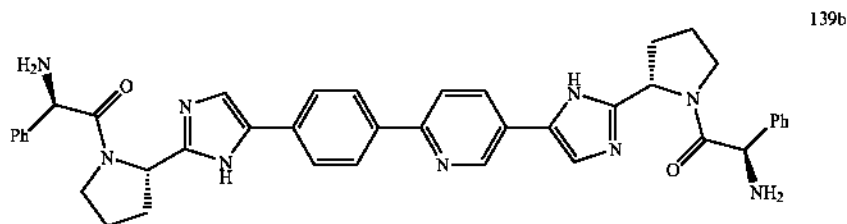
extracted with CH₂Cl₂ (2 \times). The combined organic phase was dried (MgSO₄), filtered, and concentrated in vacuo. Carbamate 139a was obtained as a white film of foam (82.3 mg).

[0654] LC (Cond. 1): RT=1.97 min; >95% homogeneity index.

[0655] LC/MS: Anal. Calcd. for [M+H]⁺ C₅₁H₅₈N₉O₆: 892.45; found 892.72

Example 139b, Step b

[0656]



139b

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[0657] Carbamate 139a was deprotected to amine 139b by using the procedure described for the preparation of pyrrolidine 132e from 132d.

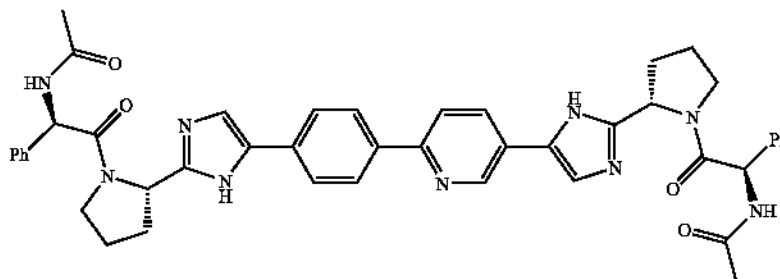
[0658] LC (Cond. 1): RT=1.37 min; >95% homogeneity index

[0659] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_2$: 692.35; found 692.32

Example 139

N-((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)acetamide

[0660]



[0661] Acetic anhydride (20 μ L, 0.212 mmol) was added to a DMF (1.5 mL) solution of 139b (31.2 mg, 0.045 mmol), and the reaction mixture was stirred for 1 hr. NH_3 /MeOH (1.0 mL of 2N) was added to the reaction mixture and stirring continued for 100 min. The volatile component was removed in vacuo and the resulting crude material was purified by a reverse phase HPLC (H_2O /MeOH/TFA) to afford the TFA salt of Example 139 as a light yellow solid (24.1 mg).

[0662] LC (Cond. 1): RT=1.53 min; >98% homogeneity index

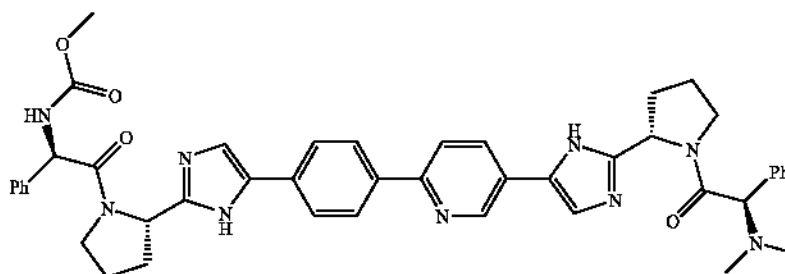
[0663] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.37; found 776.38

[0664] HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.3673; found 776.3680

Example 140

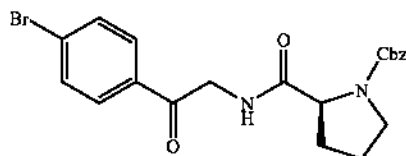
methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate

[0665]



Example 140, Step a

[0666]



140a

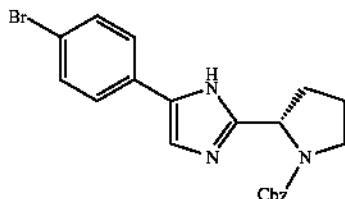
[0667] HATU (19.868 g, 52.25 mmol) was added to a heterogeneous mixture of N-Cbz-L-proline (12.436 g, 49.89 mmol) and the HCl salt of 2-amino-1-(4-bromophenyl)ethanone (12.157 g, 48.53 mmol) in DMF (156 mL). The mixture was lowered in an ice-water bath, and immediately afterward N,N-diisopropylethylamine (27 mL, 155 mmol) was added drop wise to it over 13 min. After the addition of the base was completed, the cooling bath was removed and the reaction mixture was stirred for an additional 50 min. The volatile component was removed in vacuo; water (125 mL) was added to the resultant crude solid and stirred for about 1 hr. The off-white solid was filtered and washed with copious water, and dried in vacuo to afford ketoamide 140a as a white solid (20.68 g). ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): 8.30 (m, 1H), 7.91 (m, 2H), 7.75 (d, J=8.5, 2H), 7.38-7.25 (m, 5H), 5.11-5.03 (m, 2H), 4.57-4.48 (m, 2H), 4.33-4.26 (m, 1H), 3.53-3.36 (m, 2H), 2.23-2.05 (m, 1H), 1.94-1.78 (m, 3H).

[0668] LC (Cond. 1): RT=1.65 min; 98% homogeneity index

[0669] LC/MS: Anal. Calcd. for [M+H]⁺ C₂₁H₂₂BrN₂O₄: 445.08; found 445.31

Example 140, Step b

[0670]



140b

[0671] Ketoamide 140a (10.723 g, 24.08 mmol) was converted to 140b according to the procedure described for the synthesis of carbamate 132c, with the exception that the crude material was purified by flash chromatography (silica gel; 50% EtOAc/hexanes). Bromide 140b was retrieved as an off-white foam (7.622 g). ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): 12.23/12.04/11.97 (m, 1H), 7.73-6.96 (m, 10H),

5.11-4.85 (m, 3H), 3.61 (m, 1H), 3.45 (m, 1H), 2.33-1.84 (m, 4H).

[0672] LC (Cond. 1): RT=1.42 min; >95% homogeneity index

[0673] LC/MS: Anal. Calcd. for [M+H]⁺ C₂₁H₂₁BrN₃O₂: 426.08; found 426.31

[0674] HRMS: Anal. Calcd. for [M+H]⁺ C₂₁H₂₁BrN₃O₂: 426.0817; found: 426.0829

[0675] The optical purity of 140b was assessed using the following chiral HPLC methods, and an ee of 99% was observed.

Column: Chiralpak AD, 10 μm, 4.6×50 mm

[0676] Solvent: 20% ethanol/heptane (isocratic)

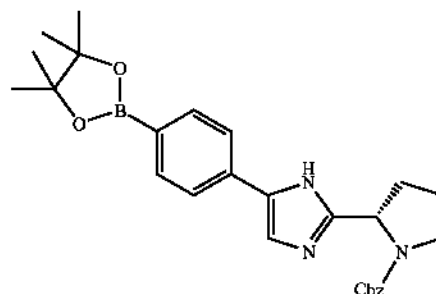
Flow rate: 1 ml/min

Wavelength: 254 nm

[0677] Relative retention time: 1.82 min (R), 5.23 min (S)

Example 140, Step c

[0678]



140c

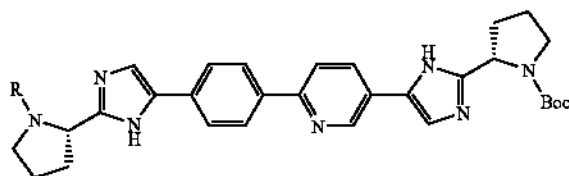
[0679] Pd(Ph₃P)₄ (208 mg, 0.180 mmol) was added to a pressure tube containing a mixture of bromide 140b (1.80 g, 4.22 mmol), bis(pinacolato)diboron (2.146 g, 8.45 mmol), KOAc (1.8 g, 11.0 mmol) and 1,4-dioxane (34 mL). The reaction flask was purged with nitrogen, capped and heated with an oil bath at 80° C. for 23 hr. The volatile component was removed in vacuo, and the residue was partitioned carefully between CH₂Cl₂ (70 mL) and an aqueous medium (22 mL water+5 mL saturated NaHCO₃ solution). The aqueous layer was extracted with CH₂Cl₂, and the combined organic phase was dried (MgSO₄), filtered, and concentrated in vacuo. The oily residue was crystallized from EtOAc/hexanes to afford two crops of boronate 140c as a yellow solid (1.52 g). The mother liquor was evaporated in vacuo and the resulting material was purified by flash chromatography (silica gel; 20-35% EtOAc/CH₂Cl₂) to afford additional 140c as an off-white solid, containing residual pinacol (772 mg).

[0680] LC (Cond. 1): RT=1.95 min

[0681] LC/MS: Anal. Calcd. for [M+H]⁺ C₂₇H₃₃BN₃O₄: 474.26; found 474.31

Example 140, Step d-e

[0682]



140d: R = Cbz
140e: R = H

[0683] Arylbromide 132c was coupled with boronate 140c to afford 140d by using the same procedure described for the synthesis of biaryl 132d. The sample contains the desbromo version of 132c as an impurity. Proceeded to the next step without further purification.

[0684] LC (Cond. 1): RT=1.72 min; ~85% homogeneity index

[0685] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}N_7O_4$: 660.33; found 660.30

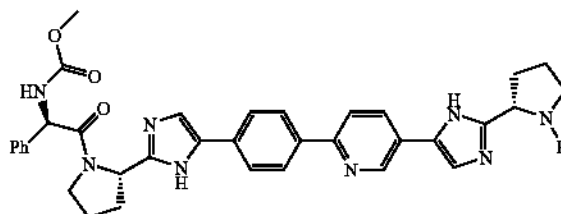
[0686] A mixture of 10% Pd/C (226 mg), biaryl 140d (1.25 g) and MeOH (15 mL) was stirred under a balloon of hydrogen for ~160 hr, where the hydrogen supply was replenished periodically as needed. The reaction mixture was filtered through a pad of diatomaceous earth (Celite®), and the filtrate was evaporated in vacuo to afford crude 140e as a yellowish-brown foam (911 mg). Proceeded to the next step without further purification.

[0687] LC (Cond. 1): RT=1.53 min

[0688] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{30}H_{36}N_7O_2$: 526.29; found 526.23

Example 140, Step f-g

[0689]



140f: R = Boc
140g: R = H

[0690] Pyrrolidine 140g was prepared from 140e and Cap-4, via the intermediacy of carbamate 140f, by sequentially employing the amide forming and Boc-deprotection protocols used in the synthesis of Example 132.

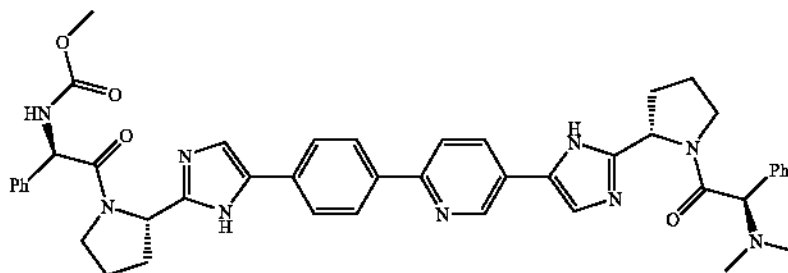
[0691] LC (Cond. 1): RT=1.09 min; ~94% homogeneity index

[0692] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{37}N_8O_3$: 617.30; found 617.38

Example 140

methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate

[0693]



[0694] The TFA salt of Example 140 was synthesized from pyrrolidine 140g and Cap-1 by using the procedure described for the preparation of Example 132 from intermediate 132e.

[0695] 1.15 min (Cond. 1); >98% homogeneity index

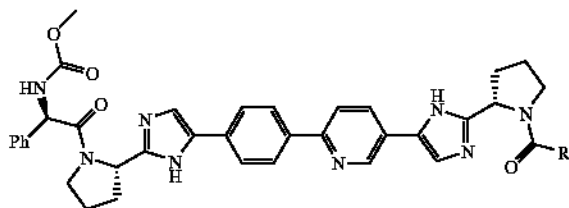
[0696] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.38; found 778.48

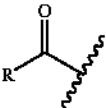
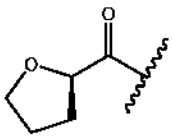
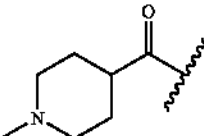
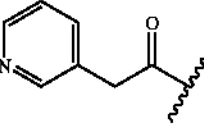
[0697] HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.3829; found 778.3849

[0698] The TFA salt of Example 141-143 were synthesized from intermediate 140g and appropriate reagents in a similar manner.

Example 141-143

[0699]

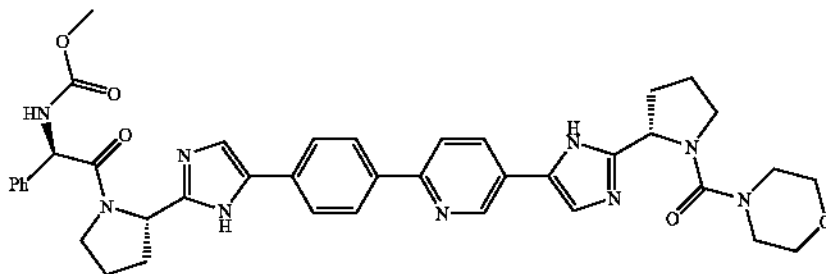


Example	Compound Name		RT (LC-Cond.); % homogeneity index; MS data
141	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.15 min (Cond. 1); >98% LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₃ N ₉ O ₅ : 715.34; found 715.44 HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₃ N ₉ O ₅ : 715.3356; found 715.3381
142	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((1-methyl-4-piperidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.07 min (Cond. 1); >98% LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₈ N ₉ O ₄ : 742.38; found 742.48 HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₈ N ₉ O ₄ : 742.3829; found 742.3859
143	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.09 min (Cond. 1); >98% LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₂ N ₉ O ₄ : 736.34; found 736.44 HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₂ N ₉ O ₄ : 736.3360; found 736.3344

Example 144

methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate

[0700]



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[0701] A DMF (1.5 mL) solution of morpholine-4-carbonyl chloride (8.5 mg, 0.057 mmol) was added to a mixture of *i*-Pr₂EtN (20 μ L, 0.115 mmol) and 140g (27.3 mg, 0.044 mmol), and stirred for 100 min. The volatile component was removed in vacuo and the residue was purified by a reverse phase HPLC (H₂O/MeOH/TFA) to afford the TFA salt of Example 144 as a yellow foam (34.6 mg).

[0702] 1.17 min (Cond. 1); >98%

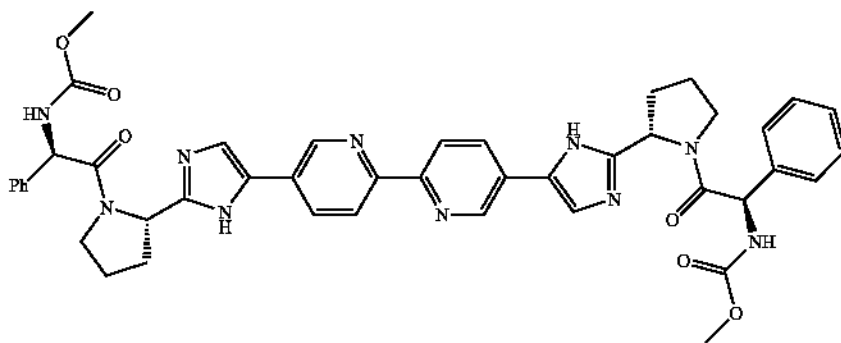
[0703] LC/MS: Anal. Calcd. for [M+H]⁺ C₄₀H₄₄N₉O₅: 730.35; found 730.42

[0704] HRMS: Anal. Calcd. for [M+H]⁺ C₄₀H₄₄N₉O₅: 730.3465; found 730.3477

Example 145

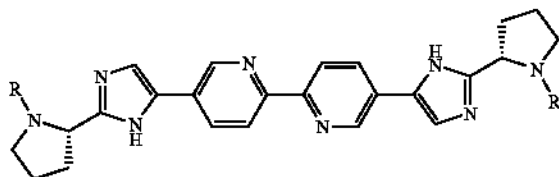
dimethyl (2,2'-bipyridine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)))biscarbamate

[0705]



Example 145, Step a-b

[0706]



145a: R = Boc
145b: R = H

[0707] Pd(PPh₃)₄ (9.6 mg, 0.008 mmol) and LiCl (28 mg, 0.67 mmol) were added to a mixture of arylbromide 132c (98.7 mg, 0.251 mmol) and hexamethylditin (51.6 mg, 0.158 mmol), and heated at 80° C. for ~3 days. The volatile component was removed in vacuo and the resultant crude material was purified by flash chromatography (silica gel; 0-10% MeOH/EtOAc) followed by a reverse phase HPLC (H₂O/

MeOH/TFA). The HPLC elute was neutralized with excess 2.0 N NH₃/MeOH, and the volatile component was removed in vacuo. The residue was partitioned between CH₂Cl₂ and water, and the aqueous phase was washed with CH₂Cl₂ (2×).

[0708] The combined organic phase was dried (MgSO₄), filtered, and concentrated in vacuo to afford carbamate 145a as a film of oil (8.7 mg).

[0709] LC (Cond. 1): RT=1.68 min; >98% homogeneity index

[0710] LC/MS: Anal. Calcd. for [M+H]⁺ C₃₄H₄₃N₈O₄: 627.34; found 627.47 Carbamate 145a was elaborated to pyrrolidine 145b according to the preparation of 132e from 132d. ¹H NMR (DMSO, δ =2.5 ppm; 400 MHz): 12.02 (br signal, 2H), 9.04 (d, J=1.6, 2H), 8.34 (d, J=8.3, 2H), 8.20 (dd, J=8.3, 2.3, 2H), 7.67 (br s, 1H), 4.21 (m, 2H), 3.00-2.85 (m, 4H), 2.12-2.04 (m, 2H), 1.95-1.68 (m, 6H). [Note: the pyrrolidine-NH signal was not observed].

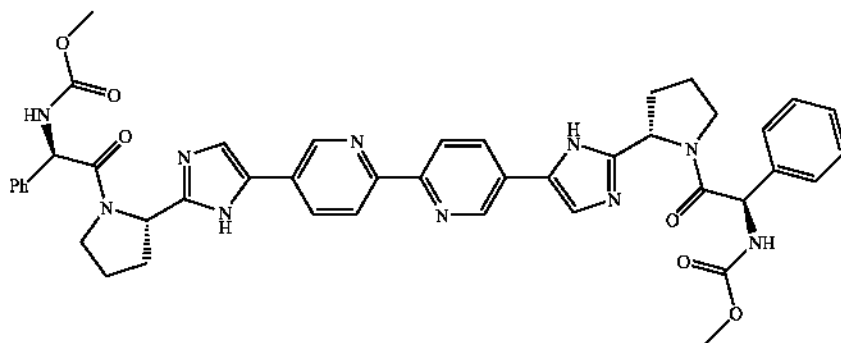
[0711] LC (Cond. 1): RT=1.17 min; >98% homogeneity index

[0712] LC/MS: Anal. Calcd. for [M+H]⁺ C₂₄H₂₇N₈: 427.24; found 427.13

Example 145

dimethyl (2,2'-bipyridine-5,5'-diylbis(1H-imidazole-5,2-diyl)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl))biscarbamate

[0713]



[0714] Example 145 (TFA salt) was synthesized from 145b according to the preparation of Example 132 from 132e.

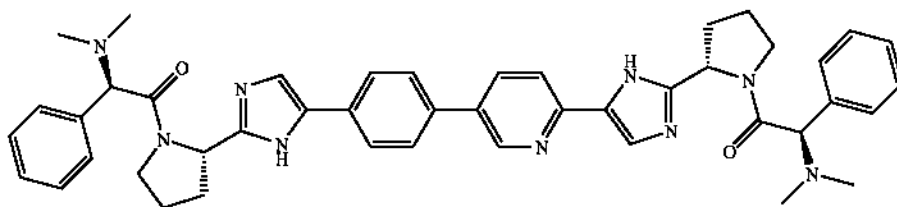
[0715] LC (Cond. 1): RT=1.63 min; 98% homogeneity index

[0716] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_{10}O_6$: 809.35; found 809.40

Example 146

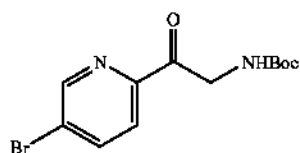
(1R)-2-((2S)-2-(5-(5-(4-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidiny)-1H-imidazol-5-yl)phenyl)-2-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidiny)-N,N-dimethyl-2-oxo-1-phenylethylamine

[0717]



Example 146, Step a

[0718]



146a.

[0719] n-BuLi (12.0 mL of 2.5M/hexanes, 30 mmol) was added drop-wise over 15 min to a cooled (-78°C .) toluene

(300 mL) semi-solution of 2,5-dibromopyridine (6.040 g, 25.5 mmol), and stirred for 2.5 hr. t-Butyl 2-(methoxy(methyl)amino)-2-oxoethylcarbamate (2.809 g, 12.87 mmol) was added in batches over 7 min, and stirring continued for 1.5 hr at -78°C . The -78°C . bath was replaced with -60°C . bath, which was allowed to warm up to -15°C . over 2.5 hr. The reaction was quenched with saturated NH_4Cl solution (20 mL), and the mixture was allowed to thaw to ambient temperature and the organic layer was separated and evaporated in vacuo. The resulting crude material was purified by flash chromatography (silica gel; 15% EtOAc/hexanes) to afford a reddish brown semisolid, which was washed with hexanes to removed the colored residue. Pyridine 146a was retrieved as an ash colored solid (842 mg). ^1H NMR (DMSO, $\delta=2.5$ ppm; 400 MHz): 8.89 (d, $J=2.3$, 1H), 8.30 (dd, $J=8.4$, 2.4, 1H), 7.90 (d, $J=8.3$, 1H), 7.03 (br t, $J=5.7$; 0.88H), 6.63

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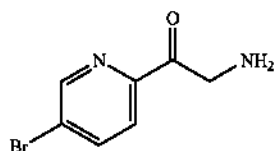
(app br s, 0.12H), 4.55 (d, J=5.8, 2H), 1.40/1.28 (two app s, 7.83H+1.17H).

[0720] LC (Cond. 1): RT=2.00 min; >95% homogeneity index

[0721] LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{12}H_{15}BrNaN_2O_3$: 337.02; found 337.13

Example 146, Step b

[0722]



146b

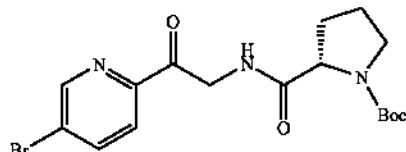
[0723] 48% HBr (1.0 mL) was added drop-wise to a dioxane (5.0 mL) solution of carbamate 146a (840 mg, 2.66 mmol) over 3 min, and the reaction mixture was stirred at ambient temperature for 17.5 hr. The precipitate was filtered and washed with dioxane, and dried in vacuo to afford amine the HBr salt of 146b as an off-white solid (672.4 mg; the exact mole equivalent of the HBr salt was not determined). 1H NMR (DMSO, δ =2.5 ppm; 400 MHz): 8.95 (d, J=2.3, 1H), 8.37 (dd, J=8.4, 2.3, 1H), 8.2 (br s, 3H), 8.00 (d, J=8.3, 1H), 4.61 (s, 2H).

[0724] LC (Cond. 1): RT=0.53 min

[0725] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_8BrN_2O$: 214.98; found 215.00

Example 146, Step c

[0726]



146c

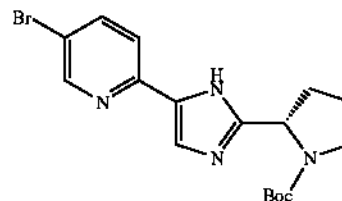
[0727] *i*-Pr₂EtN (2.3 mL, 13.2 mmol) was added drop-wise over 15 min to a heterogeneous mixture of amine 146b (1.365 g), (S)-Boc-proline (0.957 g, 4.44 mmol) and HATU (1.70 g, 4.47 mmol) in DMF (13.5 mL), and stirred at ambient temperature for 1 hr. The volatile component was removed in vacuo and the residue was partitioned between EtOAc (40 mL) and an aqueous medium (20 mL water+1 ml saturated NaHCO₃ solution). The aqueous layer was washed with EtOAc (20 mL), and the combined organic phase was dried (MgSO₄), filtered, and concentrated in vacuo. The resultant crude material was purified by flash chromatography (silica gel; 40-50% EtOAc/hexanes) to afford ketoamide 146c as a faint-yellow foam (1.465 g). 1H NMR (DMSO, δ =2.5 ppm; 400 MHz): 8.90 (d, J=2.3, 1H), 8.30 (dd, J=8.5, 2.4, 1H), 8.01-8.07 (m, 1H), 7.90 (d, J=8.3, 1H), 4.6 (m, 1H), 4.64 (dd, J=19.1, 5.5, 1H); 4.19 (m, 1H), 3.39 (m, 1H), 3.32-3.26 (m, 1H), 2.20-2.01 (m, 1H), 1.95-1.70 (m, 3H), 1.40/1.35 (two app s, 9H).

[0728] LC (Cond. 1): RT=1.91 min

[0729] LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{22}BrN_3NaO_4$: 434.07; found 433.96.

Example 146, Step d

[0730]



146d

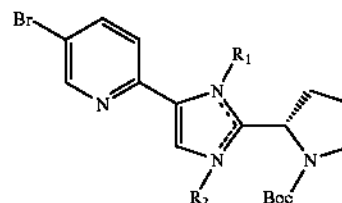
[0731] A mixture of ketoamide 146c (782.2 mg, 1.897 mmol) and NH₄OAc (800 mg, 10.4 mmol) in xylenes was heated with a microwave (140° C.) for 90 min. The volatile component was removed in vacuo and the residue was carefully partitioned between CH₂Cl₂ and water, where enough saturated NaHCO₃ solution was added to neutralize it. The aqueous phase was extracted with CH₂Cl₂ (2×), and the combined organic phase was dried (MgSO₄), filtered, and concentrated in vacuo. The resultant crude material was purified by flash chromatography (silica gel; 50% CH₂Cl₂/EtOAc) to afford imidazole 146d as an off-white solid (552.8 mg). 1H NMR (DMSO, δ =2.5 ppm; 400 MHz): 12.49/12.39/12.15/12.06 (br s, 1H), 8.62 (app br s, 0.2H), 8.56 (d, J=2, 0.8H), 8.02 (br d, J=8.5, 0.2H), 7.97 (br d, J=7.8, 0.8H), 7.77 (d, J=8.6, 0.8H), 7.72 (d, J=8.6, 0.2H), 7.61-7.49 (m, 1H), 4.93-4.72 (m, 1H), 3.53 (m, 1H), 3.41-3.32 (m, 1H), 2.33-1.77 (m, 4H), 1.39/1.14 (app br s, 3.7H+5.3H).

[0732] LC (Cond. 1): RT=1.67 min; >95% homogeneity index

[0733] LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{21}BrN_4NaO_2$: 415.08; found 415.12

Example 146, Step e

[0734]



146e

(R₁ = H, R₂ = SEM) or (R₁ = SEM, R₂ = H)

[0735] NaH (60%; 11.6 mg, 0.29 mmol) was added in one batch to a heterogeneous mixture of imidazole 146d (80 mg, 0.203 mmol) and DMF (1.5 mL), and stirred at ambient condition for 30 min. SEM-Cl (40 μ L, 0.226 mmol) was added drop-wise over 2 min to the above reaction mixture, and stirring was continued for 14 hr. The volatile component was removed in vacuo and the residue was partitioned between water and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂, and the combined organic phase was dried

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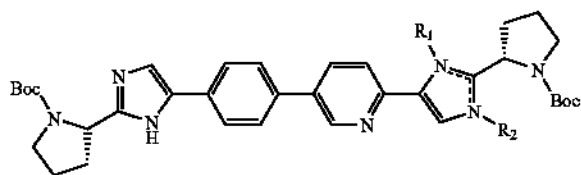
(MgSO₄), filtered, and concentrated in vacuo. The crude material was purified by a flash chromatography (silica gel; 20% EtOAc/hexanes) to afford 146e as a colorless viscous oil (87.5 mg). The exact regiochemistry of 146e was not determined. ¹H NMR (CDCl₃, δ=7.4 ppm; 400 MHz): 8.53 (d, J=2.2, 1H), 7.90-7.72 (m, 2H), 7.52 (s, 1H), 5.87 (m, 0.46H), 5.41 (m, 0.54H), 5.16 (d, J=10.8, 1H), 5.03-4.85 (m, 1H), 3.76-3.42 (m, 4H), 2.54-1.84 (m, 4H), 1.38/1.19 (br s, 4.3H+4.7H), 0.97-0.81 (m, 2H), -0.03 (s, 9H).

[0736] LC (Cond. 1): RT=2.1 min

[0737] LC/MS: Anal. Calcd. for [M+H]⁺ C₂₃H₃₆BrN₄O₃Si: 523.17; found 523.24

Example 146, Step f

[0738]



146f: (R₁ = H, R₂ = SEM) or (R₁ = SEM, R₂ = H)

[0739] Pd(PPh₃)₄ (24.4 mg, 0.021 mmol) was added to a mixture of imidazole 146e (280 mg, 0.535 mmol), 1c (241.5 mg, 0.55 mmol) and NaHCO₃ (148.6 mg, 1.769 mmol) in 1,2-dimethoxyethane (4.8 mL) and water (1.6 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 80° C. for ~24 hr and then the volatile component was removed in vacuo. The residue was partitioned between CH₂Cl₂ and water, and the organic phase was dried (MgSO₄), filtered, and concentrated in vacuo. The crude material was purified by a Biotage system (silica gel; 75-100% EtOAc/hexanes) followed by a reverse phase HPLC (H₂O/MeOH/TFA). The HPLC elute was neutralized with 2M NH₃/MeOH and evaporated in vacuo, and the residue was partitioned between water and CH₂Cl₂. The organic layer was dried

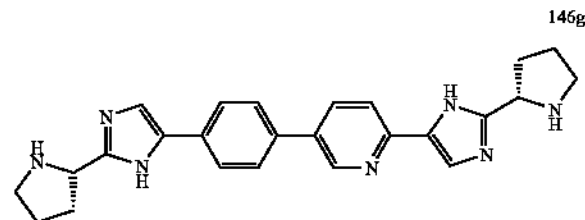
(MgSO₄), filtered, and concentrated in vacuo to afford 146f as a white foam (162 mg).

[0740] LC (Cond. 1): RT=2.1 min

[0741] LC/MS: Anal. Calcd. for [M+H]⁺ C₄₁H₅₈N₇O₅Si: 756.43; found 756.55

Example 146, Step g

[0742]



[0743] Carbamate 146f (208 mg, 0.275 mmol) was treated with 25% TFA/CH₂Cl₂ (4.0 mL) and stirred at ambient temperature for 10 hr. The volatile component was removed in vacuo and the residue was first free-based by MCX (MeOH wash; 2.0 M NH₃/MeOH elution) and then purified by a reverse phase HPLC (H₂O/MeOH/TFA), and the resultant material was free-based again (MCX) to afford pyrrolidine 146g as a film of oil (53.7 mg). ¹H NMR (DMSO, δ=2.5 ppm; 400 MHz): 1.88 (app br s, 2H), 8.83 (d, J=2.1, 1H), 8.07 (dd, J=8.3/2.3, 1H), 7.87 (d, J=8.5, 1H), 7.84 (d, J=8.3, 2H), 7.71 (d, J=8.3, 2H), 7.55 (s, 1H), 7.50 (br s, 1H), 4.18 (m, 2H), 3.00-2.94 (m, 2H), 2.89-2.83 (m, 2H), 2.11-2.02 (m, 2H), 1.95-1.86 (m, 2H), 1.83-1.67 (m, 4H).

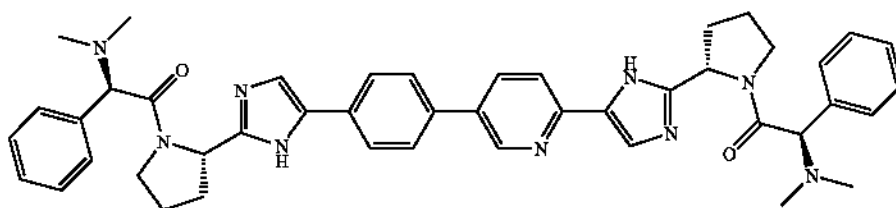
[0744] LC (Cond. 1): RT=0.95 min; >98% homogeneity index

[0745] LC/MS: Anal. Calcd. for [M+H]⁺ C₂₅H₂₈N₇: 426.24; found 426.27

Example 146

(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine

[0746]



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[0747] Example 146 (TFA salt) was synthesized from pyrrolidine 146g according to the preparation of Example 132 from intermediate 132e.

[0748] LC (Cond. 1): RT=1.42 min; 96.5% homogeneity index

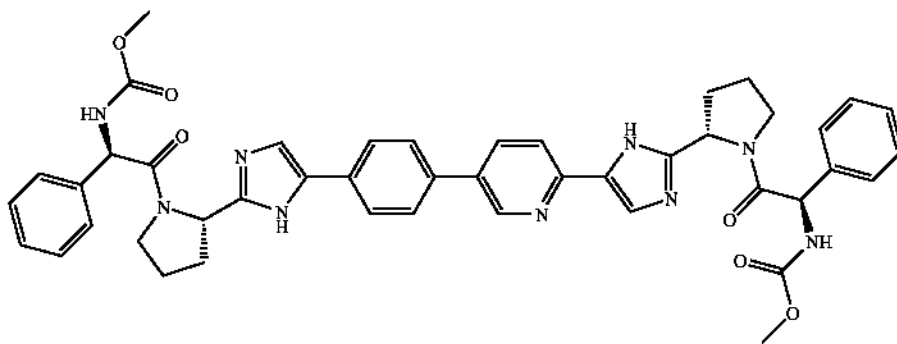
[0749] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.41; found 748.57

[0750] HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.4087; found 748.4100

Example 147

methyl ((1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl) carbamate

[0751]



[0752] The TFA salt of Example 147 was prepared similarly from intermediate 146g by using Cap-4.

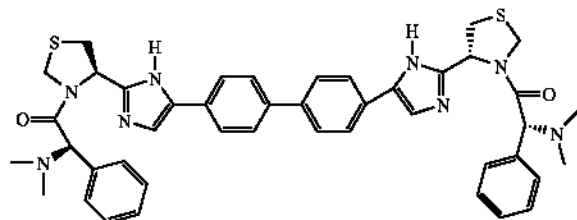
[0753] LC (Cond. 1): RT=1.66 min; 95% homogeneity index

[0754] LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; found 808.55

Example 148

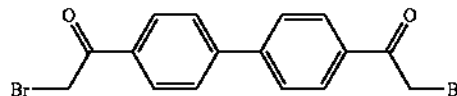
(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

[0755]



Example 148, Step a

[0756]



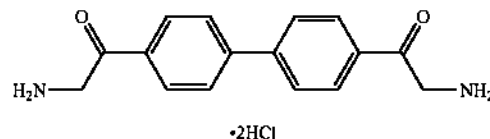
[0757] A solution of bromine (1.3 mL, 25.0 mmol) in 15 mL glacial acetic acid was added drop-wise to a solution of 4,4'-diacetyl biphenyl (3.0 g, 12.5 mmol) in 40 mL acetic acid at 50° C. Upon completion of addition the mixture was stirred at room temperature overnight. The precipitated product was filtered off and re-crystallized from chloroform to give 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (3.84 g, 77.5%) as a white solid.

[0758] 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 8.09 (4H, d, J=7.93 Hz) 7.75 (4H, d, J=8.24 Hz) 4.47 (4H, s)

[0759] Nominal/LRMS—Anal. Calcd. for 369.07 found; $(M+H)^+$ —397.33, $(M-H)^-$ —395.14

Example 148, Step b

[0760]



[0761] Sodium diformylamide (3.66 g, 38.5 mmol) was added to a suspension of 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (6.1 g, 15.4 mmol) in 85 mL acetonitrile. The mixture was heated at reflux for 4 hours and concentrated under reduced pressure. The residue was suspended in 300 mL 5% HCl in ethanol and heated at reflux for 3.5 hours. Reaction was cooled to room temperature and placed in the freezer for 1 hour. Precipitated solid was collected, washed with 200 mL 1:1 ethanol/ether followed by 200 mL pentane, and dried under vacuum to give 1,1'-(biphenyl-4,4'-diyl)bis(2-aminoethanone) dihydrochloride (4.85 g, 92%). Carried on without further purification.

[0762] 1H NMR (300 MHz, DMSO- d_6) δ ppm 8.47-8.55 (4H, m) 8.11-8.17 (4H, m) 8.00 (4H, d, J=8.42 Hz) 4.59-4.67 (4H, m).

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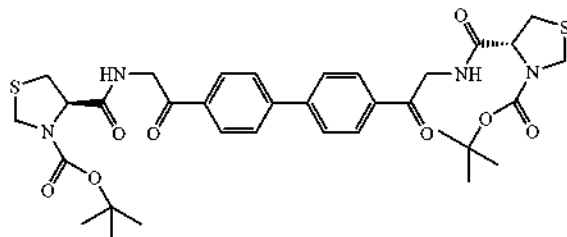
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[0763] LCMS—Phenomenex C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, t_R =0.44 minutes, Anal. Calcd. for $C_{16}H_{16}N_2O_2$ 268.31 found; 269.09 (M+H)⁺.

Example 148, Step c

[0764]



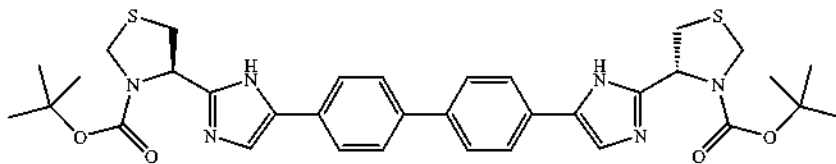
[0765] To a stirred solution of 1,1'-(biphenyl-4,4'-diyl)bis(2-aminoethanone) dihydrochloride (0.7 g, 2.1 mmol), N-(tert-butoxy carbonyl)-L-thiopropine (0.96 g, 4.2 mmol), and HATU (1.68 g, 4.4 mmol) in 14 mL DMF was added diisopropylethyl amine (1.5 mL, 8.4 mmol) drop-wise over 5 minutes. The resulting clear yellow solution was stirred at room temperature overnight (14 hours) and concentrated under reduced pressure. The residue was partitioned between 20% methanol/chloroform and water. The aqueous phase was washed once with 20% methanol/chloroform. The combined organics were washed with brine, dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude product was chromatographed on silica gel by gradient elution with 10-50% ethyl acetate/CH₂Cl₂ to give (4S,4'S)-tert-butyl 4,4'-(2,2'-(biphenyl-4,4'-diyl)bis(2-oxoethane-2,1-diyl))bis(azanediy)bis(oxomethylene)dithiazolidine-3-carboxylate (0.39 g, 27%) as an orange foam.

[0766] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.38 (2H, s) 8.12 (4H, d, J=8.56 Hz) 7.94 (4H, d, J=8.56 Hz) 4.60-4.68 (4H, m) 4.33-4.38 (2H, m) 3.58-3.68 (2H, m) 3.38 (2H, s) 3.08-3.18 (2H, m) 1.40 (18H, s)

[0767] LCMS—Water-Sunfire C-18 4.6×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, t_R =3.69 min., Anal. Calcd. for $C_{34}H_{42}N_4O_8S_2$ 698.85 found; 699.12 (M+H)⁺.

Example 148, Step d

[0768]



[0769] (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dithiazolidine-3-carboxylate (0.39 g, 0.56 mmol) and ammonium acetate (0.43 g, 5.6 mmol)

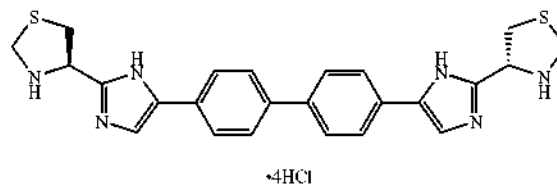
were suspended in 8 mL o-xylene in a microwave reaction vessel. The mixture was heated under standard microwave conditions at 140° C. for 70 minutes and concentrated under reduced pressure. The residue was dissolved in 30 mL 20% methanol/chloroform and washed with 10% NaHCO₃(aq). The organic layer was washed with brine, dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude product was chromatographed on silica gel by gradient elution with 1-6% methanol/CH₂Cl₂ to give (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dithiazolidine-3-carboxylate (0.15 g, 41%) as a yellow solid.

[0770] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 12.02 (2H, s) 7.70-7.88 (10H, m) 5.28-5.37 (2H, m) 4.68 (2H, d, J=9.16 Hz) 4.47-4.55 (2H, m) 3.46 (2H, s) 3.23 (2H, s) 1.26-1.43 (18H, m)

[0771] LCMS—Luna C-18 3.0×50 mm, 0 to 100% B over 3.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate, t_R =1.96 min., Anal. Calcd. for $C_{34}H_{40}N_6O_4S_2$ 660.85 found; 661.30 (M+H)⁺, 659.34 (M-H)⁻

Example 148, Step e

[0772]



[0773] To a solution of (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dithiazolidine-3-carboxylate in 1 mL dioxane was added 0.3 mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 3 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 4,4'-bis(2-((S)-thiazolidin-4-yl)-1H-imidazol-5-yl)-biphenyl tetrahydrochloride (0.12 g, 100%) as a yellow solid.

[0774] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.09 (2H, s) 8.01 (4H, d, J=8.55 Hz) 7.90 (4H, d, J=8.55 Hz) 5.08 (2H, t, J=6.10 Hz) 4.38 (2H, d, J=9.16 Hz) 4.23 (2H, d, J=9.46 Hz) 3.48-3.54 (2H, m,) 3.35-3.41 (2H, m)

[0775] LCMS—Luna C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile,

5% water, 10 mm ammonium acetate, t_R =1.70 min., Anal. Calcd. for $C_{24}H_{24}N_6S_2$ 460.62 found; 461.16 (M+H)⁺, 459.31 (M-H)⁻

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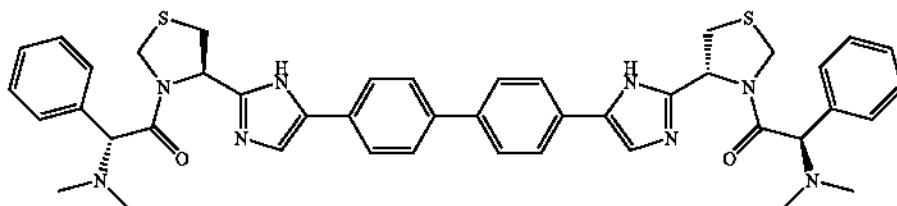
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Example 148

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

[0776]



[0777] To a stirred solution of (4,4'-bis(2-((S)-thiazolidin-4-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride (0.028 g, 0.046 mmol), (R)-2-(dimethylamino)-2-phenylacetic acid (Cap-1, 0.017 g, 0.010 mmol), and HATU (0.039 g, 0.10 mmol) in 2 mL DMF was added diisopropylethyl amine (0.05 mL, 0.28 mmol). The reaction was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The crude product was purified by reverse-phase preparative HPLC to provide (2R,2'R)-1,1'-((4S,4'S)-4,4'-(5,5'-(biphenyl-4,4'-diyl))bis(1H-imidazole-5,2-diyl))bis(thiazolidine-4,3-diyl))bis(2-(dimethylamino)-2-phenylethanone), TFA salt (0.012 g, 21%)

[0778] ^1H NMR (500 MHz, DMSO- d_6) δ ppm 7.59-7.91 (20H, m) 5.62 (2H, dd, $J=6.56, 2.59$ Hz) 4.99 (2H, d, $J=8.85$

Hz) 4.82/4.35 (2H, s) 4.22 (2H, s) 3.42 (2H, s) 3.25 (2H, s) 2.35-2.61 (12H, m)

[0779] LCMS—Luna C-18 3.0x50 mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mM ammonium acetate, B=95% acetonitrile, 5% water, 10 mM ammonium acetate mobile phase $t_R=3.128$ min.

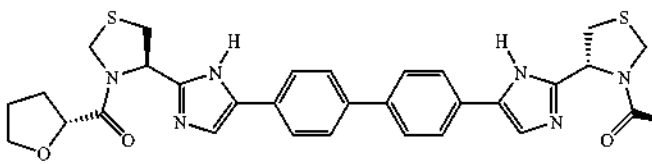
[0780] Nominal/LRMS—Calcd. for $\text{C}_{44}\text{H}_{46}\text{N}_8\text{O}_2\text{S}_2$ 783.03; found 783.28 (M+H) $^+$

[0781] Accurate/HRMS—Calcd. for $\text{C}_{44}\text{H}_{47}\text{N}_8\text{O}_2\text{S}_2$ 783.3263; 783.3246 (M+H) $^+$

[0782] Examples 149 and 150 were prepared in similar fashion as described for the preparation of example 148.

Example	Compound Name	Structure	Data
Example 149	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediy))biscarbamate	<p>from 148c and Cap-4</p>	$t_R = 3.36$ min (LCMS—Luna C-18 3.0 x 50 mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10 mM ammonium acetate, B = 95% acetonitrile, 5% water, 10 mM ammonium acetate) LRMS: Anal. Calcd. for $\text{C}_{44}\text{H}_{42}\text{N}_8\text{O}_6\text{S}_2$ 842.99 found: 843.25 (M + H) $^+$ HRMS: Anal. Calcd. for $\text{C}_{44}\text{H}_{43}\text{N}_8\text{O}_6\text{S}_2$ 843.2747 found: 843.2724 (M + H) $^+$

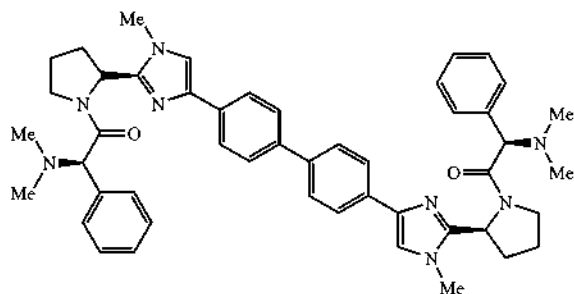
-continued

Example	Compound Name	Structure	Data
Example 150	(4R,4'R)-4,4'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl)bis(3-((2R)-tetrahydro-2-furanylcarbonyl)-1,3-thazolidine)		$t_R = 4.32$ min (HPLC-X-Terra C-18 4.6 x 50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time. A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA) LRMS: Anal. Calcd. for $C_{34}H_{36}N_6O_4S_2$ 656.83 found: 657.32 (M + H) ⁺

Example 151

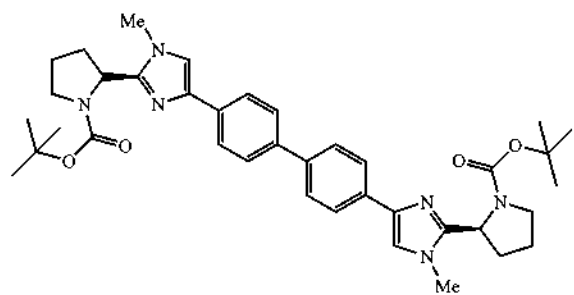
(1R,1'R)-2,2'-(4,4'-biphenyldiyl)bis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

[0783]



Example 151, Step a

[0784]

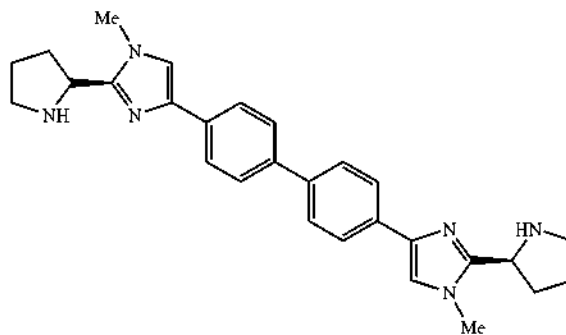


[0785] To a stirred solution of 1d, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (100 mg, 0.16 mmole) and iodomethane (40 μ L, 0.16 mmole) in CH_2Cl_2 (2 mL) was

added sodium hydride (40%) (21.2 mg, 0.352 mmole). After five hours at ambient temperature, it was concentrated under reduced pressure. The crude reaction product 151a, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (~90 mg) was moved onto next step without further purification (purity ~85%) LCMS: Anal. Calcd. for: $C_{38}H_{48}N_6O_4$ 652.83; Found: 653.51 (M+H)⁺. It should be recognized that multiple methylation isomers are possible in this reaction and no attempt to assign these was made.

Example 151, Step b

[0786]



[0787] 151a, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (100 mg, 0.153 mmole) treated with 4 M HCl/dioxane (20 mL). After three hours at ambient temperature, it was concentrated under reduced pressure. The crude reaction product, 4,4'-bis(1-methyl-2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)biphenyl (~110 mg, HCl salt) was moved onto the next step without further purification (purity 85%) LCMS: Anal. Calcd. for: $C_{28}H_{32}N_6$ 452.59; Found: 453.38 (M+H)⁺. Multiple imidazole isomers were present and carried forward.

Example 151

[0788] HATU (58.9 mg, 0.150 mmol) was added to a mixture of 151b, 4,4'-bis(1-methyl-2-((S)-pyrrolidin-2-yl)-1H-

imidazol-4-yl)biphenyl (45.0 mg, 0.075 mmol), (i-Pr)₂EtN (78 μ L, 0.451 mmol) and Cap-1, (R)-2-(dimethylamino)-2-phenylacetic acid (0.026 mg 0.150 mmol) in DMF (1.0 mL). The resultant mixture was stirred at ambient temperature until the coupling was complete as determined by LC/MS analysis. Purification was accomplished by reverse-phase preparative HPLC (Waters-Sunfire 30 \times 100 mm S5, detection at 220 nm, flow rate 30 mL/min, 0 to 90% B over 14 min; A=90% water, 10% ACN, 0.1% TFA, B=10% water, 90% ACN, 0.1% TFA) to provide two isomer of 151, (2R,2'R)-1,1'-((2S,2'S)-2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-(dimethylamino)-2-phenylethanone), TFA salts.

Isomer 1: (1R,1'R)-2,2'-(4,4'-biphenyldiylbis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

[0789] (8 mg, 8.6%) as a colorless wax.

[0790] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.84-2.25 (m, 8H) 2.32-2.90 (m, 12H) 3.67-3.92 (m, 8H) 4.07 (s, 2H) 5.23 (s, 2H) 5.51 (s, 2H) 7.51-7.91 (m, 20H)

[0791] HPLC Xterra 4.6 \times 50 mm, 0 to 100% B over 10 minutes, one minutes hold time, A=90% water, 10% methanol, 0.2% phosphoric acid, B=10% water, 90% methanol, 0.2% phosphoric acid, RT=2.74 min, 98%.

[0792] LCMS: Anal. Calcd. for: C₄₈H₅₄N₈O₂ 775.02; Found: 775.50 (M+H)⁺.

Isomer 2: (1R,1'R)-2,2'-(4,4'-biphenyldiylbis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

[0793] (10.2 mg, 11%) as a colorless wax.

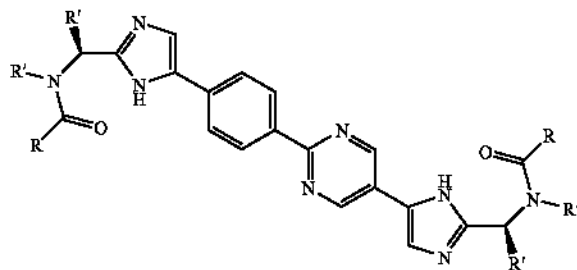
[0794] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.83-2.26 (m, 8H) 2.30-2.92 (m, 12H) 3.68-3.94 (m, 8H) 4.06 (s, 2H) 5.25 (d, J=2.14 Hz, 2H) 5.50 (s, 2H) 7.52-7.91 (m, 20H).

[0795] HPLC Xterra 4.6 \times 50 mm, 0 to 100% B over 10 minutes, one minutes hold time, A=90% water, 10% methanol, 0.2% phosphoric acid, B=10% water, 90% methanol, 0.2% phosphoric acid, RT=2.75 min, 90%.

[0796] LCMS: Anal. Calcd. for: C₄₈H₅₄N₈O₂ 775.02; Found: 775.52 (M+H)⁺.

Example 152

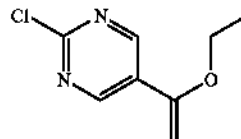
[0797]



Example 152a-1 Step a

2-Chloro-5-(1-ethoxyvinyl)pyrimidine

[0798]



[0799] To a solution of 5-bromo-2-chloropyrimidine (12.5 g, 64.62 mmol) in dry DMF (175 mL) under N₂ was added tributyl(1-ethoxyvinyl)tin (21.8 mL, 64.62 mmol) and dichlorobis(triphenylphosphine)palladium (II) (2.27 g, 3.23 mmol). The mixture was heated at 100° C. for 3 h before being allowed to stir at room temperature for 16 hr. The mixture was then diluted with ether (200 mL) and treated with aqueous KF soln (55 g of potassium fluoride in 33 mL of water). The two phase mixture was stirred vigorously for 1 h at room temperature before being filtered through diatomaceous earth (Celite®). The filtrate was washed with sat'd NaHCO₃ soln and brine prior to drying (Na₂SO₄). The original aqueous phase was extracted with ether (2 \times) and the organic phase was treated as above. Repetition on 13.5 g of 5-bromo-2-chloropyrimidine and combined purification by Biotage™ flash chromatography on silica gel (gradient elution on a 65M column using 3% ethyl acetate in hexanes to 25% ethyl acetate in hexanes with 3.0 L) afforded the title compound as a white, crystalline solid (18.2 g, 73%).

[0800] ¹H NMR (500 MHz, DMSO-d₆) δ 8.97 (s, 2H), 5.08 (d, J=3.7 Hz, 1H), 4.56 (d, J=3.4 Hz, 1H), 3.94 (q, J=7.0 Hz, 2H), 1.35 (t, J=7.0 Hz, 3H).

[0801] LCMS Phenomenex LUNA C-18 4.6 \times 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.53 min, 98.8% homogeneity index.

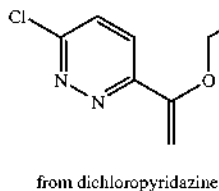
[0802] LCMS: Anal. Calcd. for C₈H₁₀ClN₂O 185.05; found: 185.04 (M+H)⁺.

[0803] HRMS: Anal. Calcd. for C₈H₁₀ClN₂O 185.0482; found: 185.0490 (M+H)⁺.

[0804] The same method was used for the preparation of Examples 152a-2 & 152a-3:

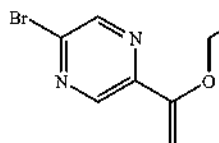
[0805] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6 \times 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

[0806] Condition 2: Phenomenex LUNA C-18 4.6 \times 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

Example
152a-2

from dichloropyridazine

$t_R = 2.24$ min 96.4%,
condition 1
LRMS: Anal.
Calcd. for
 $C_8H_{10}ClN_2O$ 185.05;
found: 185.06 (M + H)⁺.
HRMS: Anal. Calcd. for
 $C_8H_{10}ClN_2O$ 185.0482;
found: 185.0476
(M + H)⁺.

Example
152a-3

from dibromopyrazine

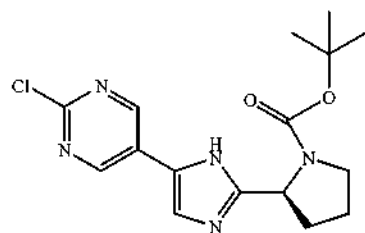
$t_R = 2.82$ min (52.7%,
inseparable with 2,5-
dibromopyrazine
($t_R = 1.99$ min,
43.2%)); condition 1
LRMS: Anal.
Calcd. for
 $C_8H_{10}BrN_2O$ 229.00;
found: 228.93 (M + H)⁺.

Example 152d-1 to 152d-6

Example 152b-1, Step b

(S)-tert-Butyl 2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate or (S)-2-[5-(2-Chloro-pyrimidin-5-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester

[0807]



[0808] NBS (16.1 g, 90.7 mmol) was added in one portion to a stirred solution of 2-chloro-5-(1-ethoxyvinyl)pyrimidine (152a-1, 18.2 g, 98.6 mmol) in THF (267 mL) and H₂O (88 mL) at 0° C. under N₂. The mixture was stirred for 1 h at 0° C. before it was diluted with more H₂O and extracted with ethyl acetate (2×). The combined extracts were washed with sat'd NaHCO₃ soln and brine prior to drying (Na₂SO₄), filtration, and solvent evaporation. LCMS Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=1.52 min (unsymmetrical peak). LCMS: Anal. Calcd. for $C_8H_{14}BrClN_2O$ 235.92; found: 236.85 (M+H)⁺.

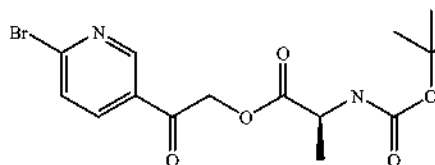
Example 152c-1, Step c

[0809] Half of the crude residue (2-bromo-1-(2-chloropyrimidin-5-yl)ethanone, ~14.5 g) was dissolved into anhydrous acetonitrile (150 mL) and treated directly with N-Boc-L-proline (9.76 g, 45.35 mmol) and diisopropylethylamine (7.9 mL, 45.35 mmol). After being stirred for 3 h, the solvent was removed in vacuo and the residue was partitioned into ethyl acetate and water. The organic phase was washed with 0.1N hydrochloric acid, sat'd NaHCO₃ soln and brine prior to drying (Na₂SO₄), filtration, and concentration. LCMS Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.66 min.

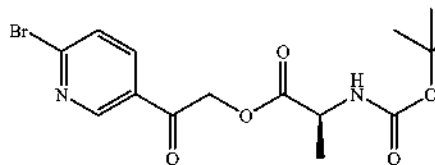
[0810] The same method was used to prepare Examples 152c through 152c-6.

[0811] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

[0812] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

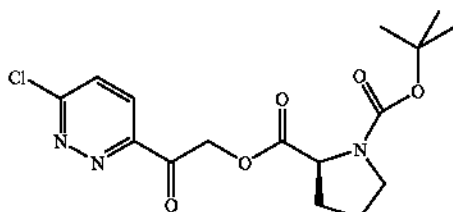
Example
152c-2

$t_R = 1.81$ min (condition
2, ~95%)
LRMS: Anal.
Calcd. for
 $C_{15}H_{19}BrN_4O_2$ 386.05
found: 387.07 (M + H)⁺.

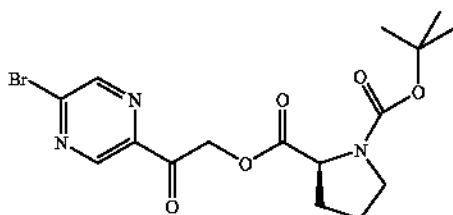
Example
152c-3

$t_R = 1.84$ min (condition
2, 94%)
LRMS: Anal.
Calcd. for
 $C_{15}H_{19}BrN_4O_2$ 386.05;
found: 387.07 (M + H)⁺.

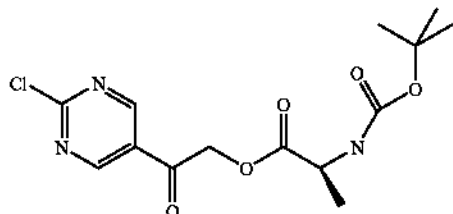
-continued

Example
152c-3a

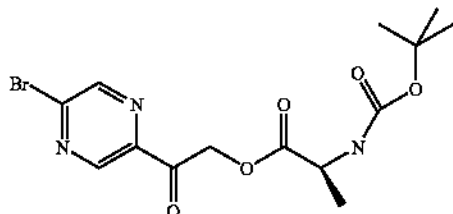
t_R = 2.65 min; condition 1
LCMS: Anal.
Calcd. for
 $C_{16}H_{20}ClN_3O_5$ 369.11
found: 391.89 (M + Na)⁺.

Example
152c-4

t_R = 1.94 min, (condition 2)
LCMS: Anal.
Calcd. for
 $C_{16}H_{21}BrN_3O_5$ 414.07
found: 414.11 (M + H)⁺.

Example
152c-5

t_R = 2.22 min; condition 1
LCMS: Anal.
Calcd. for
 $C_{14}H_{18}ClN_3O_5$ 343.09
found: undetermined.

Example
152c-6

t_R = 2.41 min, condition 1
LCMS: Anal.
Calcd. for
 $C_{14}H_{18}^{37}BrN_3O_5$ 389.04
found: 412.03 (M + Na)⁺.

Example 152d-1, Step d

[0813] This residue ((S)-1-tert-butyl 2-(2-(2-chloropyrimidin-5-yl)-2-oxoethyl)pyrrolidine-1,2-dicarboxylate) was taken up in xylenes (200 mL) and treated to NH_4OAc (17.5 g, 0.23 mol). The mixture was heated at 140° C. for 2 hr in a thick-walled, screw-top flask before it was cooled to ambient temperature and suction-filtered. The filtrate was then concentrated, partitioned into ethyl acetate and sat'd $NaHCO_3$ soln and washed with brine prior to drying (Na_2SO_4), filtration, and concentration. The original precipitate was partitioned into aqueous $NaHCO_3$ soln and ethyl acetate and sonicated for 2 min before being suction-filtered. The filtrate was washed with brine, dried over (Na_2SO_4), filtered, and concentrated to dryness. Purification of the combined residues by Biotage™ flash chromatography on silica gel (65M column, preequilibration with 2% B for 900 mL followed by gradient elution with 2% B to 2% B for 450 mL followed by 2% B to 40% B for 300 mL where B=methanol and A=dichloromethane) afforded the title compound (7.0 g, 44% yield, 2 steps, pure fraction) as a yellowish orange foam. The mixed fractions were subjected to a second Biotage™ chromatography on silica gel (40M column, preequilibration with 1% B for 600 mL followed by gradient elution with 1% B to 1% B for 150 mL followed by 1% B to 10% B for 1500 mL

where B=MeOH and A= CH_2Cl_2) afforded additional title compound (2.8 g, 18%) as a brownish-orange foam. 1H NMR (500 MHz, $DMSO-d_6$) δ 12.24-12.16 (m, 1H), 9.05 (s, 2H), 7.84-7.73 (m, 1H), 4.90-4.73 (m, 1H), 3.59-3.46 (m, 1H), 3.41-3.31 (m, 1H), 2.32-2.12 (m, 1H), 2.03-1.77 (m, 3H), 1.39 and 1.15 (2s, 9H).

[0814] LCMS Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=1.92 min, 94.7% homogeneity index.

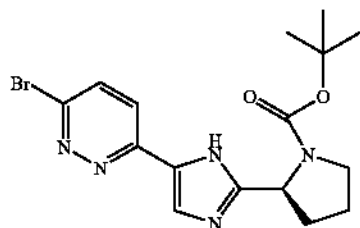
[0815] LRMS: Anal. Calcd. for $C_{16}H_{21}ClN_3O_2$ 350.14; found: 350.23 (M+H)⁺.

[0816] HRMS: Anal. Calcd. for $C_{16}H_{21}ClN_3O_2$ 350.1384; found: 350.1398 (M+H)⁺.

[0817] The same method was used to prepare Examples 152d-2 through 152d-6.

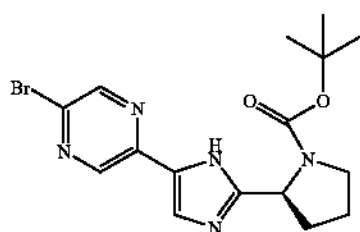
[0818] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

[0819] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

**Example
152d-2**

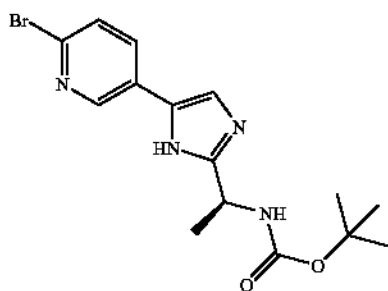
from 152c-3a

t_R = 1.92 min (86.5%);
condition 1
LRMS: Anal.
Calcd. for
 $C_{16}H_{21}ClN_5O_2$ 350.14;
found: 350.23 (M + H)⁺.
HRMS: Anal.
Calcd. for
 $C_{16}H_{21}ClN_5O_2$ 350.1384;
found: 350.1393 (M + H)⁺.

**Example
152d-3**

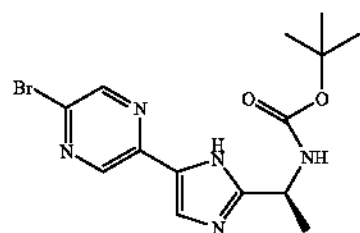
from 152c-4

t_R = 1.90 min (>95%);
condition 1
LRMS: Anal.
Calcd. for
 $C_{16}H_{21}BrN_5O_2$ 394.09;
found: 393.82 (M + H)⁺.
HRMS: Anal.
Calcd. for
 $C_{16}H_{21}BrN_5O_2$ 394.0879;
found: 394.0884 (M + H)⁺.

**Example
152d-4**

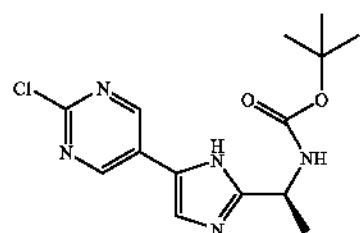
from 152c-3

t_R = 1.45 min
(condition 2,
100%)
LRMS: Anal.
Calcd. for
 $C_{15}H_{19}BrN_4O_2$ 366.07
found: 367.07 (M + H)⁺.

**Example
152d-5**

from 152c-6

t_R = 1.88 min (>95%);
condition 1
LRMS: Anal.
Calcd. for
 $C_{14}H_{18}BrN_5O_2$ 367.06;
found: 368.10 (M + H)⁺.

**Example
152d-6**

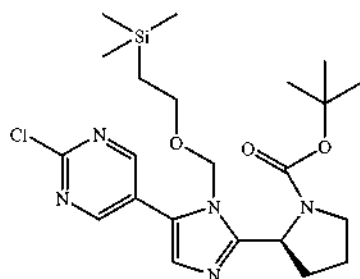
from 152c-5

t_R = 1.66 min (85%);
condition 1
LRMS: Anal.
Calcd. for
 $C_{14}H_{18}ClN_5O_2$ 323.11;
found: 324.15 (M + H)⁺.

Example 152e-1, Step e

Example 152e-1: (S)-tert-Butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[0820]



[0821] Sodium hydride (60% dispersion in mineral oil, 0.23 g, 5.72 mmol) was added in one portion to a stirred solution of (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (152d-1, 2.0 g, 5.72 mmol) in dry DMF (45 mL) at ambient temperature under N_2 . The mixture was stirred for 5 min. before SEM chloride (1.01 mL, 5.72 mmol) was added in approx. 0.1 mL increments. The mixture was stirred for 3 h before being quenched with

sat'd NH_4Cl soln and diluted with ethyl acetate. The organic phase was washed with sat'd $NaHCO_3$ soln and brine, dried over (Na_2SO_4), filtered, and concentrated. The original aqueous phase was extracted twice more and the combined residue was purified by BiotageTM flash chromatography (40M column, 50 mL/min, preequilibration with 5% B for 750 mL, followed by step gradient elution with 5% B to 5% B for 150 mL, 5% B to 75% B for 1500 mL, then 75% B to 100% B for 750 mL where solvent B is ethyl acetate and solvent A is hexanes). Concentration of the eluant furnished the title compound as a pale yellow foam (2.35 g, 85%).

[0822] 1H NMR (500 MHz, $DMSO-d_6$) δ 9.04 (s, 2H), 7.98-7.95 (m, 1H), 5.70-5.31 (3m, 2H), 5.02-4.91 (m, 1H), 3.59-3.49 (m, 3H), 3.45-3.35 (m, 1H), 2.30-2.08 (m, 2H), 1.99-1.83 (m, 2H), 1.36 and 1.12 (2s, 9H), 0.93-0.82 (m, 2H), -0.02 (s, 9H).

[0823] LCMS Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 2 minutes, 2 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.38 min, 95% homogeneity index.

[0824] LRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.22; found: 480.23 (M+H)⁺.

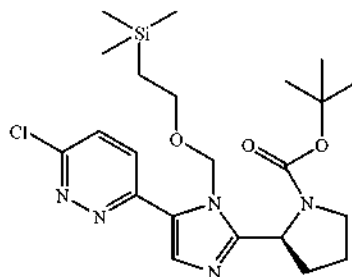
[0825] HRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.2198; found: 480.2194 (M+H)⁺.

[0826] The same method was used to prepare 152e-2 through 152e-4

[0827] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

[0828] Condition 2: Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

Example 152e-2

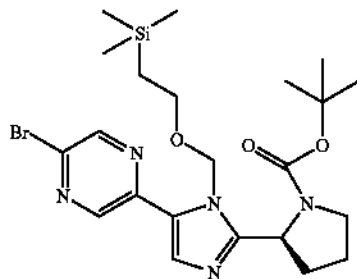


from 152d-2

t_R = 2.34 min (85.7%);
condition 1
LCMS: Anal. Calcd. for
 $C_{22}H_{35}ClN_5O_3Si$ 480.22;
found: 480.22 (M + H)⁺.
HRMS: Anal. Calcd. for
 $C_{22}H_{35}ClN_5O_3Si$ 480.2198;
found: 480.2198 (M + H)⁺.

-continued

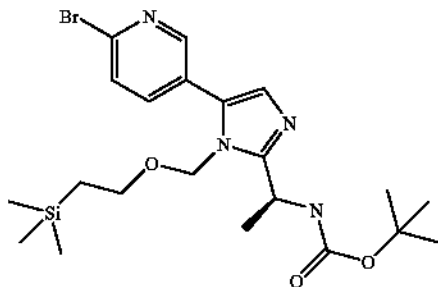
Example 152e-3



from 152d-3

$t_R = 3.18$ min (>95%);
condition 1
LCMS: Anal. Calcd. for
 $C_{22}H_{35}^{37}BrN_5O_3Si$ 526.17;
found: 525.99 (M + H)⁺.
HRMS: Anal. Calcd. for
 $C_{22}H_{35}^{37}BrN_5O_3Si$ 526.1692;
found: 526.1674 (M + H)⁺.

Example 152e-4



from 152d-4

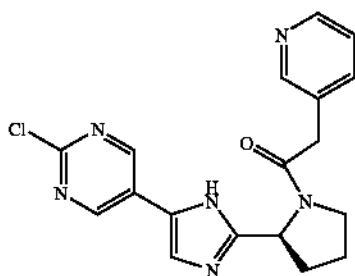
$t_R = 2.14$ min (condition 2,
96%)
LRMS: Anal. Calcd. For
 $C_{21}H_{33}BrN_4O_3Si$ 496.15
found: 497.13 (M + H)⁺.

Examples 152f-1 to 152f-2

Example 152f-1

(S)-1-(2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-(pyridin-3-yl)ethanone

[0829]



[0830] Cold (0° C.) 4 NHCl in dioxanes (5 mL) was added via syringe to (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (152d-1, 0.50 g, 1.43 mmol) in a 100 mL pear-shaped flask followed by MeOH (1.0 mL). The suspension was stirred at room temperature for 4 h before it was concentrated down to dryness and placed under high vacuum for 1 h. There was isolated intermediate (S)-2-chloro-5-(2-(pyrrolidin-2-yl)-1H-imidazol-5-yl)pyrimidine trihydrochloride as a pale yellow solid (with an orange tint) which was used without further purification.

[0831] HATU (0.60 g, 1.57 mmol) was added in one portion to a stirred solution of intermediate (S)-2-chloro-5-(2-(pyrrolidin-2-yl)-1H-imidazol-5-yl)pyrimidine trihydrochloride (0.46 g, 1.43 mmol, theoretical amount), 2-(pyridin-3-yl)acetic acid (0.25 g, 1.43 mmol) and DIEA (1.0 mL, 5.72 mmol) in anhydrous DMF (10 mL) at ambient temperature. The mixture was stirred at room temperature for 2 h before the DMF was removed in vacuo. The residue was taken up in CH_2Cl_2 and subjected to Biotage™ flash chromatography on silica gel (40M column, preequilibration with 0% B for 600 mL followed by step gradient elution with 0% B to 0% B for 150 mL followed by 0% B to 15% B for 1500 mL followed by 15% B to 25% B for 999 mL where B=MeOH and A= CH_2Cl_2). There was isolated the title compound (0.131 g, 25%, 2 steps) as a yellow solid.

[0832] ¹H NMR (500 MHz, DMSO- d_6) δ 9.10-9.08 (2s, 2H), 8.72-8.55 (series of m, 2H), 8.21-8.20 and 8.11-8.10 (2m, 1H), 8.00 and 7.93 (2s, 1H), 7.84-7.77 (series of m, 1H), 5.43-5.41 and 5.17-5.15 (2m, 1H), 4.02-3.94 (3m, 2H), 3.90-3.58 (3m, 2H), 2.37-2.26 (m, 1H), 2.16-1.85 (2m, 3H).

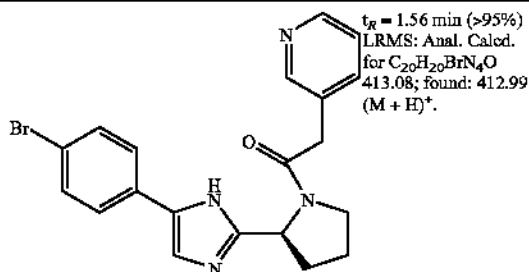
[0833] LCRMS Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=0.92 min, 95.1% homogeneity index.

[0834] LRMS: Anal. Calcd. for $C_{18}H_{18}ClN_6O$ 369.12; found: 369.11 (M+H)⁺.

[0835] HRMS: Anal. Calcd. for $C_{18}H_{18}ClN_6O$ 369.1231; found: 369.1246 (M+H)⁺.

[0836] Example 152f-2 LCMS conditions: Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

Example 152f-2

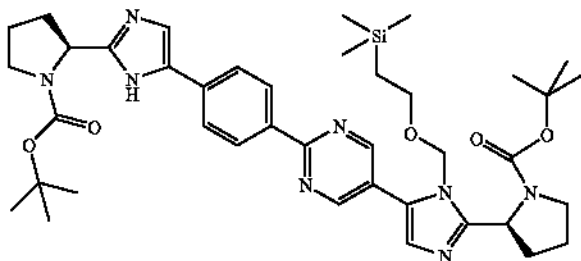


prepared from 1b with same procedure
describing the preparation of 152f-1
from 152d-1

Examples 152g-1 to 152g-16

Example 152g-1 from 1c and 152e-1. (S)-2-[5-(2-[4-[2-((S)-1-tert-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl]-pyrimidin-5-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester

[0837]



[0838] $Pd(Ph_3)_4$ (0.12 g, 0.103 mmol) was added in one portion to a stirred suspension of (S)-tert-butyl 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-ylpyrrolidine-1-carboxylate (1c, 1.00 g, 2.27 mmol), (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (152c-1, 0.99 g, 2.06 mmol) and $NaHCO_3$ (0.87 g, 10.3 mmol) in a solution of DME (20 mL) and H_2O (6 mL) at room temperature under N_2 . The vessel was sealed and the mixture was placed into a preheated (80° C.) oil bath and stirred at 80° C. for 16 h before additional catalyst (0.12 g) was added. After heating the mixture for an additional 12 h at 80° C., the mixture was cooled to ambient temperature, diluted with ethyl acetate and washed with sat'd $NaHCO_3$

soln and brine prior to drying over anhydrous sodium sulfate and solvent concentration. Purification of the residue by Biotage™ flash chromatography on silica gel using a 40M column (preequilibrated with 40% B followed by step gradient elution with 40% B to 40% B for 150 mL, 40% B to 100% B for 1500 mL, 100% B to 100% B for 1000 mL where B=ethyl acetate and A=hexanes) furnished the title compound as a yellow foam (1.533 g, 98%). A small amount of the yellow foam was further purified for characterization purposes by pHPLC (Phenomenex GEMINI, 30×100 mm, S10, 10 to 100% B over 13 minutes, 3 minute hold time, 40 mL/min, A=95% water, 5% acetonitrile, 10 mM NH_4OAc , B=10% water, 90% acetonitrile, 10 mM NH_4OAc) to yield 95% pure title compound as a white solid.

[0839] 1H NMR (500 MHz, $DMSO-d_6$) δ 12.30-11.88 (3m, 1H), 9.17-9.16 (m, 2H), 8.43-8.31 (m, 2H), 7.99-7.35 (series of m, 4H), 5.72-5.30 (3m, 2H), 5.03-4.76 (2m, 2H), 3.64-3.50 (m, 4H), 3.48-3.31 (m, 2H), 2.36-2.07 (m, 2H), 2.05-1.80 (m, 4H), 1.46-1.08 (2m, 18H), 0.95-0.84 (m, 2H), -0.01 (s, 9H).

[0840] HPLC Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.91 min, 95% homogeneity index.

[0841] LRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 757.42 (M+H)⁺.

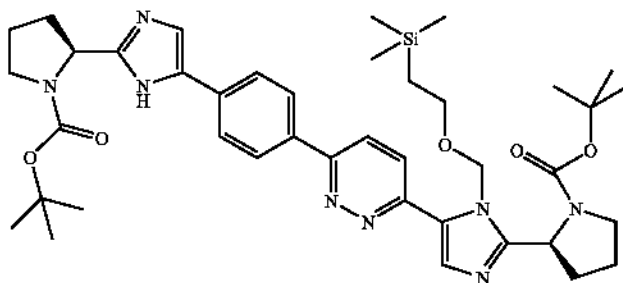
[0842] HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4191 (M+H)⁺.

[0843] The same procedure was used to prepare Examples 152g-2 through 152g-17:

[0844] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

[0845] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

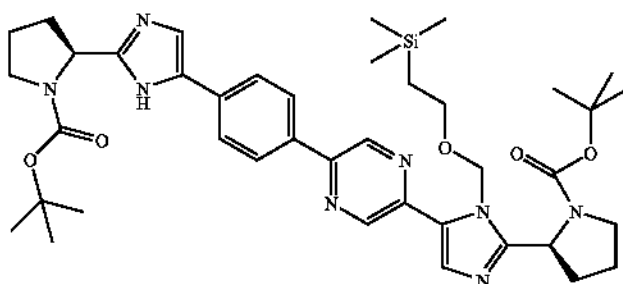
Example 152g-2



t_R = 2.81 min (79%); Condition 1
 LRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 758.05 ($M + H$)⁺.
 HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4196 ($M + H$)⁺.

Prepared from 1c and 152e-2

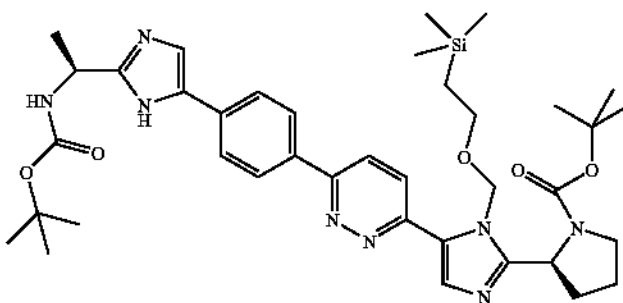
Example 152g-3



t_R = 2.89 min (>95%); Condition 1
 LRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 757.35 ($M + H$)⁺.
 HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4191 ($M + H$)⁺.

Prepared from 1c and 152e-3

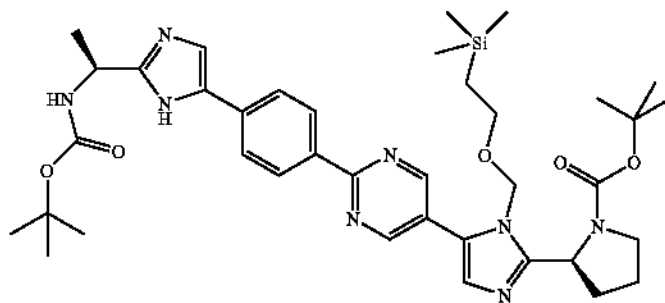
Example 152g-4



t_R = 2.87 min (97%); Condition 1
 LRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.41; found: 731.26 ($M + H$)⁺.
 HRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.4065; found: 731.4070 ($M + H$)⁺.

Prepared from 1-6c and 152e-2

Example 152g-5

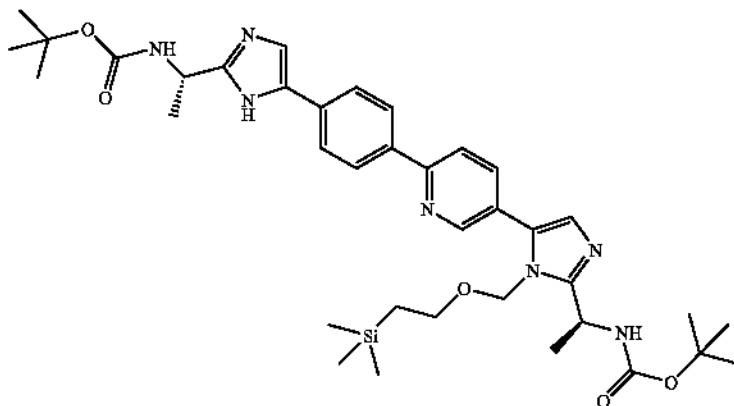


t_R = 2.94 min (>95%); Condition 1
 LRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.41; found: 731.26 ($M + H$)⁺.
 HRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.4065; found: 731.4046 ($M + H$)⁺.

Prepared from 1-6c and 152e-1

-continued

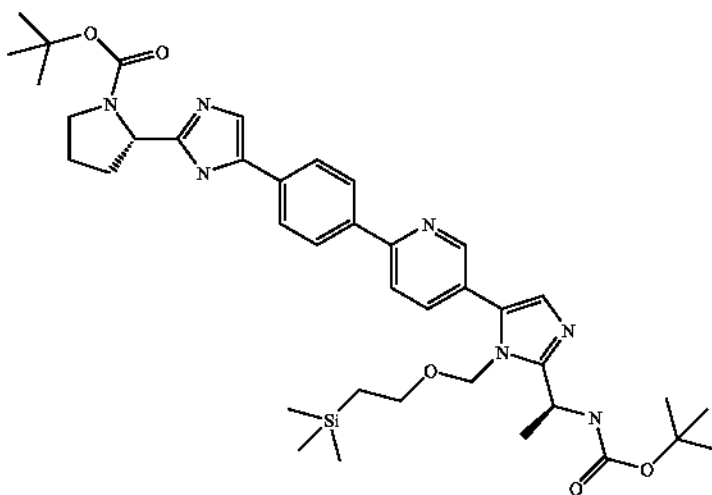
Example 152g-6



$t_R = 1.99$ min (condition 2, 96%)
LRMS: Anal. Calcd. for
 $C_{37}H_{53}N_7O_5Si$ 703.39; found:
704.34 ($M + H$)⁺.

Prepared from 1-6c and 152e-4

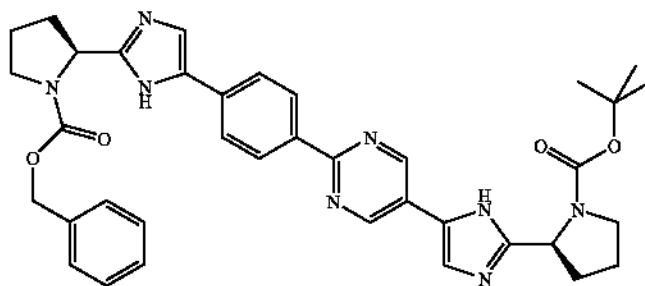
Example 152g-7



$t_R = 1.99$ min (condition 2, 96%)
LRMS: Anal. Calcd. for
 $C_{39}H_{55}N_7O_5Si$ 729.40; found:
730.42 ($M + H$)⁺.

Prepared from 1c and 152e-4

Example 152g-8

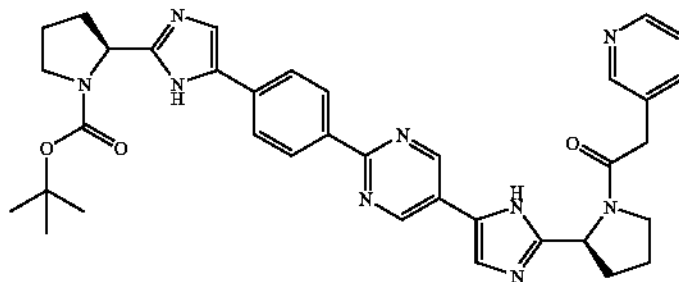


$t_R = 2.15$ min (>95%); Condition 1
LRMS: Anal. Calcd. for
 $C_{37}H_{41}N_8O_4$ 661.33; found:
661.39 ($M + H$)⁺.
HRMS: Anal. Calcd. for
 $C_{37}H_{41}N_8O_4$ 661.3251; found:
661.3268 ($M + H$)⁺.

Prepared from 1-5c and 152d-1

-continued

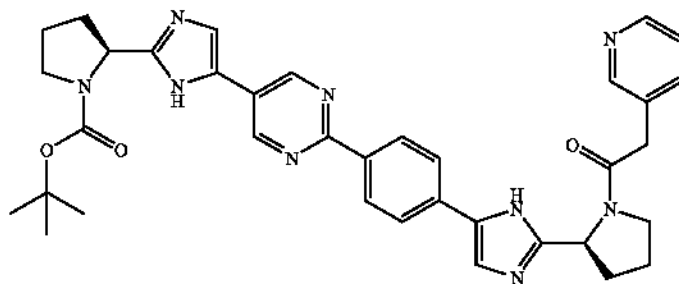
Example 152g-9



$t_R = 1.71$ min (>95%); Condition 1
 LRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.76; found: 646.47 (M + H)⁺.
 HRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ not done found: not done (M + H)⁺.

Prepared from 1c and 152f-1

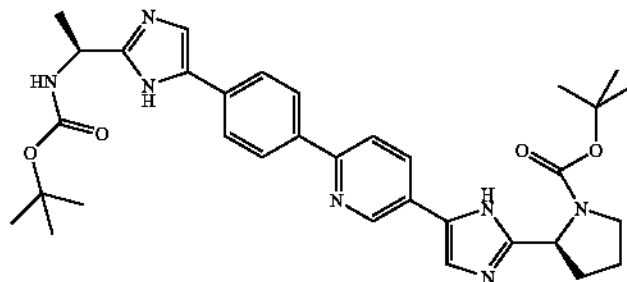
Example 152g-10



$t_R = 1.71$ min (>95%); Condition 1
 LRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.33; found: 646.37 (M + H)⁺.
 HRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.3254; found: 646.3240 (M + H)⁺.

Prepared from 152d-1 and 1-10c

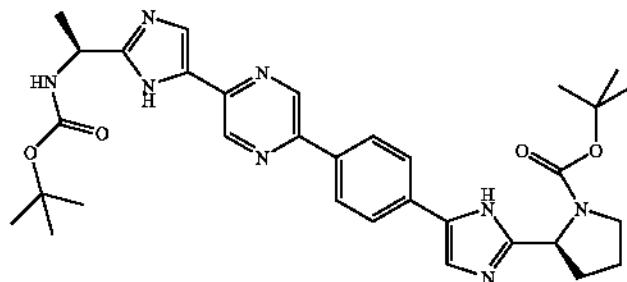
Example 152g-11



$t_R = 2.12$ min (>93.9%); Condition 1
 LRMS: Anal. Calcd. for $C_{33}H_{42}N_7O_4$ 600.33; found: 600.11 (M + H)⁺.
 HRMS: Anal. Calcd. for $C_{33}H_{42}N_7O_4$ 600.3298; found: 600.3312 (M + H)⁺.

Prepared from 1-6c and 152e-4

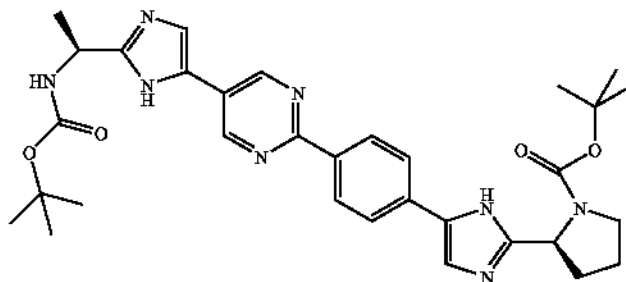
Example 152g-12



$t_R = 2.13$ min (97.3%); Condition 1
 LRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.33; found: 601.36 (M + H)⁺.
 HRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.3251; found: 601.3253 (M + H)⁺.

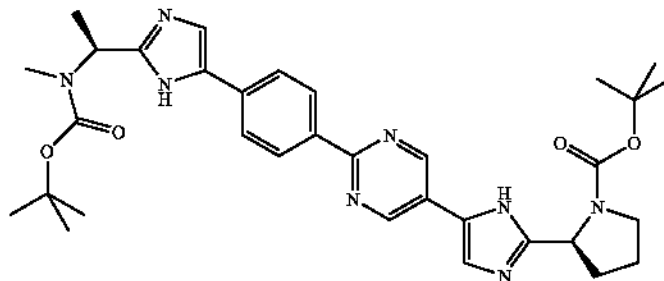
Prepared from 1c and 152d-5

-continued

Example 152g-
13

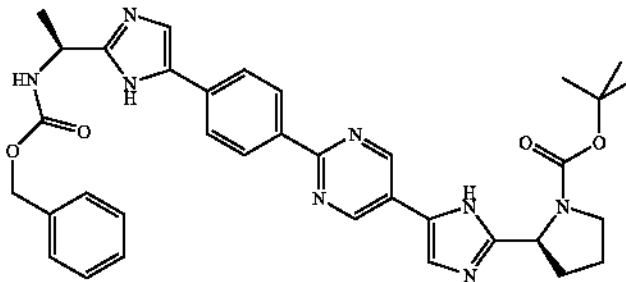
$t_R = 2.11$ min (98.5%); Condition 1
LRMS: Anal. Calcd. for
 $C_{32}H_{41}N_8O_4$ 601.33; found:
601.36 (M + H)⁺.
HRMS: Anal. Calcd. for
 $C_{32}H_{41}N_8O_4$ 601.3251; found:
601.3253 (M + H)⁺.

Prepared from 1c and 152d-6

Example 152g-
14

$t_R = 2.18$ min (>95%); Condition 1
LRMS: Anal. Calcd. for
 $C_{33}H_{43}N_8O_4$ 615.38; found:
615.36 (M + H)⁺.
HRMS: Anal. Calcd. for
 $C_{33}H_{43}N_8O_4$ 615.3407; found:
615.3433 (M + H)⁺.

Prepared from 1-8c and 152d-1

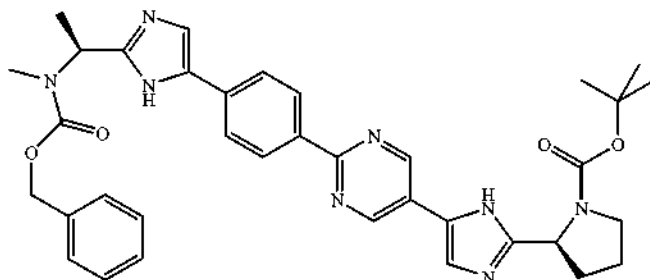
Example 152g-
15

$t_R = 2.20$ min (97.7%); Condition 1
LRMS: Anal. Calcd. for
 $C_{35}H_{49}N_8O_4$ 635.31; found:
635.36 (M + H)⁺.
HRMS: Anal. Calcd. for
 $C_{35}H_{49}N_8O_4$ 635.3094; found:
635.3119 (M + H)⁺.

Prepared from 1c and 152d-1

-continued

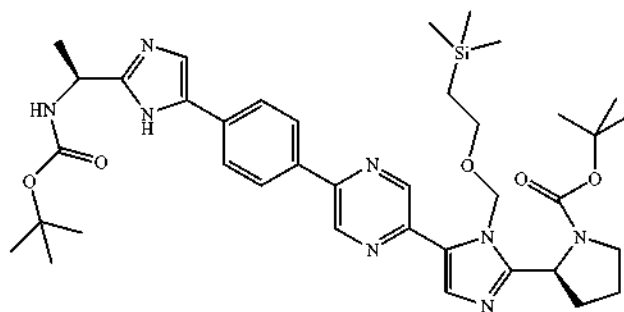
Example 152g-16



$t_R = 2.26$ min (>95%); Condition 1
LRMS: Anal. Calcd. for $C_{36}H_{41}N_8O_4$ 649.33; found: 649.39 (M + H)⁺.
HRMS: Anal. Calcd. for $C_{36}H_{41}N_8O_4$ 649.3251; found: 649.3276 (M + H)⁺.

Prepared from 1-9c and 152d-1

Example 152g-17



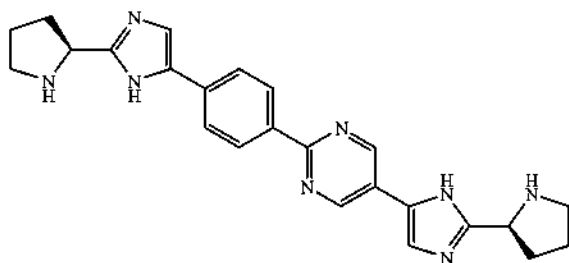
$t_R = 2.98$ min (98.5%); Condition 1
LRMS: Anal. Calcd. for $C_{38}H_{44}N_8O_5Si$ 730.39; found: 731.40 (M + H)⁺.
HRMS: Anal. Calcd. for $C_{38}H_{44}N_8O_5Si$ 731.4065; found: 731.4045 (M + H)⁺.

Prepared from 1-6c and 152e-3

Example 152h-1-152h-7

Example 152h-1 from 152g-1. 5-((S)-2-Pyrrolidin-2-yl-3H-imidazol-4-yl)-2-[4-((S)-2-pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-pyrimidine

[0846]



[0847] TFA (8 mL) was added in one portion to a stirred solution of (S)-2-[5-(2-{4-[2-((S)-1-tert-butoxycarbonylpyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-pyrimidin-5-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (1.50 g, 1.98 mmol) in dry CH_2Cl_2 (30 mL) at room temperature. The flask was sealed and the mixture was stirred at room temperature for 16 h before the solvent(s) were removed in vacuo. The residue was taken up in methanol, filtered through a PVDF syringe filter (13 mm×0.45 μm), distributed to 8 pHPLC vials and chromatographed by HPLC (gradient elution from 10%

B to 100% B over 13 min on a Phenomenex C18 column, 30×100 mm, 10 μm, where A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA). After concentration of the selected test tubes by speed vacuum evaporation, the product was dissolved in methanol and neutralized by passing the solution through an UCT CHQAX 110M75 anion exchange cartridge. There was isolated the title compound as a yellow mustard-colored solid (306.7 mg, 36% yield) upon concentration of the eluant.

[0848] ¹H NMR (500 MHz, DMSO- d_6) μ 12.50-11.80 (br m, 2H), 9.18 (s, 2H), 8.36 (d, J=8.5 Hz, 2H), 7.89 (d, J=8.2 Hz, 2H), 7.77 (s, 1H), 7.61 (s, 1H), 4.34-4.24 (m, 2H), 3.09-2.89 (m, 4H), 2.18-2.07 (m, 2H), 2.02-1.89 (m, 2H), 1.88-1.72 (m, 4H).

[0849] LCMS Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=1.33 min, >95% homogeneity index.

[0850] LRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.01 (M+H)⁺.

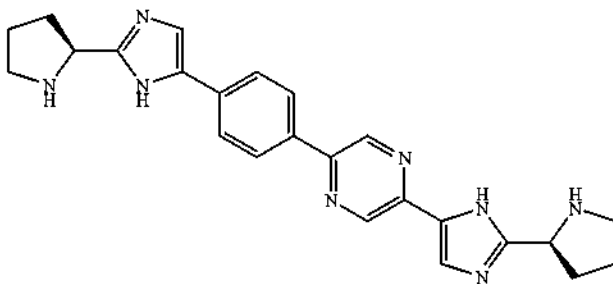
[0851] HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2363 (M+H)⁺.

[0852] The same conditions were used to prepare Examples 152h-2 through 152h-14.

[0853] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

[0854] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

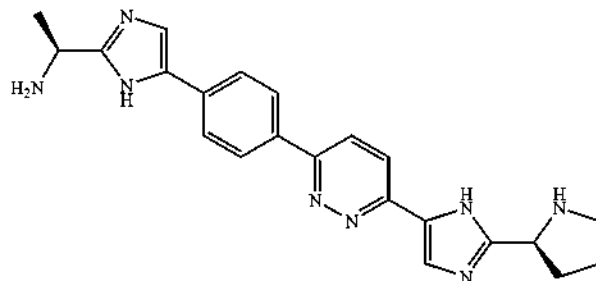
Example 152h-2



Prepared from 152g-3

$t_R = 1.36$ min (98%);
Condition 1
LRMS: Anal. Calcd.
for $C_{24}H_{27}N_8$ 427.24;
found: 427.48 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{24}H_{27}N_8$ 427.2359;
found: 427.2339
(M + H)⁺.

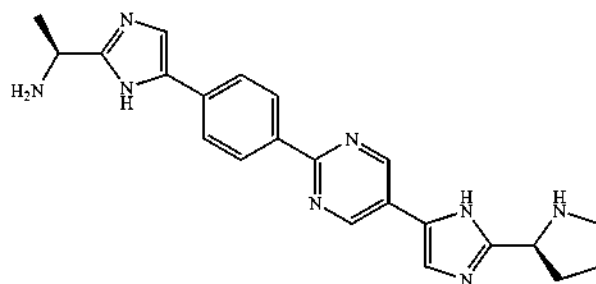
Example 152h-3



Prepared from 152g-4

$t_R = 1.17$ min (>95%);
Condition 1
LRMS: Anal. Calcd.
for $C_{22}H_{25}N_8$ 401.22;
found: 401.16 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{22}H_{25}N_8$ 401.2202;
found: 401.2193
(M + H)⁺.

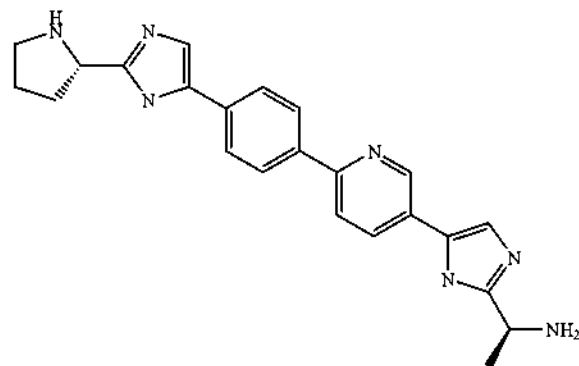
Example 152h-4



Prepared from 152g-5

$t_R = 1.28$ min (89.3%);
Condition 1
LRMS: Anal. Calcd.
for $C_{22}H_{25}N_8$ 401.22;
found: 401.16 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{22}H_{25}N_8$ 401.2202;
found: 401.2201
(M + H)⁺.

Example 152h-5

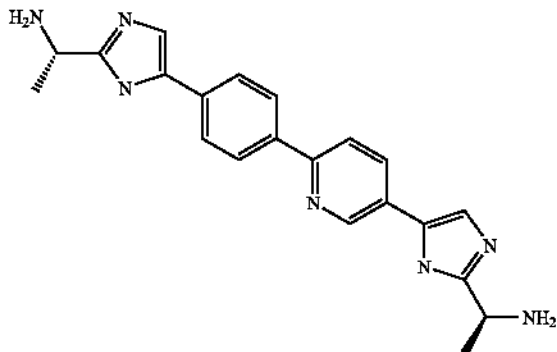


Prepared from 152g-7

$t_R = 0.93$ min;
Condition 2
LRMS: Anal. Calcd.
for $C_{23}H_{25}N_7$ 399;
found: 400 (M + H)⁺.

-continued

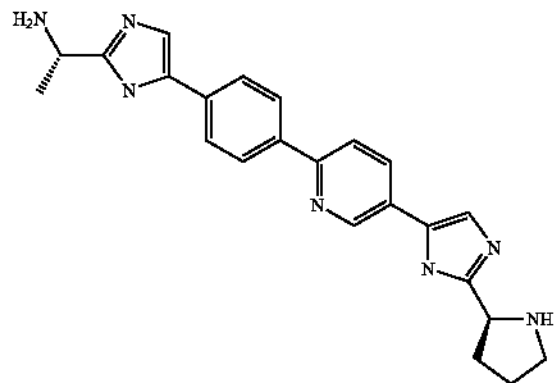
Example 152h-6



Prepared from 152g-6

t_R = 0.81 min;
Condition 2
LRMS: Anal. Calcd.
for $C_{21}H_{23}N_7$ 373;
found: 374 (M + H)⁺.

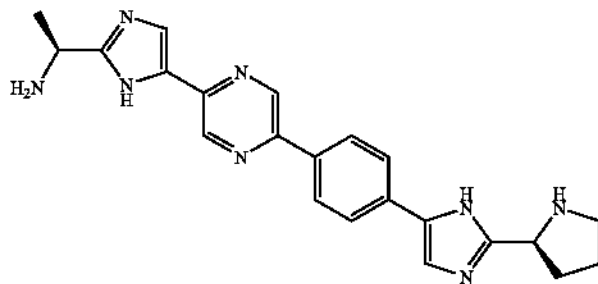
Example 152h-7



Prepared from 152g-11

t_R = 1.14 min (>95%);
Condition 1
LRMS: Anal. Calcd.
for $C_{23}H_{26}N_7$ 400.23;
found: 400.14 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{23}H_{26}N_7$ 400.2250;
found: 400.2234
(M + H)⁺.

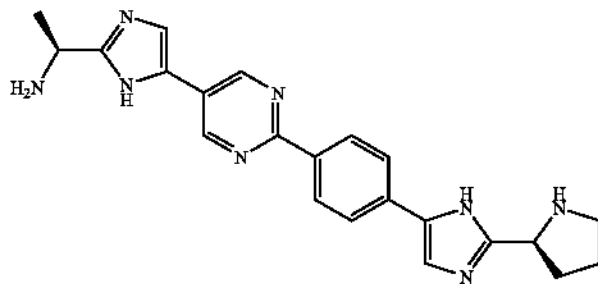
Example 152h-8



Prepared from 152g-12

t_R = 1.29 min (>95%);
Condition 1
LRMS: Anal. Calcd.
for $C_{22}H_{25}N_8$ 401.22;
found: 401.21 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{22}H_{25}N_8$ 401.2202;
found: 401.2204
(M + H)⁺.

Example 152h-9

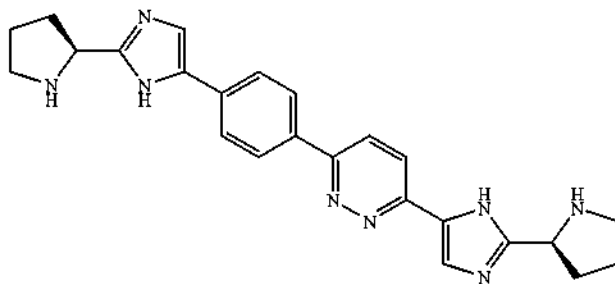


Prepared from 152g-13

t_R = 1.29 min (97.6%);
Condition 1
LRMS: Anal. Calcd.
for $C_{22}H_{25}N_8$ 401.22;
found: 401.21 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{22}H_{25}N_8$ 401.2202;
found: 401.2220
(M + H)⁺.

-continued

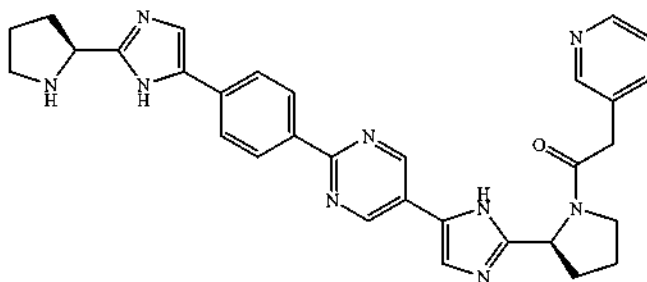
Example 152h-10



t_R = 1.26 min (86.4%);
Condition 1
LRMS: Anal. Calcd.
for $C_{24}H_{27}N_8$ 427.24;
found: 427.48 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{24}H_{27}N_8$ 427.2359;
found: 427.2339
(M + H)⁺.

Prepared from 152g-2

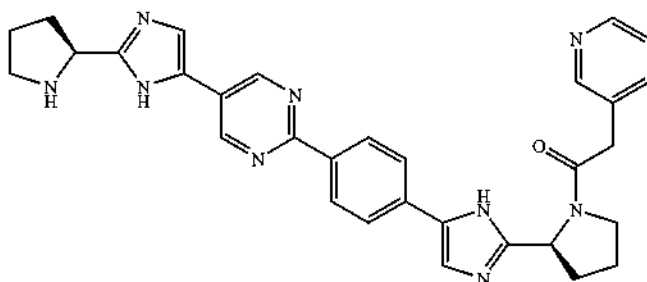
Example 152h-11



t_R = 1.26 min (>95%);
Condition 1
LRMS: Anal. Calcd.
for $C_{31}H_{32}N_9O$ 546.27;
found: 546.28 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{31}H_{32}N_9O$ 546.2730;
found: 546.2739
(M + H)⁺.

Prepared from 152g-9

Example 152h-12

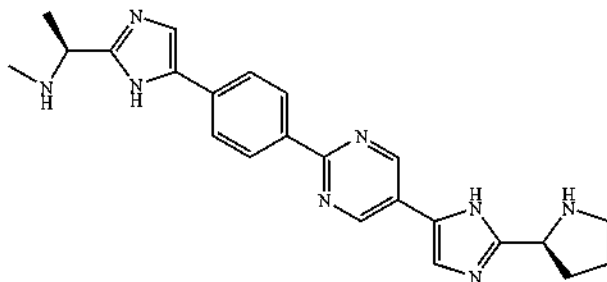


t_R = 1.39 min (95%);
Condition 1
LRMS: Anal. Calcd.
for $C_{31}H_{32}N_9O$ 546.27;
found: 546.32 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{31}H_{32}N_9O$ 546.2730;
found: 546.2719
(M + H)⁺.

Prepared from 152g-10

-continued

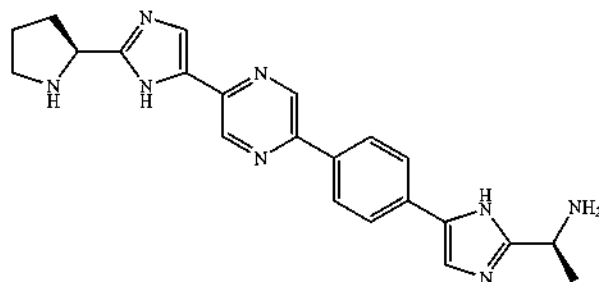
Example 152h-13



Prepared from 152g-14

$t_R = 1.42$ min;
Condition 1
LRMS: Anal. Calcd.
for $C_{23}H_{26}N_8$ 414.24;
found: 415.27 ($M + H$)⁺.
HRMS: Anal. Calcd.
for $C_{23}H_{26}N_8$ 415.2359;
found: 415.2371
($M + H$)⁺.

Example 152h-14



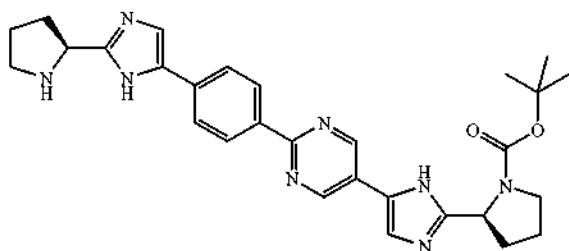
Prepared from 152g-17

$t_R = 1.30$ min;
Condition 1
LRMS: Anal. Calcd.
for $C_{23}H_{26}N_8$ 400.21;
found: 401.24 ($M + H$)⁺.
HRMS: Anal. Calcd.
for $C_{23}H_{26}N_8$ 401.2202;
found: 401.2198
($M + H$)⁺.

Example 152i-1 to 152i-3

Example 152i-1 from 152g-8. (S)-2-[5-{2-[4-((S)-2-Pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-pyrimidin-5-yl}-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester

[0855]



[0856] A solution of (S)-2-[5-{2-[4-((S)-1-Benzyloxy-carbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl]-pyrimidin-5-yl}-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (317.1 mg, 0.48 mmol) in MeOH (1 mL) was added to a stirred suspension of 10% palladium on carbon (60 mg) and K_2CO_3 (70 mg) in a solution of MeOH (5 mL) and H_2O (0.1 mL) at room temperature under N_2 . The flask was charged and evacuated three times with H_2 and stirred for 3 h at atmosphere pressure. Additional catalyst (20 mg) was then added and the reaction mixture was stirred further for 3 h before it was suction-filtered through diatomaceous earth

(Celite®) and concentrated. The residue was diluted with MeOH, filtered through a PVDF syringe filter (13 mm×0.45 μ m), distributed into 4 pHPLC vials and chromatographed (gradient elution from 20% B to 100% B over 10 min on a Phenomenex-Gemini C18 column (30×100 mm, 10 μ m) where A=95% water, 5% acetonitrile, 10 mM NH_4OAc , B=10% water, 90% acetonitrile, 10 mM NH_4OAc). After concentration of the selected test tubes by speed vacuum evaporation, there was isolated the title compound as a yellow solid (142.5 mg, 56% yield).

[0857] 1H NMR (400 MHz, $DMSO-d_6$) δ 12.35-12.09 (br m, 1H), 9.17 (s, 2H), 8.35 (d, $J=8.3$ Hz, 2H), 7.87 (d, $J=8.3$ Hz, 2H), 7.80-7.72 (m, 1H), 7.56 (s, 1H), 4.92-4.77 (m, 1H), 4.21-4.13 (m, 1H), 3.61-3.05 (2m, 4H), 3.02-2.80 (2m, 2H), 2.37-1.67 (series of m, 6H), 1.41 and 1.17 (2s, 9H).

[0858] LCMS Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=1.77 min, >95% homogeneity index.

[0859] LRMS: Anal. Calcd. for $C_{29}H_{35}N_8O_2$ 527.29; found: 527.34 ($M+H$)⁺.

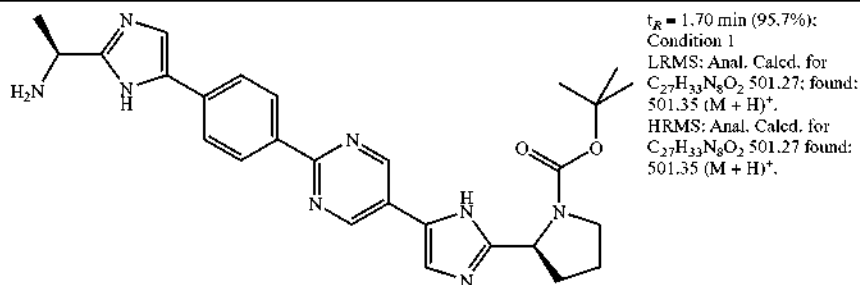
[0860] HRMS: Anal. Calcd. for $C_{29}H_{35}N_8O_2$ 527.2883; found: 527.2874 ($M+H$)⁺.

[0861] The same procedure was used to prepare Examples 152i-2 through 152i-3.

[0862] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

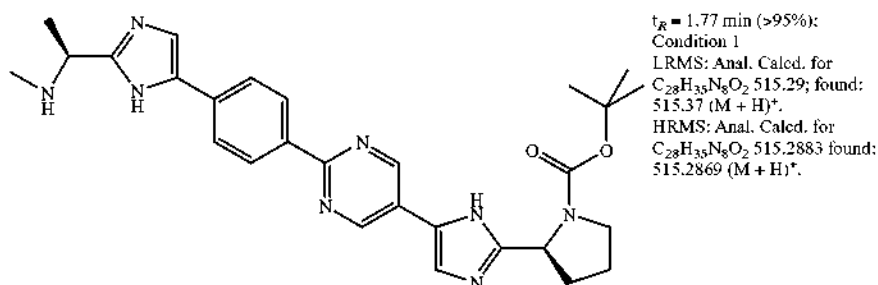
[0863] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

Example 152i-2



Prepared from 152g-15

Example 152i-3



Prepared from 152g-16

Examples 152j-1 to 152j-28

[0864] Examples 152j were isolated as TFA or AcOH salts prepared using the procedure to convert Example 148e to 148.

[0865] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold

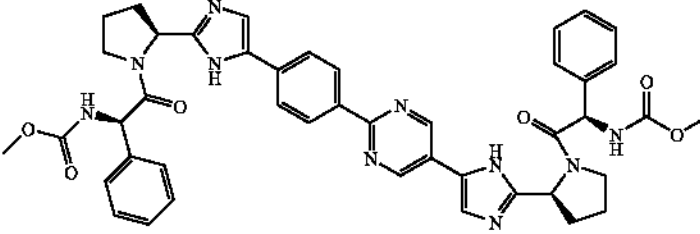
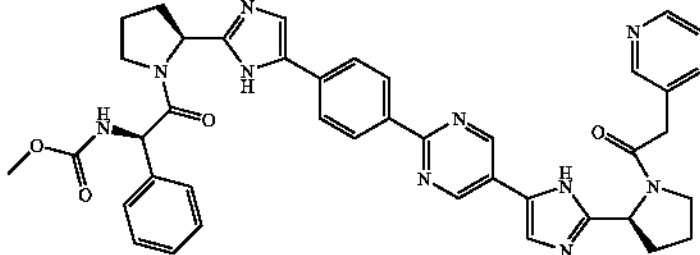
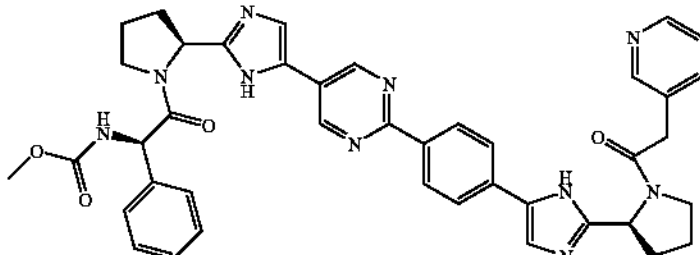
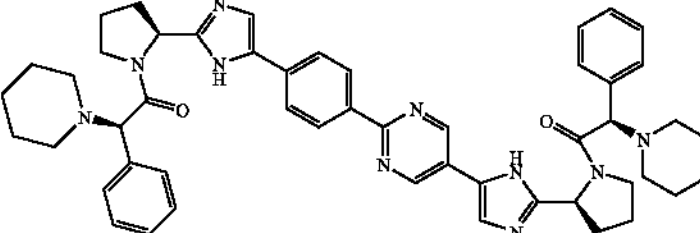
time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

[0866] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

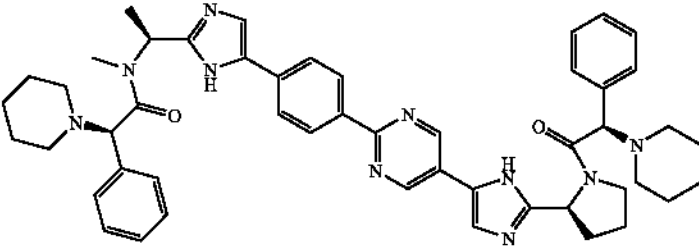
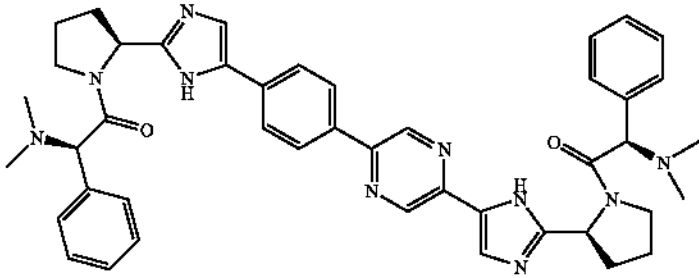
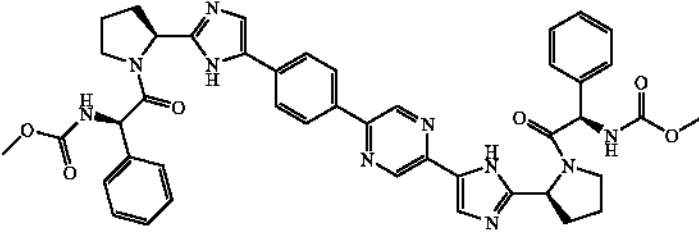
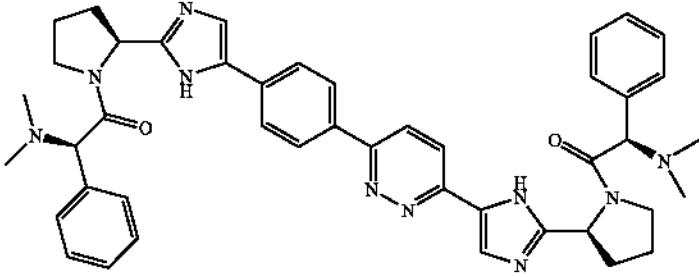
Example	Compound Name	Structure	Data
Example 152j-1	(1R)-2-((2S)-2-(3-(2-(4-(2-(2S)-1-(2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		$t_R = 1.61$ min; (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.40 found: 749.32 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4042 (M + H) ⁺

Prepared from 152h-1 and Cap-1.

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Example	Compound Name	Structure	Data
Example 152j-2	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-carbamate		$t_R = 1.99$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found; 809.17 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3524 found; 809.3505 (M + H) ⁺
		Prepared from 152h-1 and Cap-4	
Example 152j-3	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-carbamate		$t_R = 1.65$ min (92.3%); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_2$ 737.33 found; 737.49 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found; 737.3342 (M + H) ⁺
		Prepared from 152h-11 and Cap-4	
Example 152j-4	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(2-(4-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-ethyl)-carbamate		$t_R = 1.64$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.33 found; 737.75 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found; 737.3284 (M + H) ⁺
		Prepared from 152h-12 and Cap-4	
Example 152j-5	5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-(4-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)pyrimidine		$t_R = 1.70$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{50}H_{57}N_{10}O_2$ 829.47 found; 829.39 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{50}H_{57}N_{10}O_2$ 829.4666 found; 829.4658 (M + H) ⁺
		Prepared from 152h-12 and Cap-14	

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Example	Compound Name	Structure	Data
Example 152j-6	(2R)-N-methyl-2-phenyl-N-((1S)-1-(4-(5-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-(1-piperidinyl)acetamide		t _R = 1.66 min (>95%); Condition 1 LRMS: Anal. Calcd. for C ₄₉ H ₅₇ N ₁₀ O ₂ 817.47 found: 817.44 (M + H) ⁺ HRMS: Anal. Calcd. for C ₄₉ H ₅₇ N ₁₀ O ₂ 817.4666 found: 817.4673 (M + H) ⁺
		Prepared from 152h-13 and Cap-14	
Example 152j-7	(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		t _R = 1.60 min (>95%); Condition 1 LRMS: Anal. Calcd. for C ₄₁ H ₄₉ N ₁₀ O ₂ 749.40 found: 749.31 (M + H) ⁺ HRMS: Anal. Calcd. for C ₄₄ H ₄₉ N ₁₀ O ₂ 749.4040 found: 749.4031 (M + H) ⁺
		Prepared from 152h-2 and Cap-1	
Example 152j-8	methyl ((1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		t _R = 2.01 min (>95%); Condition 1 LRMS: Anal. Calcd. for C ₄₄ H ₄₅ N ₁₀ O ₆ 809.35 found: 809.24 (M + H) ⁺ HRMS: Anal. Calcd. for C ₄₄ H ₄₅ N ₁₀ O ₆ 809.3523 found: 809.3493 (M + H) ⁺
		Prepared from 152h-2 and Cap-4	
Example 152j-9	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		t _R = 1.76 min (>95%); Condition 1 LRMS: Anal. Calcd. for C ₄₄ H ₄₉ N ₁₀ O ₂ 749.40 found: not obsd (M + H) ⁺ HRMS: Anal. Calcd. for C ₄₄ H ₄₉ N ₁₀ O ₂ 749.4040 found: 749.4056 (M + H) ⁺
		Prepared from 152h-10 and Cap-1	

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Example	Compound Name	Structure	Data
Example 152j-10	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 2.17$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found: 809.59 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3524 found: 809.3499 (M + H) ⁺
Prepared from 152h-10 and Cap-4			
Example 152j-11	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide		$t_R = 1.56$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{43}H_{48}N_9O_2$ 722.39 found: 722.89 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{43}H_{48}N_9O_2$ 722.3931 found: 722.3930 (M + H) ⁺
Prepared from 152h-7 and Cap-1			
Example 152j-12	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((1S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.95$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.34 found: 782.93 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.3415 found: 782.3398 (M + H) ⁺
Prepared from 152h-7 and Cap-4			
Example 152j-13	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(6-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-pyridazinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide		$t_R = 1.55$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.88 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3903 (M + H) ⁺
Prepared from 152h-3 and Cap-1			

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Example	Compound Name	Structure	Data
Example 152j-14	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((1S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)amino)-ethyl)-1H-imidazol-5-yl)phenyl)-3-pyridazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.95$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.95 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3337 (M + H) ⁺
		Prepared from 152h-3 and Cap-4	
Example 152j-15	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((1S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)amino)-ethyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.97$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.97 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3357 (M + H) ⁺
		Prepared from 152h-4 and Cap-4	
Example 152j-16	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(2-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide		$t_R = 1.61$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.52 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3893 (M + H) ⁺
		Prepared from 152h-9 and Cap-1	
Example 152j-17	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)amino)-ethyl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.99$ min (95.6%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.44 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3328 (M + H) ⁺
		Prepared from 152h-9 and Cap-4	

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Example	Compound Name	Structure	Data
Example 152j-18	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide		$t_R = 1.60$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.47 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3861 (M + H) ⁺
Prepared from 152h-8 and Cap-1			
Example 152j-19	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-((2R)-2-(methoxycarbonyl)-amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)-2-pyrazinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.97$ min (94.7%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.69 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3345 (M + H) ⁺
Prepared from 152h-8 and Cap-4			
Example 152j-20	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)-N-methyl-2-phenylacetamide		$t_R = 1.54$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{43}H_{49}N_{10}O_2$ 737.40 found: 737.54 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{43}H_{49}N_{10}O_2$ 737.4040 found: 737.4066 (M + H) ⁺
Prepared from 152h-13 and Cap-1			
Example 152j-21	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((1S)-1-((2R)-2-(methoxycarbonyl)-amino)-2-phenylacetyl)(methyl)-amino)ethyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 2.00$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{43}H_{45}N_{10}O_6$ 797.35 found: 797.38 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{43}H_{45}N_{10}O_6$ 797.3524 found: 797.3528 (M + H) ⁺
Prepared from 152h-13 and Cap-4			

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Example	Compound Name	Structure	Data
Example 152j-22	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)amino)-ethyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.46$ min (condition 2, 98%) LRMS: Anal. Calcd. for $C_{43}H_{43}N_9O_6$ 781.33; found: 782.34 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.3415 found: 782.3417 (M + H) ⁺

Prepared from 152h-5 and Cap-4

Example 152j-23	methyl ((1R)-2-(((1S)-1-(5-(6-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)amino)-ethyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-ethyl)amino)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.44$ min condition 2, 90%) LRMS: Anal. Calcd. for $C_{41}H_{41}N_9O_6$ 755.32; found: 756.35 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{41}H_{42}N_9O_6$ 756.3258 found: 756.3239 (M + H) ⁺
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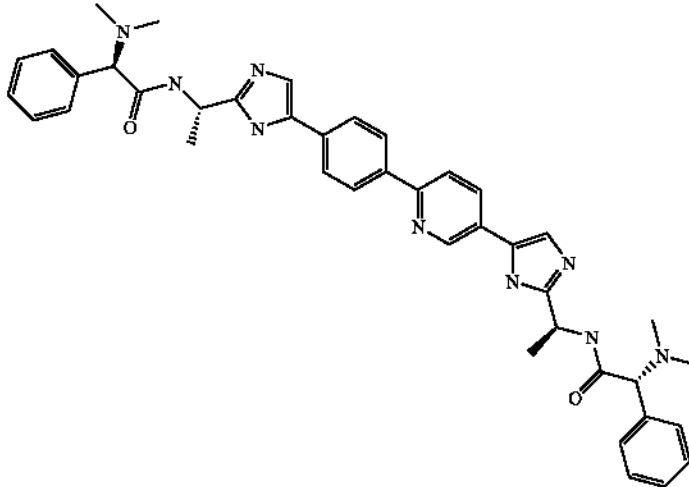
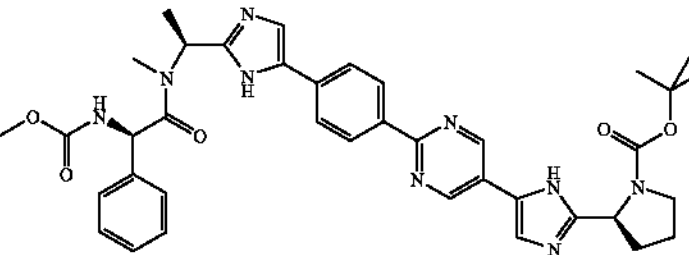
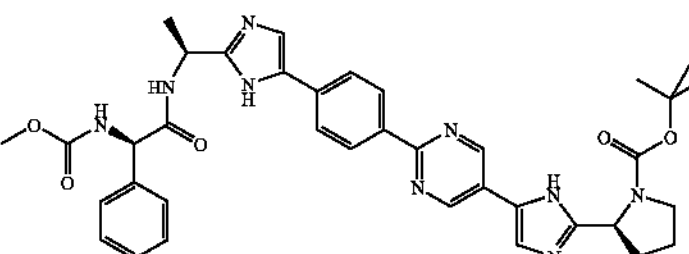
Prepared from 152h-6 and Cap-4

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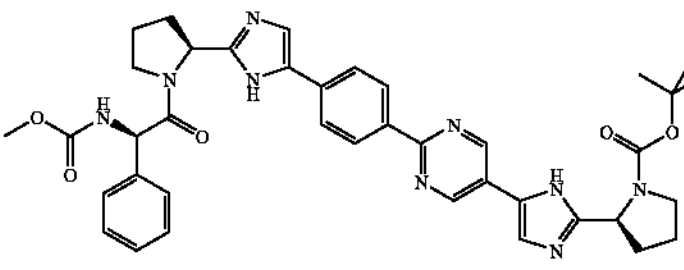
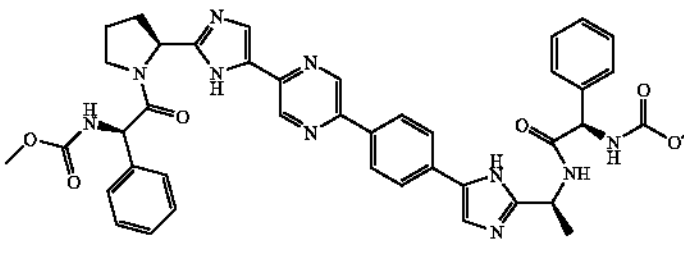
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Example	Compound Name	Structure	Data
Example 152j-24	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(6-(4-(2-((1S)-1-(((2R)-2-(dimethylamino)-2-phenylacetyl)amino)-ethyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-ethyl)-2-phenylacetamide		$t_R = 1.18$ min (condition 2, 91%) LRMS: Anal. Calcd. for $C_{41}H_{45}N_9O_2$ 695.37; found: 696.37 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{41}H_{46}N_9O_2$ 696.3774 found: 696.3806 (M + H) ⁺ .
		Prepared from 152h-6 and Cap 1	
Example 152j-25			$t_R = 2.08$ min (95.8%); Condition 1 LRMS: Anal. Calcd. for $C_{38}H_{44}N_9O_5$ 706.35; found: 706.53 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{38}H_{44}N_9O_5$ 706.3465; found: 706.3492 (M + H) ⁺ .
		Prepared from 152i-3 and Cap-4	
Example 152j-26			$t_R = 2.04$ min (96.4%); Condition 1 LRMS: Anal. Calcd. for $C_{37}H_{42}N_9O_5$ 692.33; found: 692.49 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{37}H_{42}N_9O_5$ 692.3309; found: 692.3322 (M + H) ⁺ .
		Prepared from 152i-2 and Cap-4	

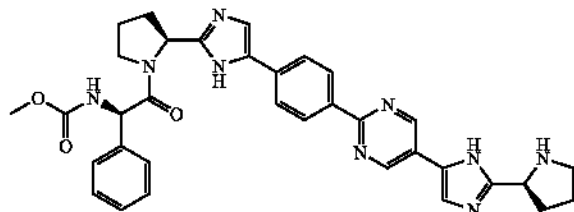
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Example	Compound Name	Structure	Data
Example 152j-27			$t_R = 2.04$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{30}H_{44}N_9O_5$ 718.35; found: 718.49 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{30}H_{44}N_9O_5$ 718.3465; found: 718.3483 (M + H) ⁺ .
		Prepared from 152i-1 and Cap-4	
Example 152j-28	methyl ((1R)-2-((2S)-2-(5-(5-(4-(2-((1S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)amino)-ethyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 2.00$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34; found: 783.96 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367; found: 783.3375 (M + H) ⁺ .
		Prepared from 152i-14 and Cap-4	

Examples 152k-1 to 152k-

Example 152k-1 from 152j-27. {(R)-2-Oxo-1-phenyl-2-[(S)-2-(5-{4-[5-((S)-2-pyrrolidin-2-yl-3H-imidazol-4-yl)-pyrimidin-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidin-1-yl]-ethyl}-carbamic acid methyl ester

[0867]



[0868] Cold (0° C.) 4 NHCl in dioxanes (4 mL) was added via syringe to (S)-2-{5-[2-(4-{2-[(S)-1-(R)-2-methoxycarbonylamino-2-phenylacetyl]-pyrrolidin-2-yl]-3H-imidazol-4-yl]-phenyl}-pyrimidin-5-yl]-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (104.6 mg, 0.146 mmol) in a 100 mL pear-shaped flask followed by MeOH (0.5 mL). The homogeneous mixture was stirred at room temperature for 15 min before a precipitate was observed. After stir-

ring further for 1.75 h, the suspension was diluted with ether and hexanes. Suction-filtration of a small portion of the suspension yielded the title compound as a yellow solid which was used for characterization purposes. The balance of the suspension was concentrated down to dryness and placed under high vacuum for 16 h. There was isolated the rest of the title compound also as a yellow solid (137.7 mg, 123%) which was used without further purification.

[0869] ¹H NMR (500 MHz, DMSO-d₆) δ 15.20 and 14.66 (2m, 1H), 10.29 (br s, 0.7H), 9.38-9.36 (m, 2H), 8.55-8.00 (series of m, 4H), 7.42-7.28 (2m, 3H), 5.53-4.00 (series of m, 7H), 3.99-3.13 (series of m, 4H), 3.57 and 3.52 (2s, 3H), 2.50-1.84 (series of m, 8H).

[0870] LCMS Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=1.79 min, >95% homogeneity index.

[0871] LRMS: Anal. Calcd. for $C_{34}H_{36}N_9O_3$ 618.29; found: 618.42 (M+H)⁺.

[0872] HRMS: Anal. Calcd. for $C_{34}H_{36}N_9O_3$ 618.2921; found: 618.2958 (M+H)⁺.

[0873] The same procedure was used to prepare Examples 152k-2 through 152k-3.

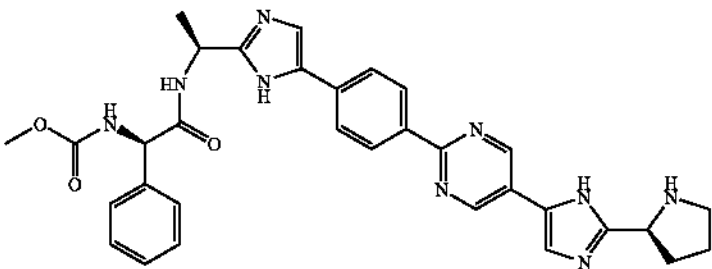
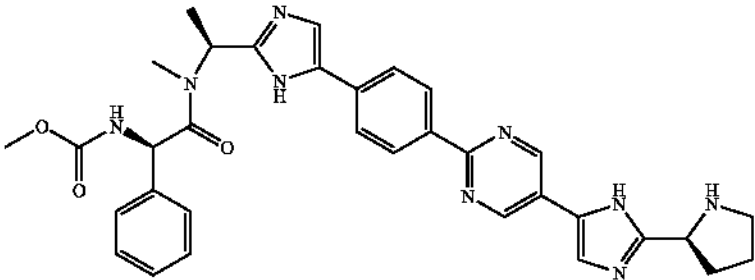
[0874] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

[0875] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

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Example	Compound Name	Structure	Data
Example 152k-2			$t_R = 1.74$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{32}H_{34}N_9O_3$ 592.28; found: 592.41 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{32}H_{34}N_9O_3$ 592.2785; found: 592.2775 (M + H) ⁺ .
		Prepared from 152j-26	
Example 152k-3			$t_R = 1.79$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{33}H_{36}N_9O_3$ 606.29; found: 606.43 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{33}H_{36}N_9O_3$ 606.2941; found: 606.2925 (M + H) ⁺ .
		Prepared from 152j-25	

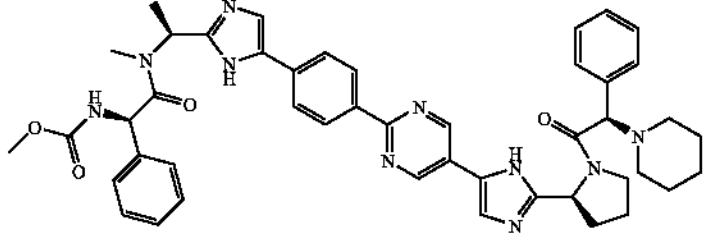
Examples 152l-1 to 152l-

[0876] Examples 152l-1 through 152l-3 were isolated as TFA or AcOH salts prepared using the same procedure to convert Example 148e to 148.

[0877] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold

time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

[0878] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

Example	Compound Name	Structure	Data
Example 152l-1	methyl ((1R)-2-(methyl((1S)-1-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.87$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{46}H_{51}N_{10}O_4$ 807.41; found: 807.57 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{46}H_{51}N_{10}O_4$ 807.4095; found: 807.4128 (M + H) ⁺ .
		Prepared from 152k-3 and Cap-14	

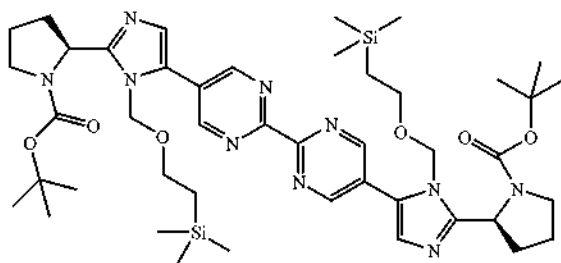
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Example	Compound Name	Structure	Data
Example 1521-2	methyl ((1R)-2-oxo-1-phenyl-2-(((1S)-1-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)amino)ethyl) carbamate		$t_R = 1.83$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{45}H_{49}N_{10}O_4$ 793.39 found: 793.52 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{45}H_{49}N_{10}O_4$ 793.3938 found: 793.3934 (M + H) ⁺
		Prepared from 152k-2 and Cap-14	
Example 1521-3	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl) carbamate		$t_R = 1.87$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{47}H_{51}N_{10}O_4$ 819.41 found: 819.50 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{47}H_{51}N_{10}O_4$ 819.4095 found: 819.4127 (M + H) ⁺
		Prepared from 152k-1 and Cap-14	

Example 153a-1 from 153a-4

Example 153a-1 prepared from 152e-1. (S)-2-[5-{5'-[2-((S)-1-tert-Butoxycarbonyl-pyrrolidin-2-yl)-3-(2-trimethylsilyl-ethoxymethyl)-3H-imidazol-4-yl]-[2,2']bipyrimidin-5-yl]-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester

[0879]



[0880] To a stirred solution of (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1.0 g, 2.08 mmol) and dichlorobis(benzonitrile) palladium (40 mg, 0.104 mmol) in dry DMF (10 mL) at room temperature under argon was added neat tetrakis(dimethylamino)ethylene (1.0 mL, 4.16 mmol). The mixture was heated to 60° C. for 15 h before it was diluted with ethyl acetate and suction-filtered through diatomaceous earth (Celite®). The filtrate was washed with sat'd NaHCO_3 soln and brine prior to drying over Na_2SO_4 and solvent evaporation. Purification of the residue by Biotage™

flash chromatography on silica gel (step gradient elution with 15% B to 15% B for 150 mL, 15% B to 75% B for 1500 mL, 75% B to 100% B for 1000 mL, 100% B to 100% B for 1000 mL where B=ethyl acetate and A=hexane followed by a second gradient elution with 10% B to 100% B for 700 mL where B=methanol and A=ethyl acetate) furnished the title compound as a caramel-colored, viscous oil (487.8 mg, 26% yield).

[0881] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.27 (s, 4H), 8.09-8.06 (m, 2H), 5.73-5.66 and 5.50-5.44 (2m, 2H), 5.06-4.93 (m, 2H), 3.60-3.39 (2m, 8H), 2.32-2.08 (3m, 4H), 2.00-1.85 (m, 4H), 1.37 and 1.14 (2s, 18H), 0.95-0.84 (m, 4H), -0.01 (s, 18H).

[0882] LCMS Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=3.37 min, >95% homogeneity index.

[0883] LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6S_{12}$ 889.49; found: 889.57 (M+H)⁺.

[0884] HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6S_{12}$ 889.4940; found: 889.4920 (M+H)⁺.

[0885] The same procedure was used to prepare Examples 153a-2 through 153a-4.

[0886] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

[0887] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μL injection volume.

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Example	Compound Name	Structure	Data
Example 153a-2			$t_R = 3.37$ min (89.6%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.56 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.494; found: 889.4951 (M + H) ⁺ .
		Prepared from 152e-2	
Example 153a-3			$t_R = 3.37$ min (95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.51 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; found: 889.4915 (M + H) ⁺ .
		Prepared from 152e-3	
Example 153a-4			$t_R = 2.3$ min (condition 2) LRMS: Anal. Calcd. for $C_{42}H_{66}N_8Si_2$ 834; found: 835 (M + H) ⁺ .
		Prepared from 152e-4	

Example 153b-1-153b-3

[0888] The hydrolysis reactions was performed as above for Example 152h.

[0889] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold

time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

[0890] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

Example	Compound Name	Structure	Data
Example 153b-1			$t_R = 1.18$ min ($>95\%$); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.23; found: 429.01 ($M + H$) ⁺ . HRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.2264; found: 429.2259 ($M + H$) ⁺ .
		Prepared from 153a-1	
Example 153b-2			$t_R = 1.26$ min ($>95\%$); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_2$ 737.33 found: 737.49 ($M + H$) ⁺ . HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found: 737.3342 ($M + H$) ⁺
		Prepared from 153a-2	
Example 153b-3			$t_R = 1.40$ min ($>95\%$); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.23; found: 429.20 ($M + H$) ⁺ . HRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$: 429.2264; Found: 429.2254 ($M + H$) ⁺
		Prepared from 153a-3	
Example 153b-4			$t_R = 0.85$ min (condition 1) LCMS: Anal. Calcd. for $C_{20}H_{22}N_8$ 374; found 375 ($M + H$) ⁺ .
		Prepared from 153a-4	

Examples 153c-1 to 153c-7

[0891] Examples 153c-1 through 153c-7 were isolated as TFA or AcOH salts using the procedure used to convert Example 148e to 148.

[0892] LC conditions: Condition 1: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 3 minutes, 1 minute hold

time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

[0893] Condition 2: Phenomenex LUNA C-18 4.6×50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, 220 nm, 5 μ L injection volume.

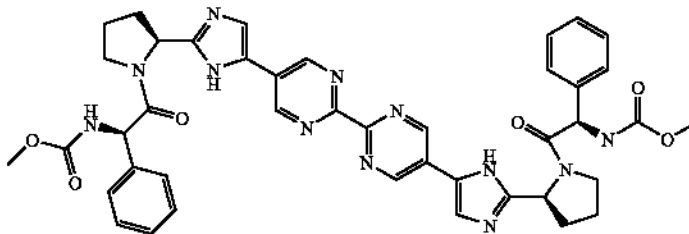
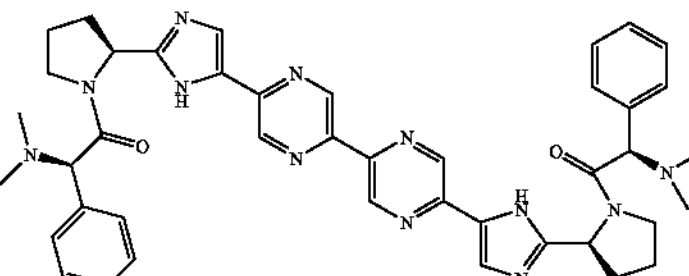
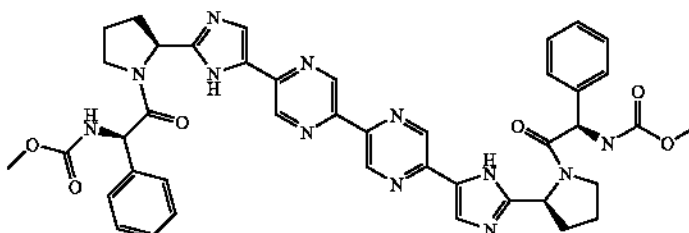
Example	Compound Name	Structure	Data
Example 153c-1	(1R,1'R)-2,2'-(3,3'-bipyridazine-6,6'-diyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)) bis(N,N-dimethyl-2-oxo-1-phenylethanamine)		$t_R = 1.55$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.64 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3936 (M + H) ⁺
Prepared from 153b-2 and Cap-1			
Example 153c-2	dimethyl (3,3'-bipyridazine-6,6'-diyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)) biscardamate		$t_R = 1.95$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.22 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3406 (M + H) ⁺
Prepared from 153b-2 and Cap-4			
Example 153c-3	(1R,1'R)-2,2'-(2,2'-bipyrimidine-5,5'-diyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)		$t_R = 1.51$ min (>90%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.21 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3921 (M + H) ⁺
Prepared from 153b-1 and Cap-1			

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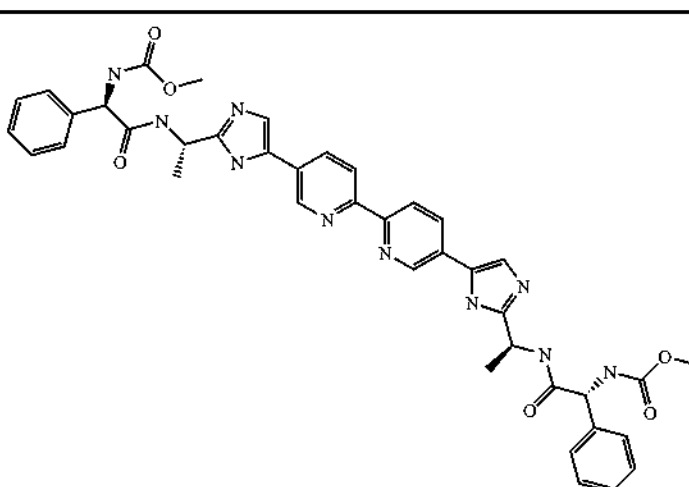
Example	Compound Name	Structure	Data
Example 153c-4	dimethyl (2,2'-bipyrimidine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediy))) bis(carbamate		$t_R = 1.88$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.10 ($M + H$) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3401 ($M + H$) ⁺
Prepared from 153b-1 and Cap-4			
Example 153c-5	(1R,1'R)-2,2'-(2,2'-bipyrazine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)) bis(N,N-dimethyl-2-oxo-1-phenyl-ethanamine)		$t_R = 1.61$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.30 ($M + H$) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3943 ($M + H$) ⁺
Prepared from 153b-3 and Cap-1			
Example 153c-6	dimethyl (2,2'-bipyrazine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediy))) bis(carbamate		$t_R = 2.00$ min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.23 ($M + H$) ⁺ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3407 ($M + H$) ⁺
Prepared from 153b-3 and Cap-4			

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Example	Compound Name	Structure	Data
Example 153c-7	dimethyl (2,2'-bipyridine-5,5'-diylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediylimino(1R)-2-oxo-1-phenyl-2,1-ethanediy))) biscarbamate		$t_R = 1.42$ min (condition 2, 94%) LRMS: Anal. Calcd. for $C_{40}H_{40}N_{10}O_6$ 756.31; found: 757.34 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{40}H_{40}N_{10}O_6$ 757.3211 found: 757.3180 (M + H) ⁺ .

Prepared from 153b-4 and
Cap-4

Section LS LC Conditions:

[0894] Condition 1: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 3.0×5.0 mm S10; Wavelength: 220 nm; Flow rate: 4 mL/min; 0% B to 100% B over 4 min with a 1 min hold time

[0895] Condition 2: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0×5.0 mm; Wavelength: 220 nm; Flow rate: 4 mL/min; 0% B to 100% B over 4 min with a 1 min hold time

[0896] Condition 3: Solvent A: 5% acetonitrile/95% water/10 mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10 mmol ammonium acetate; Column: Phenomenex 10u C18 4.6×5.0 mm; Wavelength: 220 nm; Flow rate: 4 mL/min; 0% B to 100% B over 4 min with a 1 min hold time

[0897] Condition 4: Solvent A: 5% acetonitrile/95% water/10 mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10 mmol ammonium acetate; Column: Luna 4.6×50 mm S10; Wavelength: 220 nm; Flow rate: 4 mL/min; 0% B to 100% B over 3 min with a 1 min hold time

[0898] Condition 5: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0×5.0 mm; Wavelength: 220 nm; Flow rate: 4 mL/min; 0% B to 100% B over 3 min with a 1 min hold time

[0899] Condition 6: Solvent A: 5% acetonitrile/95% water/10 mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10 mmol ammonium acetate; Column: Phenomenex-Luna 3.0×50 mm S10; Wavelength: 220 nm; Flow rate: 4 mL/min; 0% B to 100% B over 8 min with a 2 min hold time

[0900] Condition 7: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 3.0×5.0 mm S10; Wavelength: 220 nm; Flow rate: 4 mL/min; 0% B to 100% B over 3 min with a 1 min hold time

[0901] Condition 8: Solvent A: 10% methanol/90% water/0.2% H_3PO_4 ; Solvent B: 90% methanol/10% water/0.2% H_3PO_4 ; Column: YMC ODS-A 4.6×50 mm S5; Wavelength: 220 nm; Flow rate: 4 mL/min; 0% B to 100% B over 4 min with a 1 min hold time

[0902] Condition 9: Solvent A: 10% methanol/90% water/0.2% H_3PO_4 ; Solvent B: 90% methanol/10% water/0.2% H_3PO_4 ; Column: YMC ODS-A 4.6×50 mm S5; Wavelength: 220 nm; Flow rate: 2.5 mL/min; 0% B to 50% B over 8 min with a 3 min hold time

[0903] Condition 10: Xbridge C18, 150×4.6 mm I.D. S-3.5 um; Mobile Phase A: 95% Water-5% Acetonitrile with 10 mM ammonium acetate (pH=5); Mobile phase B: 95% Acetonitrile-5% Water with 10 mM ammonium acetate (pH=5); Isocratic 30% B for 20 min; Flow rate: 1 mL/min; UV detection: 220 nm

[0904] Condition 11: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0×5.0 mm; Wavelength: 220 nm; Flow rate: 4 mL/min; 30% B to 100% B over 4 min with a 1 min hold time

[0905] Condition 12: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0×5.0 mm; Wavelength: 220 nm; Flow rate: 4 mL/min; 20% B to 100% B over 4 min with a 1 min hold time

[0906] Condition 13: Solvent A: 10% methanol/90% water/0.2% H_3PO_4 ; Solvent B: 90% methanol/10% water/0.2% H_3PO_4 ; Column: YMC ODS-A 4.6×50 mm S5; Wavelength: 220 nm; Flow rate: 2.5 mL/min; 0% B to 100% B over 8 min with a 3 min hold time

Section LS Preparative HPLC Conditions:

[0907] Condition 1: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 30×100 mm S10; Wavelength: 220 nm; Flow rate: 30 mL/min; 0% B to 100% B over 10 min with a 2 min hold time

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[0908] Condition 2: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Xterra Prep MS C18 30x50 mm 5u; Wavelength: 220 nM; Flow rate: 30 mL/min; 0% B to 100% B over 8 min with a 3 min hold time

[0909] Condition 3: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Xterra Prep MS C18 30x50 mm 5u; Wavelength: 220 nM; Flow rate: 25 mL/min; 10% B to 100% B over 8 min with a 2 min hold time

[0910] Condition 4: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Xterra 19x100 mm S5; Wavelength: 220 nM; Flow rate: 20 mL/min; 30% B to 100% B over 5 min with a 3 min hold time

[0911] Condition 5: Solvent A: 10% methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 30x100 mm S10; Wavelength: 220 nM; Flow rate: 30 mL/min; 10% B to 100% B over 8 min with a 2 min hold time

[0912] Condition 6: Solvent A: 10% Acetonitrile/90% water/0.1% TFA; Solvent B: 90% Acetonitrile/10% water/0.1% TFA; Column: Phenomenex-Luna 21x100 mm S10; Wavelength: 220 nM; Flow rate: 25 mL/min; 0% B to 60% B over 10 min with a 5 min hold time

Experimentals:

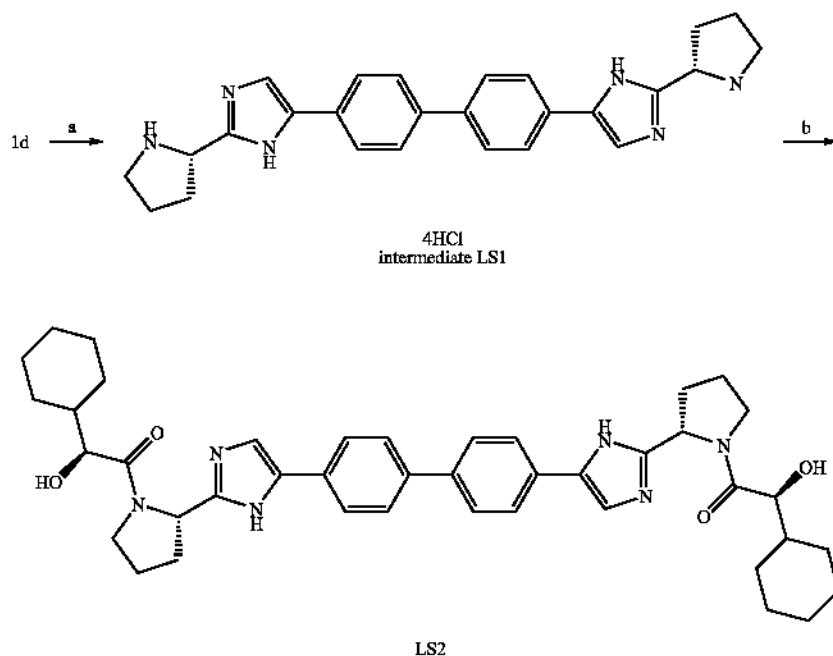
Compound LS2

(1S,1'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl (2S)-2,1-pyrrolidinediyl))bis(1-cyclohexyl-2-oxoethanol)

[0913]

[0914] Step a: To 1d (1.4 g; 2.24 mmol) was added 30 mL 4N HCl in dioxane. After 3 h, 60 mL ether was added and the precipitate was filtered and dried under high vacuum providing 1.02 g (80%) intermediate LS1 as a pale yellow powder. ¹H NMR (DMSO-d₆, δ=2.5 ppm, 500 MHz): δ 10.41 (s, 2H), 9.98 (s, 2H), 8.22 (s, 2H), 8.06 (d, J=8.54 Hz, 4H), 7.92 (d, J=8.55 Hz, 4H), 5.07 (s, 2H), 3.43-3.54 (m, 2H), 3.33-3.43 (m, 2H), 2.43-2.59 (m, 4H), 2.16-2.28 (m, 2H), 1.94-2.09 (m, 2H). LC (Cond. 1): RT=1.28 min; MS: Anal. Calcd. for [M+H]⁺ C₂₆H₂₈N₆: 425.24; found 425.56.

[0915] Step b: To intermediate LS1 (200 mg; 0.35 mmol) in 2 mL DMF was added DIPEA (0.30 mL; 1.75 mmol), (S)-2-cyclohexyl-2-hydroxyacetic acid (61 mg; 0.39 mmol), followed by HATU (147 mg; 0.38 mmol). After stirring at ambient temperature for 18 h, the reaction mixture was split into two portions and purified via preparative HPLC (Cond'n 1). Fractions containing desired product were pooled and passed through an MCX cartridge (Oasis; 6 g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided 65 mg of LS2 (26%) as a colorless powder. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.87-1.30 (m, 12H) 1.38-1.53 (m, J=24.72, 11.90 Hz, 4H) 1.54-1.75 (m, 8H) 1.95-2.21 (m, 6H) 3.72-3.86 (m, 6H) 5.13 (t, J=6.56 Hz, 2H) 7.87 (d, J=7.93 Hz, 4H) 7.96 (d, J=6.41 Hz, 4H) 8.13 (s, 2H) (imidazole NH and hydroxyl protons unaccounted for). LC (Cond'n 2): RT=3.07 min; MS: Anal. Calcd. for [M+H]⁺ C₄₂H₅₂N₆O₄: 705.9; found 705.6.



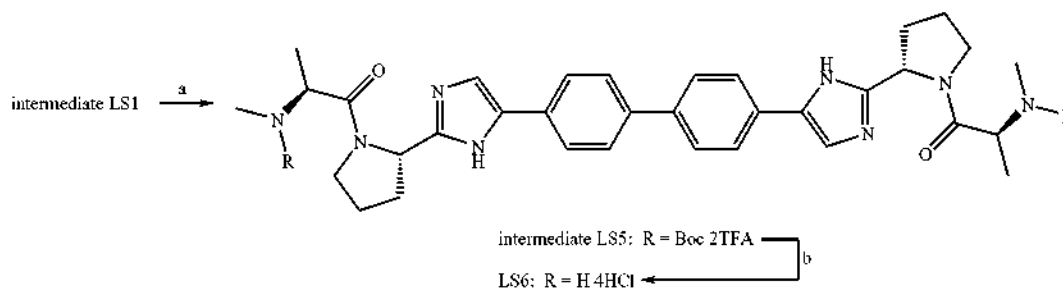
[0916] The following analogs were prepared in similar fashion to the preparation of LS2 from intermediate LS1 employing the appropriate carboxylic acid:

Example Number	Compound Name	Structure	Analytical Data
LS3	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(4-methyl-1-oxo-2-pentanol)		LC/MS: 2.02 min (Cond'n 1); Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₈ N ₆ O ₄ : 653.4; found 653.2.
LS4	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol)		LC/MS: 1.99 min (Cond'n 3); Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₄ N ₆ O ₄ : 625.3; found 625.3.
LS16	3-buten-1-yl(((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(((3-buten-1-yloxy)carbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		¹ H NMR (500 MHz, CH ₃ OD) δ ppm 0.81-1.10 (m, 12 H) 1.90-2.15 (m, 4 H) 2.15-2.51 (m, 8 H) 3.82-3.96 (m, 2 H) 3.97-4.05 (m, 2 H) 4.05-4.19 (m, 4 H) 4.25 (d, J = 7.02 Hz, 2 H) 4.62 (s, 2 H) 5.00-5.17 (m, 4 H) 5.20 (t, J = 5.65 Hz, 2 H) 5.79-5.93 (m, 2 H) 7.20-7.47 (m, 2 H) 7.59-7.90 (m, 8 H)

Example LS6

(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-methyl-1-oxo-2-propanamine)

[0917]



[0918] Step a: To intermediate LS1 (64 mg; 0.11 mmol) in 1 mL DMF was added (S)-2-(tert-butoxycarbonyl(methyl) amino)propanoic acid (48 mg; 0.24 mmol), Hunig's base (0.12 mL; 0.67 mmol) and HATU (90 mg; 0.24 mmol). After 3 h, the reaction was purified via preparative HPLC (Cond'n 2). Fractions containing intermediate LS5 were pooled and concentrated providing intermediate LS5 as a colorless powder (43 mg; 48%) after drying under high vacuum. LC (Cond'n 4): RT=2.12 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{58}N_8O_6$: 795.4; found 795.5.

[0919] Step b: Intermediate LS5 was allowed to stir in 2 mL HCl/Dioxane (4N) for 18 h at which time 10 mL ether was added and the resultant precipitate was filtered and dried under high vacuum providing LS6 (45 mg; 155%) as a colorless solid. 1H NMR (500 MHz, DMSO- d_6) δ ppm 2.00-2.11 (m, 2H) 2.12-2.27 (m, 4H) 2.38-2.47 (m, 2H) 2.39-2.48 (m, 2H) 2.58 (t, J=5.19 Hz, 2H) 3.78-3.85 (m, 2H) 3.91-4.02 (m, 2H) 4.21-4.32 (m, 2H) 5.26 (t, J=7.17 Hz, 2H) 7.93 (d, J=7.32 Hz, 4H) 8.02 (d, J=7.94 Hz, 4H) 8.12-8.21 (m, 2H) 8.69-8.81 (m, 2H) 9.09-9.17 (m, 2H); N-Me protons obscured by DMSO peak with 2 other protons unaccounted for. LC (Cond'n 5): RT=1.71 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 595.3; found 595.6.

Example LS11

(4S,4'S)-(4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(1,3-oxazinan-2-one)

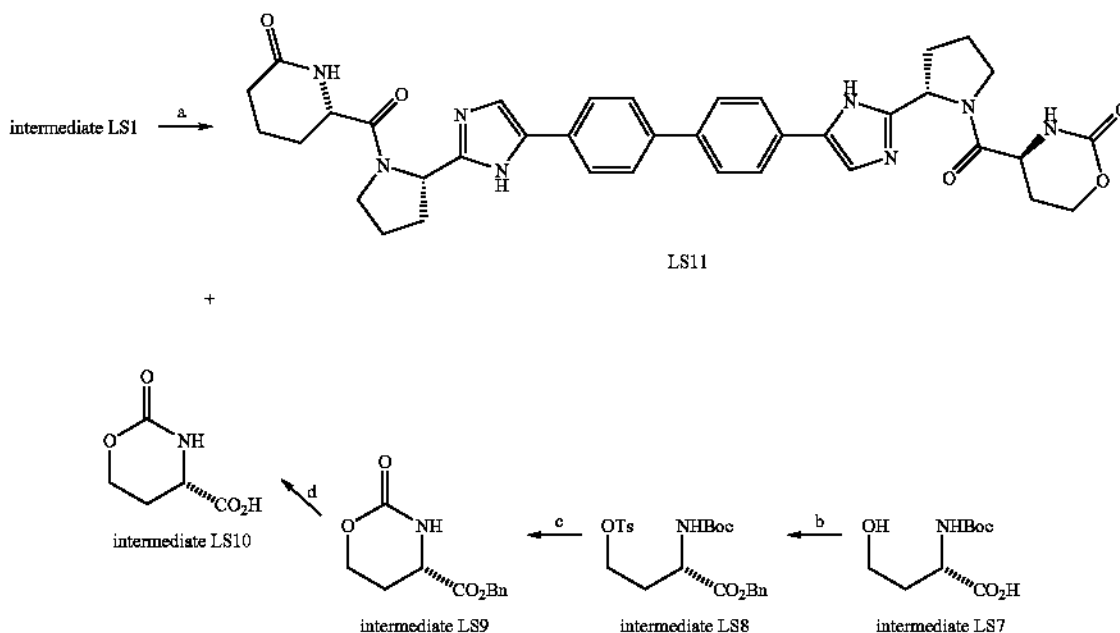
[0920]

[0921] Step a: To intermediate LS1 (65 mg; 0.11 mmol) in 1 mL DMF was added HATU (91 mg; 0.24 mmol), (S)-2-oxo-1,3-oxazinane-4-carboxylic acid (intermediate LS10; mg; 0.24 mmol), followed by DIPEA (0.12 mL; 0.68 mmol). After 3 h, the reaction mixture was twice purified via preparative HPLC (Cond'n 3). Appropriate fractions were pooled and concentrated under high vacuum providing 8 mg (10%) bis TFA LS11 as a colorless oil. 1H NMR (500 MHz, CH_3OD) δ ppm 1H NMR (500 MHz, CH_3OD) δ ppm 1.99-2.43 (m, 10H) 2.48-2.66 (m, 1.98 Hz, 2H) 3.82-3.95 (m, 4H) 4.17-4.40 (m, 4H) 4.57 (t, J=5.80 Hz, 2H) 5.23-5.41 (m, 2H) 7.73-7.97 (m, 10H); imidazole and carbamate NH protons are unaccounted for. LC (Cond'n 6): RT=2.28 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 679.3; found 679.4.

[0922] Step b: Performed as in Baldwin et al, *Tetrahedron* 1988, 44, 637

[0923] Step c: Performed as in Sakaitani and Ohfune, *J. Am. Chem. Soc.* 1990, 112, 1150 for the conversion of compound 1 to 5. Purification via Biotage (40M cartridge; 1:1 ether/ethyl acetate) then preparative HPLC (Cond'n 4) provided 77 mg (8%) intermediate LS9 as a viscous oil. 1H NMR (300 MHz, $CDCl_3$) δ ppm 2.02-2.21 (m, 1H) 2.23-2.41 (m, 1H) 4.11-4.38 (m, 3H) 5.11-5.31 (m, 2H) 6.15 (s, 1H) 7.27-7.46 (m, 5H). LC (Cond'n 7): RT=1.24 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 236.1; found 236.4.

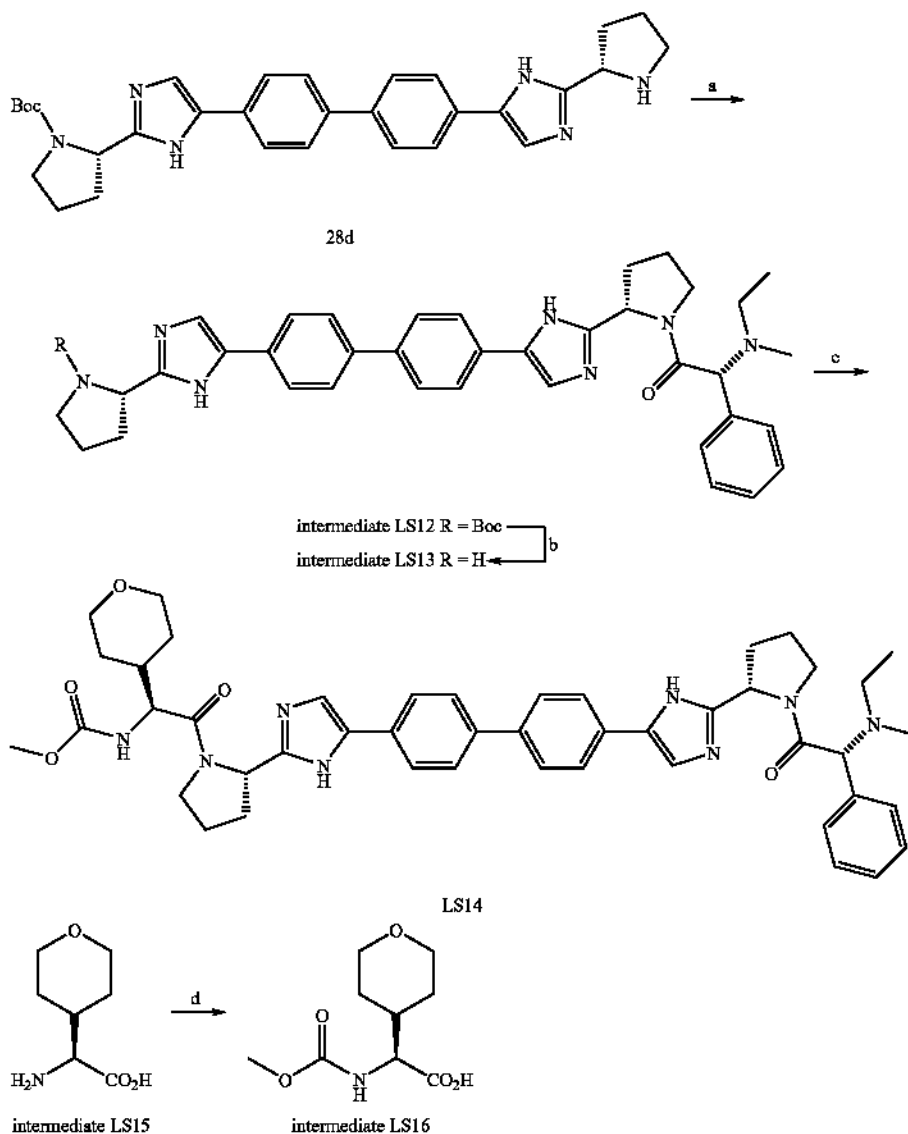
[0924] Step d: Intermediate LS9 was hydrogenated under 1 atm H_2 in 3 mL methanol with 10 mg Pd/C (10%) for 18 h. The reaction mixture was filtered through a pad of diatomaceous earth (Celite®) and concentrated to provide intermediate LS110 (40 mg; 83%) as a colorless powder. 1H NMR (500 MHz, CH_3OD) δ ppm 2.08-2.18 (m, 1H) 2.26-2.38 (m, 1H) 4.19 (t, J=5.95 Hz, 1H) 4.25-4.40 (m, 2H).



Example LS1-4

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[0925]



[0926] Step a: To 28 (1.5 g; 2.86 mmol) in 25 mL DMF was added sequentially Cap-2 (697 mg; 2.86 mmol), HATU (1.2 g; 3.14 mmol), and Hunig's base (1.5 mL; 8.57 mmol). After 3 h, the solution was concentrated to 10 mL and partitioned between chloroform and water. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to an amber oil which was subjected to silica gel chromatography (Biotage; loaded on 40 samplelet with dichloromethane; eluted on 40M cartridge with 0 to 12% dichloromethane/methanol over 1200 mL). Fractions containing intermediate LS12 were pooled and concentrated to provide material which contained residual DMF. This mate-

rial was redissolved in dichloromethane and washed with water (3x50 mL) and then brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to 761 mg powder which was repurified via silica gel chromatography (Biotage; loaded on 40 samplelet with dichloromethane; eluted on 40M cartridge with 0 to 80% 4:1 chloroform:methanol/ethyl acetate over 1500 mL) to provide intermediate LS12 (501 mg; 25%) as a colorless powder. LC (Cond'n 8): RT=1.24 min.

[0927] Step b: To intermediate LS12 (490 mg; 0.69 mmol) was added 6 mL HCl/Dioxane followed by 25 mL dichloromethane. After 24 h, 75 mL ether was added, the reaction

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mixture was filtered and the precipitate was dried under vacuum providing intermediate LS13.4HCl (434 mg; quant) as a tan solid. ¹H NMR (300 MHz, CH₃OD) δ ppm 1.16-1.29 (m, 3H) 1.37 (t, J=6.95 Hz, 3H) 1.89-2.06 (m, 6.95 Hz, 1H) 2.12-2.51 (m, 5H) 2.52-2.85 (m, 4H) 3.02-3.24 (m, 2H) 3.42-3.55 (m, 7.32 Hz, 1H) 3.58-3.71 (m, 2H) 4.26-4.41 (m, 1H) 5.18-5.37 (m, 2H) 5.65 (s, 1H) 7.57-7.66 (m, 3H) 7.67-7.75 (m, 1H) 7.86-8.04 (m, 10H) 8.14 (s, 1H). LC (Cond'n 8): RT=1.92 min.

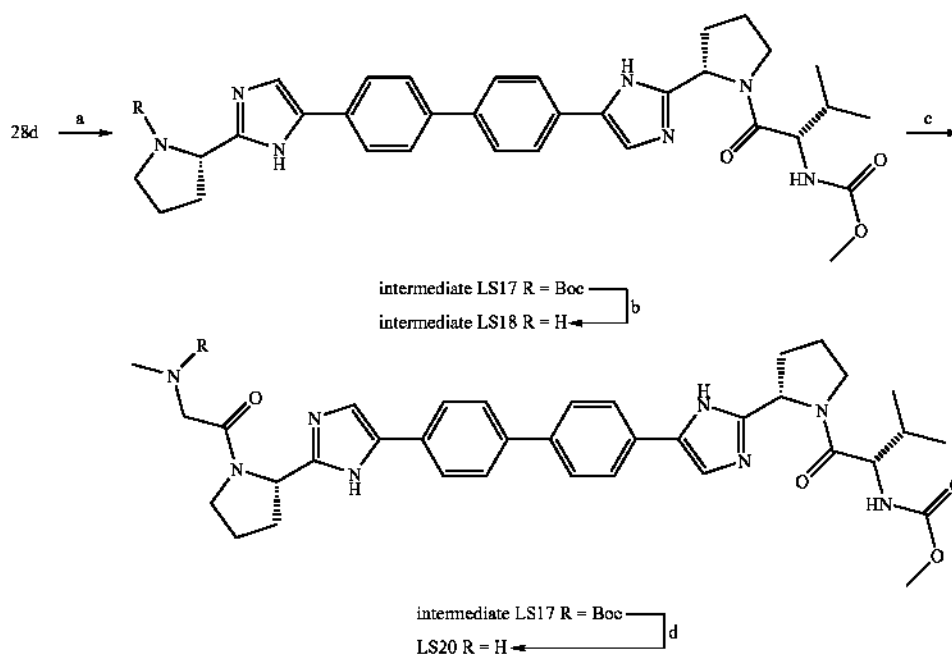
[0928] Step c: To intermediate LS13.4HCl (75 mg; 0.099 mmol) in 0.7 mL DMF was added sequentially intermediate LS16 (26 mg; 0.118 mmol), HATU (45 mg; 0.118 mmol), and Hunig's base (0.10 mL; 0.591 mmol). After 2 h, the reaction

yl)acetic acid (available from Astatech) for L-Valine. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.15-1.63 (m, 5H) 1.75-2.03 (m, 1H) 3.54 (s, 3H) 3.76-3.98 (m, 4H) 7.45 (d, J=8.42 Hz, 1H); one proton obscured by water peak.

Example LS20

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-methylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

[0930]



mixture was filtered through diatomaceous earth (Celite®), the pad washed with 0.3 mL methanol and the resultant filtrate was purified via preparative HPLC (Cond'n 5) in two separate injections. The fractions containing desired product were passed through an MCX cartridge (Oasis; 1 g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided 36 mg of LS14 as a colorless powder which was assayed to be of 82% diastereomeric purity (most likely epimeric at the stereogenic carbon in intermediate 16). Resubjected to preparative HPLC purification (2x) providing LS14 (13 mg; 16%) as a colorless solid. ¹H NMR (500 MHz, CH₃OD) δ ppm 0.99 (q, J=6.92 Hz, 6H) 1.25-1.72 (m, 5H) 1.80-2.42 (m, 10H) 2.47-2.61 (m, 3H) 2.66-2.78 (m, 2H) 3.35-3.43 (m, 2H) 3.65-3.71 (m, 3H) 3.89-4.01 (m, 4H) 4.01-4.10 (m, 1H) 4.32 (d, J=8.24 Hz, 1H) 5.11-5.22 (m, 1H) 6.95-7.17 (m, 3H) 7.30-7.44 (m, 3H) 7.53 (d, J=7.02 Hz, 1H) 7.62-7.89 (m, 8H). LC (Cond'n 9): RT=5.31 min.

[0929] Step d: Intermediate LS16 was prepared in analogous fashion to the procedure describing the synthesis of Cap-51 substituting (S)-2-amino-2-(tetrahydro-2H-pyran-4-

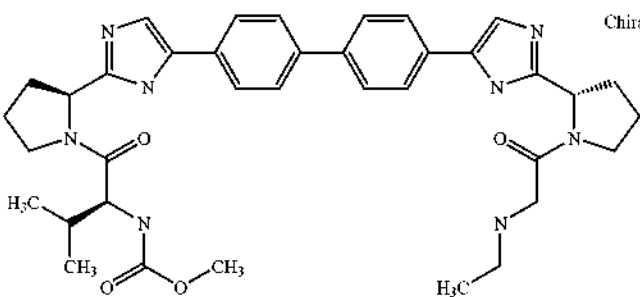
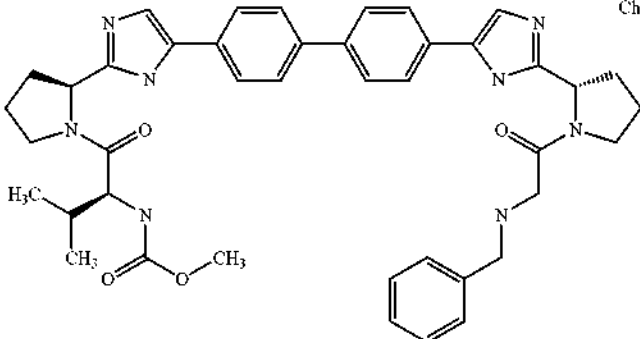
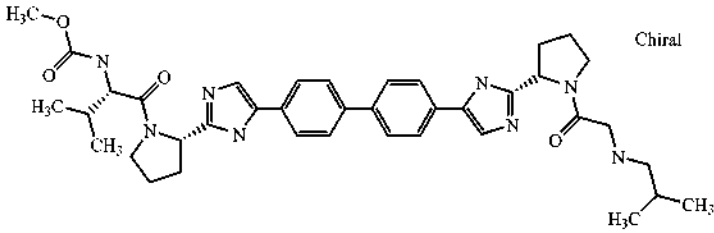
[0931] Step a & b: Intermediate LS18 was prepared in analogous fashion to the procedure describing the synthesis of intermediate LS13 substituting Cap-51 for Cap-2.

[0932] Step c: To intermediate LS18 (100 mg; 0.14 mmol) in 1.4 mL DMF was added sequentially N-Boc Sarcosine (30 mg; 0.16 mmol), Hunig's base (0.13 mL; 0.72 mmol) and HATU (60 mg; 0.16 mmol). After 2 h the reaction mixture was partitioned into dichloromethane, washed with NaHCO₃ (aq), brine, dried over magnesium sulfate, filtered and concentrated to crude intermediate LS19 which was used directly in the next step. LC (Cond'n 5): RT=2.42 min; MS: Anal. Calcd. for [M+H]⁺ C₄₁H₅₂N₈O₆: 753.4; found 753.9.

[0933] Step d: Crude intermediate LS19 was dissolved in 0.5 mL methanol and 5 mL 4N HCl/Dioxane. After stirring for 1 h, the reaction was concentrated and purified via preparative HPLC (Cond'n 6) and the fractions containing desired product were passed through an MCX cartridge (Oasis; 1 g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided LS20 (32 mg; 34%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.74-0.98 (m, 6H) 1.79-2.24 (m, 9H) 2.29-2.38 (m, 2H) 3.19-3.51 (m, 8H) 3.50-3.56 (m, 3H) 3.59-3.71 (m, 1H) 3.81 (s, 1H) 3.97-4.17 (m, 1H) 5.01-5.16 (m, 2H) 7.30 (d, J=7.93 Hz, 1H) 7.51 (s, 1H) 7.59-7.74 (m, 4H)

7.79 (d, J=7.63 Hz, 4H) 11.78 (s, 1H). LC (Cond'n 5): RT=2.00 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{44}N_8O_4$: 653.4; found 653.7.

[0934] The following analogs were prepared in similar fashion to the preparation of LS20 from LS18 substituting the appropriate carboxylic acid for N-Boc Sarcosine:

Example Number	Compound Name	Structure	Analytical Data
LS21	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-ethylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.34 min (Cond'n 2); Anal. Calcd. for $[M+H]^+$ $C_{37}H_{46}N_8O_4$: 667.4; found 667.7.
LS22	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-benzylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.34 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_8O_4$: 729.4; found 729.8.
LS23	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isobutylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.07 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{39}H_{50}N_8O_4$: 695.4; found 695.8.

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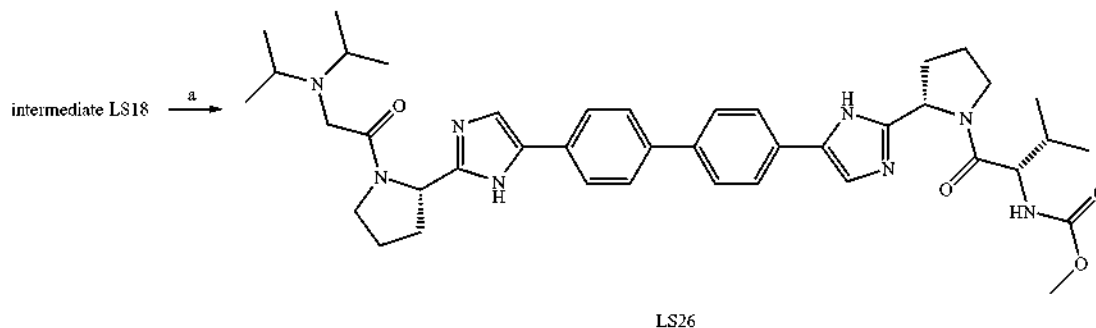
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Example Number	Compound Name	Structure	Analytical Data
LS24	methyl ((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-(N-sec-butylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.03 min (Cond'n 5); Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₅₀ N ₈ O ₄ : 695.4; found 695.9.
LS25	methyl ((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-(N-isopropylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		Chiral LC/MS: 1.97 min (Cond'n 5); Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₈ N ₈ O ₄ : 681.4; found 681.7.

Example LS26

methyl ((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-(N,N-diisopropylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[0935]



[0936] Step a: Compound LS26 was prepared in a similar fashion to the preparation of intermediate LS19 employing 2-(diisopropylamino)acetic acid as the carboxylic acid coupling partner. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.74-1.04 (m, 18H) 1.74-2.21 (m, 13H) 2.86-3.09 (m, 3H) 3.54 (s,

3H) 3.71-3.89 (m, 3H) 4.06 (t, J=8.55 Hz, 1H) 4.98-5.13 (m, 2H) 5.56 (d, J=8.55 Hz, 1H) 7.21-7.34 (m, 1H) 7.42-7.54 (m, 1H) 7.61-7.87 (m, 8H). LC (Cond'n 5): RT=1.98 min; MS: Anal. Calcd. for [M+H]⁺ C₄₁H₅₄N₈O₄: 723.4; found 723.4.

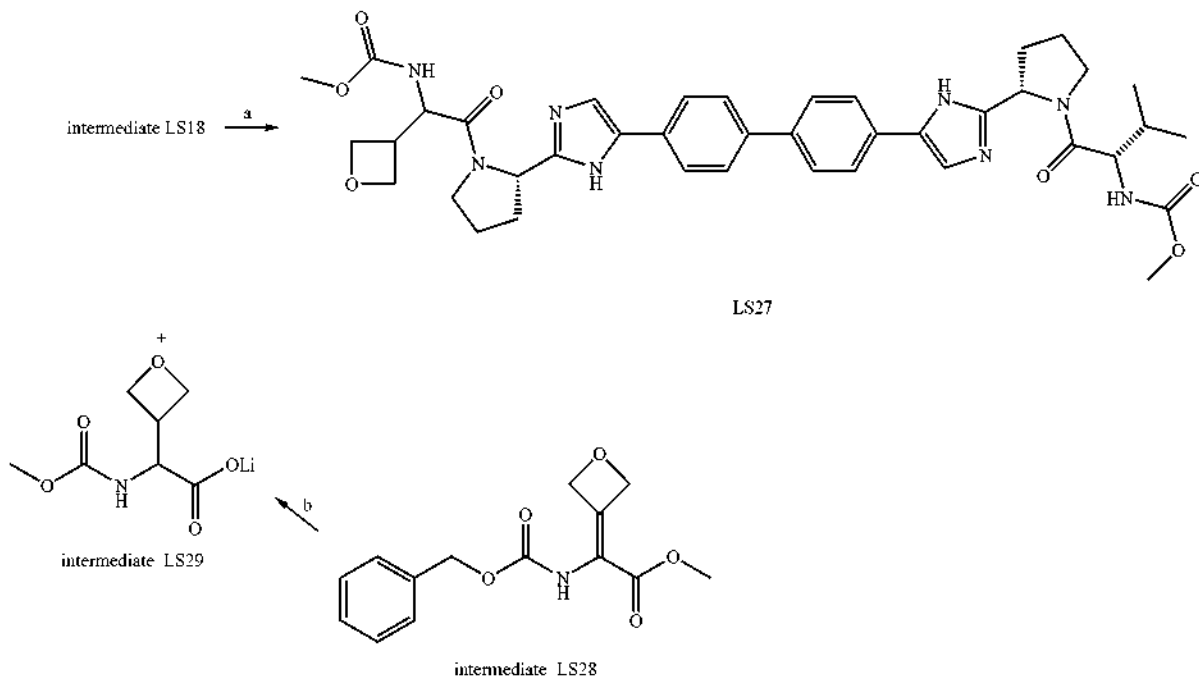
Example LS27 Diastereomer 1

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(methoxycarbonylamino)-2-(3-oxetanyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Example LS27 Diastereomer 2

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(methoxycarbonylamino)-2-(3-oxetanyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[0937]



[0938] Step a: Compound LS27 was prepared in a similar fashion to the preparation of intermediate LS19 employing 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetic acid (intermediate LS29) as the carboxylic acid coupling partner. The two diastereomers of LS27 were separated via preparative HPLC (Xbridge C18, 100×19 mm I.D. S-5 μm; Mobile Phase A: 95% Water-5% Acetonitrile with 10 mM ammonium acetate (pH=5); Mobile phase B: 95% Acetonitrile-5% Water with 10 mM ammonium acetate (pH=5); Isocratic 30% B for 7 min; Flow rate: 25 mL/min; UV detection: 220 nm; Sample amount: ~5 mg/each injection, 300 μL sample solution in methanol (~17 mg/mL)). Diastereomer 1: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.80-0.96 (m, 6H) 1.91-2.06 (m, 6H) 2.09-2.21 (m, 3H) 3.54 (s, 3H) 3.59 (s, 3H) 3.77-3.83 (m, 2H) 3.87 (t, J=7.63 Hz, 1H) 4.06 (t, J=8.24 Hz, 1H) 4.31 (t, J=6.41 Hz, 1H) 4.43 (t, J=6.10 Hz, 1H) 4.49 (t, J=7.17 Hz, 1H) 4.51-4.57 (m, 1H) 4.80 (t, J=8.55 Hz, 1H) 5.00-5.05 (m, 1H) 5.06-5.11 (m, 1H) 7.30 (d, J=8.55 Hz, 1H) 7.50 (s, 1H) 7.58-7.89 (m, 8H) 11.77 (s, 2H). LC (Cond'n 10): RT=7.14

min; MS: Anal. Calcd. for [M+H]⁺ C₄₀H₄₈N₈O₇: 753.4; found 753.9. Diastereomer 2: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.79-0.98 (m, 6H) 1.91-2.06 (m, 4H) 2.07-2.23 (m, 4H) 3.51-3.69 (m, 8H) 3.74-3.90 (m, 2H) 4.06 (t, J=7.48 Hz, 1H) 4.20-4.33 (m, 1H) 4.36-4.49 (m, 2H) 4.55 (s, 2H) 4.71 (s, 1H) 4.97-5.05 (m, 1H) 5.08 (s, 1H) 5.53 (s, 1H) 7.30 (d, J=7.93 Hz, 1H) 7.51 (s, 1H) 7.58-7.91 (m, 8H) 11.53 (s, 1H) 11.78 (s, 1H). LC (Cond'n 10): RT=8.79 min; MS: Anal. Calcd. for [M+H]⁺ C₄₀H₄₈N₈O₇: 753.4; found 753.9.

[0939] Step b: A solution of methyl 2-(benzyloxycarbonylamino)-2-(oxetan-3-ylidene)acetate (intermediate LS28; Source: Moldes et al, *II Farmaco*, 2001, 56, 609 and Wuitschik et al, *Ang. Chem. Int. Ed. Engl.*, 2006, 45, 7736; 200 mg, 0.721 mmol) in ethyl acetate (7 mL) and CH₂Cl₂ (4.00 mL) was degassed by bubbling nitrogen for 10 min. Dimethyl

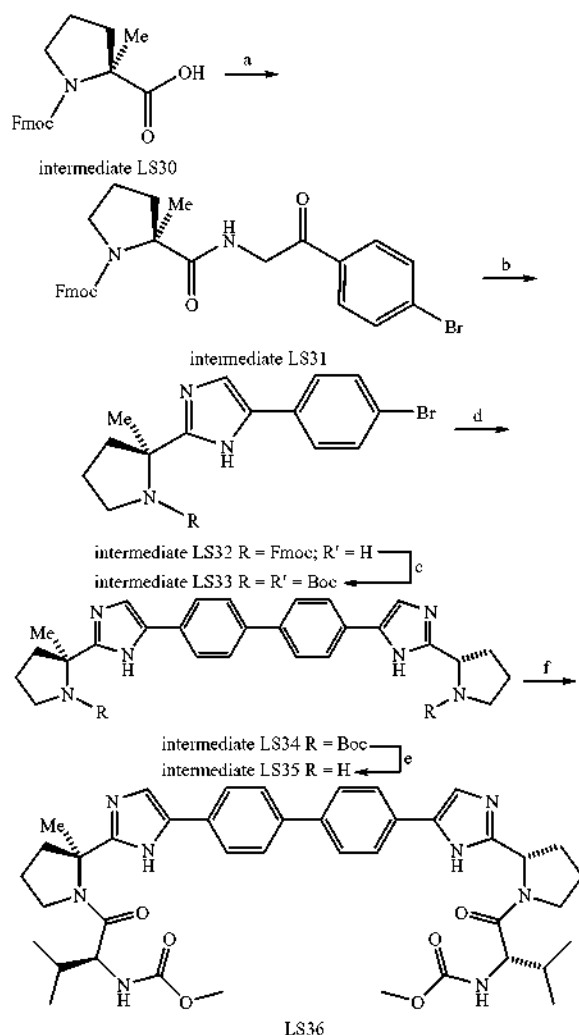
dicarbonate (0.116 mL, 1.082 mmol) and Pd/C (20 mg, 0.019 mmol) were then added, the reaction mixture was fitted with a hydrogen balloon and allowed to stir at ambient temperature overnight. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated. The residue was purified via Biotage (load with dichloromethane on 25 sample; elute on 25S column with dichloromethane for 3CV then 0 to 5% methanol/dichloromethane over 250 mL then hold at 5% methanol/dichloromethane for 250 mL; 9 mL fractions). Fractions containing the desired product were concentrated to provide 167 mg methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless oil which solidified on standing. ¹H NMR (500 MHz, CHLOROFORM-*D*) δ ppm 3.29-3.40 (m, 1H) 3.70 (s, 3H) 3.74 (s, 3H) 4.55 (t, J=6.41 Hz, 1H) 4.58-4.68 (m, 2H) 4.67-4.78 (m, 2H) 5.31 (br s, 1H). MS: Anal. Calcd. for [M+H]⁺ C₈H₁₃NO₅: 204.1; found 204.0. To methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate (50 mg, 0.246 mmol) in THF (2 mL) and Water (0.5 mL) was added lithium hydroxide monohydrate (10.33 mg, 0.246

mmol). The resultant solution was allowed to stir overnight at ambient temperature then concentrated to dryness to provide intermediate LS29 as a colorless powder. ^1H NMR (500 MHz, CH_3OD) δ ppm 3.38-3.50 (m, 1H) 3.67 (s, 3H) 4.28 (d, $J=7.63$ Hz, 1H) 4.57-4.79 (m, 4H).

Example LS36

methyl ((1S)-1-(((2S)-2-(5-(4'-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[0940]



[0941] Step a: To (S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-2-methylpyrrolidine-2-carboxylic acid (intermediate LS30; 1.5 g; 4.3 mmol) in 50 mL DMF was added sequentially 2-amino-1-(4-bromophenyl)ethanone hydrochloride (1.2 g; 4.7 mmol), HOAT (290 mg; 2.1 mmol), Hunig's base (0.7 mL; 4.3 mmol) and EDCI (1.2 g; 6.4 mmol). After 1 h, the reaction mixture was poured into 150 mL water and allowed to stir for 15 min before filtering the resultant precipitate

which was dissolved in dichloromethane and dried over magnesium sulfate. The dichloromethane mixture was filtered and applied to a Biotage 40 samplet. Chromatography on a 40M column (25 to 60% ethyl acetate/hexane over 1200 mL) provided (S)-(9H-fluoren-9-yl)methyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)-2-methylpyrrolidine-1-carboxylate (intermediate LS31; 2.4 g; quant) as a yellow foam. LC (Cond'n 11): RT=3.75 min; MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{29}\text{H}_{27}\text{BrN}_2\text{O}_4$: 547.1; found 547.0.

[0942] Step b: A mixture of ammonium acetate (844 mg; 10.97 mmol) and (S)-(9H-fluoren-9-yl)methyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)-2-methylpyrrolidine-1-carboxylate (intermediate LS31; 1.00 g; 1.83 mmol) was heated to 140°C . in 25 mL xylene for 2.5 h at which time the reaction mixture was concentrated and loaded with dichloromethane onto a Biotage 40 samplet. Purification via Biotage (5 to 60% ethyl acetate/hexane over 100 mL with 400 mL hold time) provided (S)-(9H-fluoren-9-yl)methyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (intermediate LS32; 469 mg; 49%) as an amber liquid. LC (Cond'n 12): RT=3.09 min; MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{29}\text{H}_{26}\text{BrN}_3\text{O}_2$: 528.1; found 528.5.

[0943] Step c: To (S)-(9H-fluoren-9-yl)methyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (intermediate LS32; 329 mg; 0.62 mmol) in 3 mL DMF was added 1.5 mL piperidine. The reaction mixture was concentrated via a nitrogen stream overnight. The resultant residue was washed with hexane and passed through an MCX cartridge (Oasis; 6 g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided 193 mg of (S)-5-(4-bromophenyl)-2-(2-methylpyrrolidin-2-yl)-1H-imidazole which was dissolved in 6 mL dichloromethane and combined with di-*t*-butyldicarbonate (413 mg; 1.89 mmol), DMAP (15 mg; 0.13 mmol) and TEA (0.17 mL; 1.30 mmol). After 48 h, the reaction mixture was concentrated and purified via chromatography on a Biotage system providing (S)-*tert*-butyl 5-(4-bromophenyl)-2-(1-(*tert*-butoxycarbonyl)-2-methylpyrrolidin-2-yl)-1H-imidazole-1-carboxylate (intermediate LS33; 150 mg; 48%) as an off white solid. LC (Cond'n 5): RT=3.75 min; MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{24}\text{H}_{32}\text{BrN}_3\text{O}_4$: 506.2; found 506.4.

[0944] Step d: (S)-*tert*-butyl 2-(5-(4'-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (intermediate LS34) was prepared in a similar fashion to the preparation of 1d employing intermediate LS33 in place of 1b. ^1H NMR (300 MHz, $\text{DMSO}-d_6$; 100°C) δ ppm 1.18-1.29 (m, 9H) 1.29-1.40 (m, 9H) 1.75-1.82 (m, 3H) 1.81-2.39 (m, 8H) 3.35-3.75 (m, 4H) 4.81-4.92 (m, 1H) 7.36-7.45 (m, 1H) 7.57-7.74 (m, 5H) 7.76-7.89 (m, 4H) 11.29-11.63 (m, 2H). LC (Cond'n 5): RT=2.49 min; MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{37}\text{H}_{46}\text{N}_6\text{O}_4$: 639.4; found 639.9.

[0945] Step e: 2-((S)-2-methylpyrrolidin-2-yl)-5-(4'-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazole (intermediate LS35) was prepared in a similar fashion to the preparation of 1e employing intermediate LS34 in place of 1d. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 1.76-1.83 (m, 3H) 1.92-2.23 (m, 6H) 3.31-3.49 (m, 4H) 4.88-4.97 (m, 1H) 7.76-7.88 (m, 5H) 7.90-8.04 (m, 5H) 9.72-9.82 (m, 1H) 10.04-10.16 (m, 1H); imidazole and pyrrolidine NH protons unaccounted for. LC (Cond'n 5): RT=1.79 min; MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{27}\text{H}_{30}\text{N}_6$: 439.2; found 439.5.

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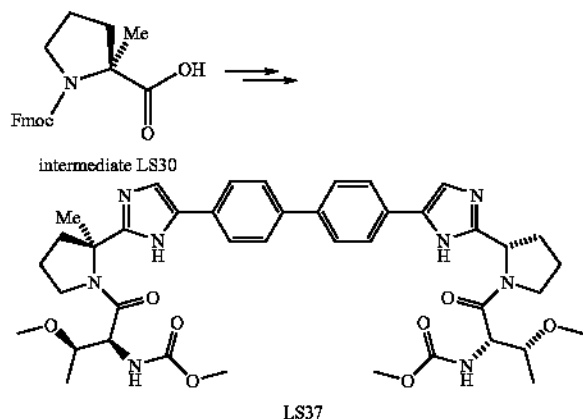
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[0946] Step f: Compound LS36 was prepared in a similar fashion to the preparation of example 1 employing intermediate LS35 in place of 1e and Cap-51 in place of Cap-1. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.72-0.97 (m, 12H) 1.77 (s, 3H) 1.86-2.08 (m, 8H) 2.09-2.19 (m, 2H) 2.25-2.39 (m, 2H) 3.49-3.59 (m, 6H) 3.81 (d, J=6.71 Hz, 4H) 4.06 (q, J=7.83 Hz, 2H) 5.08 (dd, J=7.02, 3.05 Hz, 1H) 7.12 (d, J=8.85 Hz, 1H) 7.27-7.34 (m, 1H) 7.46-7.55 (m, 1H) 7.59-7.73 (m, 4H) 7.75-7.86 (m, 3H) 11.66 (s, 1H) 11.77 (s, 1H). LC (Cond'n 5): RT=2.25 min; MS: Anal. Calcd. for [M+H]⁺ C₄₁H₅₂N₈O₆: 753.4; found 754.0.

Example LS37

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-methyl-1-pyrrolidinyl)carbonyl)propyl)carbamate

[0947]



[0948] Compound LS37 was prepared in a similar fashion to the preparation of LS36 from intermediate LS30 using Cap-86 in place of Cap-51. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.99-1.17 (m, 6H) 1.76 (s, 3H) 1.87-2.09 (m, 4H) 2.10-2.23 (m, 2H) 2.34-2.38 (m, 2H) 2.56-2.60 (m, 1H) 2.63 (d, J=1.83 Hz, 1H) 3.17 (s, 3H) 3.19 (s, 3H) 3.37-3.51 (m, 2H) 3.54 (s, 6H) 3.75-3.96 (m, 4H) 4.13-4.36 (m, 2H) 5.07 (dd, J=7.48, 3.20 Hz, 1H) 7.20 (d, J=8.54 Hz, 1H) 7.24-7.34 (m, 1H) 7.50 (dd, J=7.17, 1.98 Hz, 1H) 7.59-7.73 (m, 4H) 7.76-7.86 (m, 3H) 11.65 (s, 1H) 11.77 (s, 1H). LC (Cond'n 13): RT=4.30 min; MS: Anal. Calcd. for [M+H]⁺ C₄₁H₅₂N₈O₈: 785.4; found 785.4.

Section F LC Conditions for Determining Retention Time

Condition 1

Column: Phenomenex-Luna 4.6×50 mm S10

Start % B=0

Final % B=100

Gradient Time=4 min

[0949] Flow Rate=4 mL/Min

Wavelength=220

[0950] Solvent A=10% methanol—90% H₂O—0.1% TFA
Solvent B=90% methanol—10% H₂O—0.1% TFA

Condition 2

Column: Waters-Sunfire 4.6×50 mm S5

Start % B=0

Final % B=100

Gradient Time=2 min

[0951] Flow Rate=4 mL/Min

Wavelength=220

[0952] Solvent A=10% methanol—90% H₂O—0.1% TFA
Solvent B=90% methanol—10% H₂O—0.1% TFA

Condition 3

Column: Phenomenex 10u 3.0×50 mm

Start % B=0

Final % B=100

Gradient Time=2 min

[0953] Flow Rate=4 mL/Min

Wavelength=220

[0954] Solvent A=10% methanol—90% H₂O—0.1% TFA
Solvent B=90% methanol—10% H₂O—0.1% TFA

Condition 4

Column: Phenomenex-Luna 3.0×50 mm S10

Start % B=0

Final % B=100

Gradient Time=3 min

[0955] Flow Rate=4 mL/Min

Wavelength=220

[0956] Solvent A=10% methanol—90% H₂O—0.1% TFA
Solvent B=90% methanol—10% H₂O—0.1% TFA

Condition 5

Column: Phenomenex-Luna 4.6×50 mm S10

Start % B=0

Final % B=100

Gradient Time=3 min

[0957] Flow Rate=4 mL/Min

Wavelength=220

[0958] Solvent A=10% methanol—90% H₂O—0.1% TFA
Solvent B=90% methanol—10% H₂O—0.1% TFA

Condition 6

Column: Xbridge C18 4.6×50 mm S5

Start % B=0

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Final % B=100

Gradient Time=3 min

[0959] Flow Rate=4 mL/Min

Wavelength=220

Solvent A=H₂O:ACN 95%:5% 10 mm Ammonium AcetateSolvent B=H₂O:ACN 5%:95% 10 mm Ammonium Acetate

Condition 7

Column: Phenomenex C18 10u 4.6x30 mm

Start % B=0

Final % B=100

Gradient Time=3 min

[0960] Flow Rate=4 mL/Min

Wavelength=220

[0961] Solvent A=10% methanol—90% H₂O—0.1% TFASolvent B=90% methanol—10% H₂O—0.1% TFA

Condition 8

Column: Phenomenex LunaC18 10u 4.6x30 mm

Start % B=0

Final % B=100

Gradient Time=2 min

[0962] Flow Rate=5 mL/Min

Wavelength=220

[0963] Solvent A=10% methanol—90% H₂O—0.1% TFASolvent B=90% methanol—10% H₂O—0.1% TFA

Condition 9

Column: Phenomenex C18 10u 4.6x30 mm

Start % B=0

Final % B=100

Gradient Time=10 min

[0964] Flow Rate=4 mL/Min

Wavelength=220

Solvent A=H₂O:ACN 95%:5% 10 mm Ammonium AcetateSolvent B=H₂O:ACN 5%:95% 10 mm Ammonium Acetate

Condition 10

Column: Phenomenex 10u 3.0x50 mm

Start % B=0

Final % B=100

Gradient Time=3 min

[0965] Flow Rate=4 mL/Min

Wavelength=220

[0966] Solvent A=10% methanol—90% H₂O—0.1% TFASolvent B=90% methanol—10% H₂O—0.1% TFA

Condition 11

Column: Xterra 4.6x30 mm S5

Start % B=0

Final % B=100

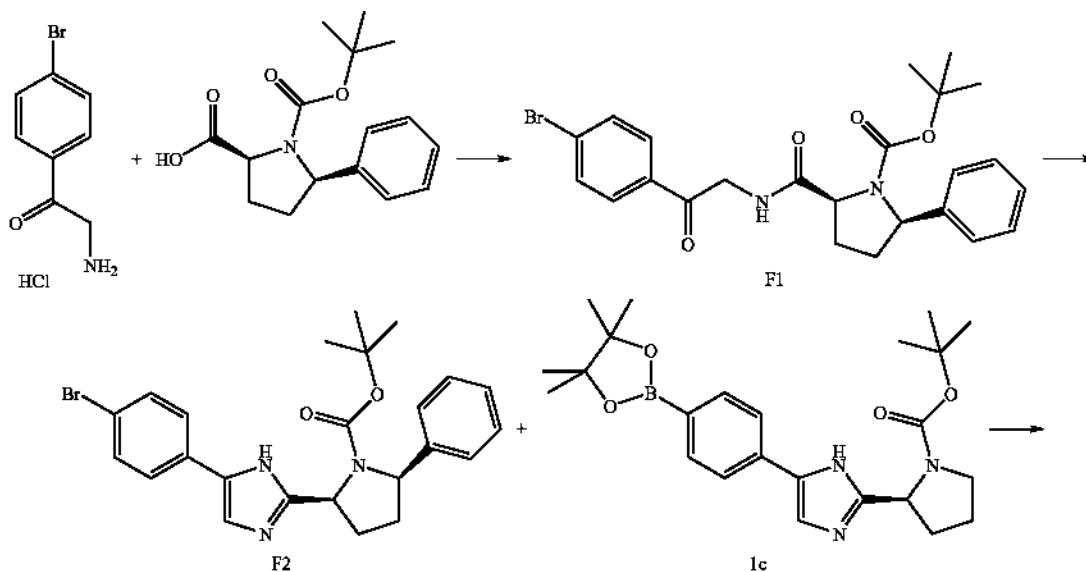
Gradient Time=2 min

[0967] Flow Rate=5 mL/Min

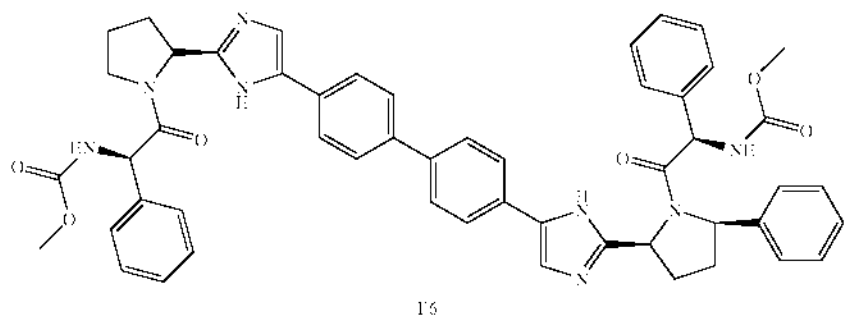
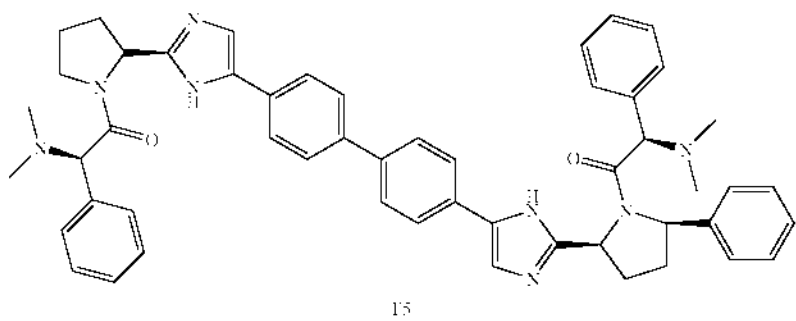
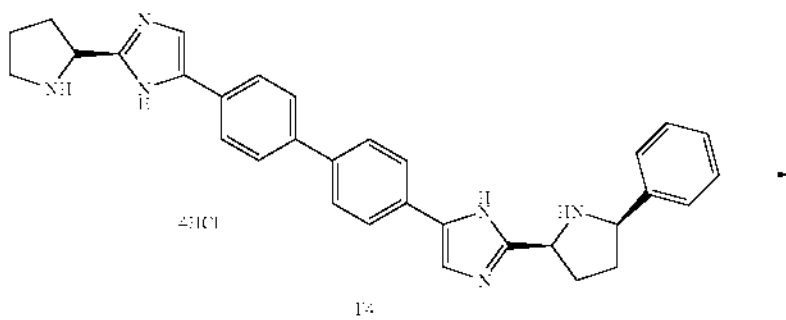
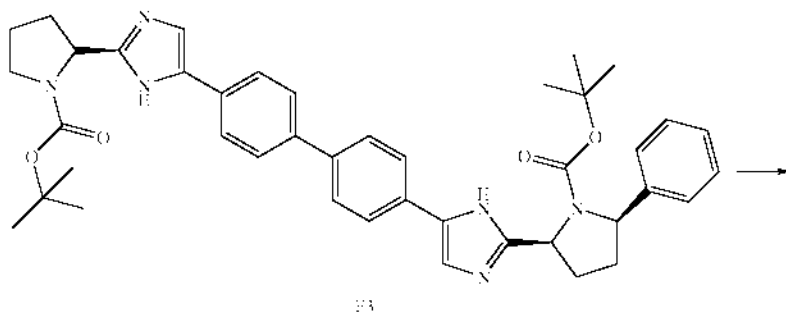
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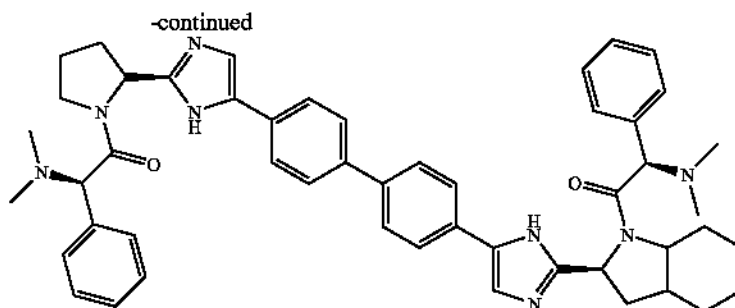
Solvent A=H₂O:ACN 95%:5% 10 mm Ammonium AcetateSolvent B=H₂O:ACN 5%:95% 10 mm Ammonium Acetate

[0968]

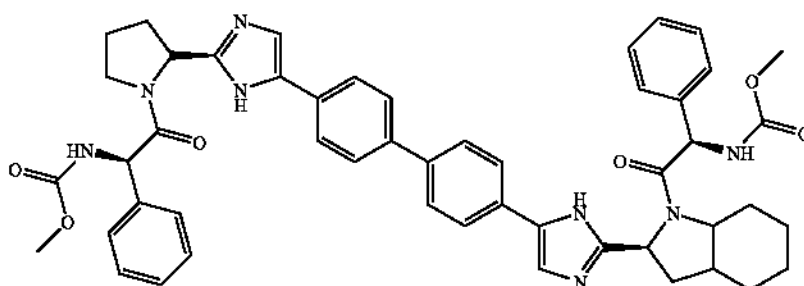


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F7



F8

[0969] Compound F1 was prepared in analogous fashion to the procedure used to synthesize 1a with following modification: (2S,5R)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid was used in place of N-Boc-L-proline.

[0970] Compound F2 was prepared in analogous fashion to the procedure used to synthesize 1b.

[0971] Compound F3 was prepared in analogous fashion to the procedure used to synthesize 1d.

[0972] Compound F4 was prepared in analogous fashion to the procedure used to synthesize 1e.

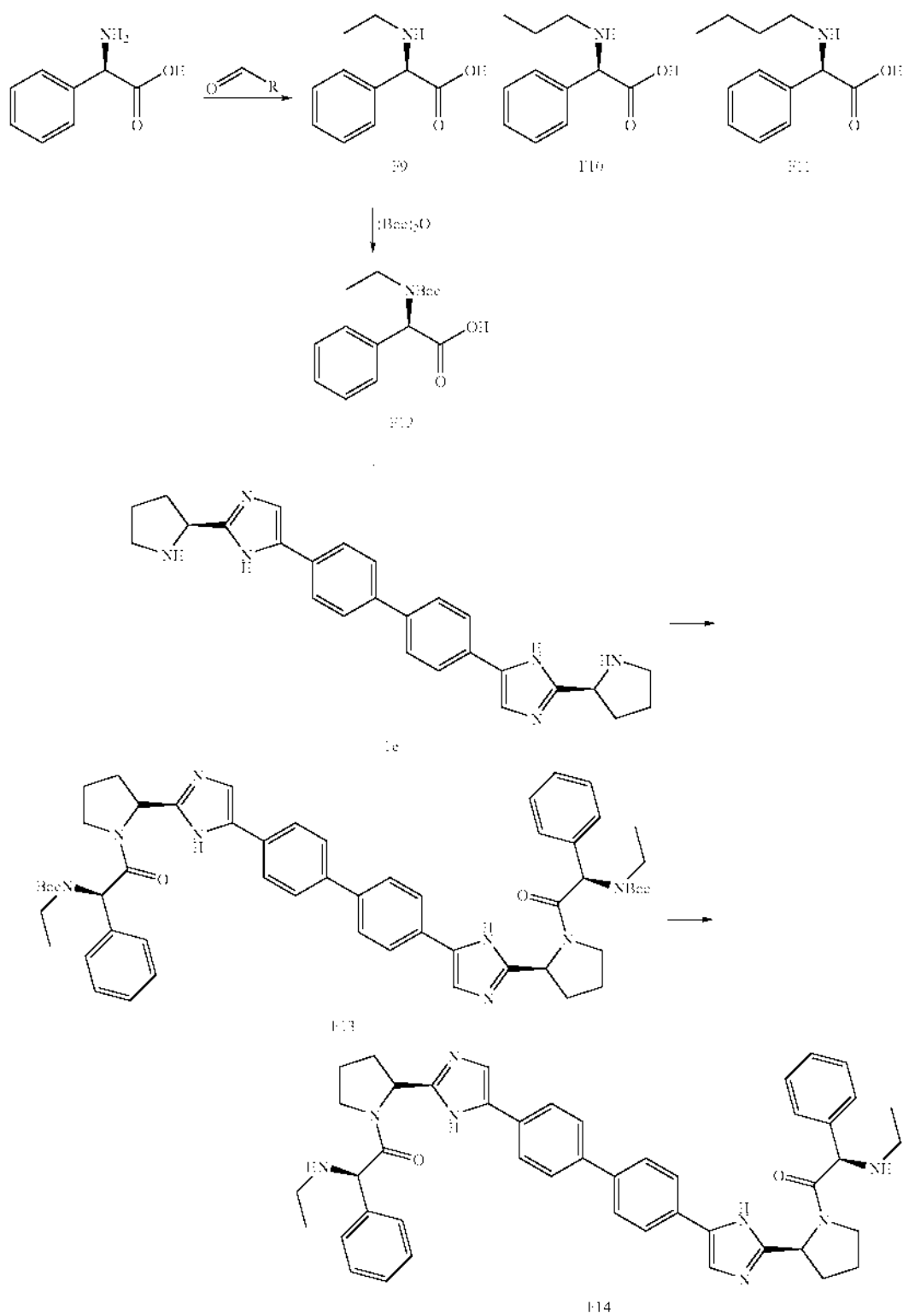
[0973] Compound F5, F6 was prepared in analogous fashion to the procedure used to synthesize example 1 from Compound F4.

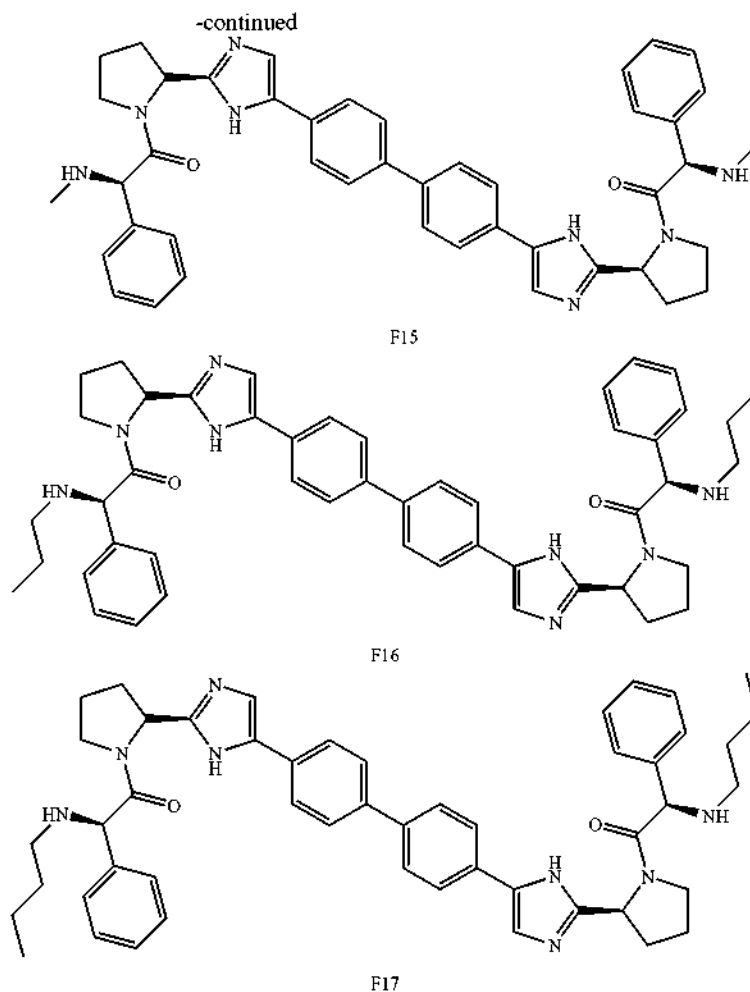
[0974] Compound F7, F8 was prepared in analogous fashion to the procedure used to synthesize F5 with following modification: (2S)-1-(tert-butoxycarbonyl)octahydro-1H-indole-2-carboxylic acid was used in place of (2S,5R)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid.

Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F1		RT = 3.838 minutes (condition 1, 94%); LRMS: Anal. Calcd. for C ₂₄ H ₂₇ BrN ₂ O ₄ 486.12; found: 487.26 (M + H) ⁺ .
F2		RT = 3.175 minutes (condition 1, 83%); LRMS: Anal. Calcd. for C ₂₄ H ₂₇ BrN ₂ O ₄ 467.12; found: 468.26 (M + H) ⁺ .
F3		RT = 2.965 minutes (condition 1, 93%); LRMS: Anal. Calcd. for C ₄₂ H ₄₈ N ₆ O ₄ 700.37; found: 701.49 (M + H) ⁺ .

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Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F4		RT = 2.083 minutes (condition 1, 98%); LRMS: Anal. Calcd. for C ₃₂ H ₃₂ N ₆ 500.27; found: 501.40 (M + H) ⁺ .
F5		RT = 1.222 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C ₅₂ H ₅₄ N ₈ O ₂ 822.44; found: 823.5 (M + H) ⁺ .
F6	methyl ((1R)-2-((2R)-2-(4'-(2-((2S,5R)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-5-phenyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	RT = 1.512 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C ₅₂ H ₅₀ N ₈ O ₆ 882.39; found: 883.45 (M + H) ⁺ .
F7	rel-(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)octahydro-1H-indol-2-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethylamine	RT = 1.223 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C ₅₀ H ₅₆ N ₈ O ₂ 800.45; found: 801.51 (M + H) ⁺ .
F8	methyl rel-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)octahydro-1H-indol-2-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	RT = 1.513 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C ₅₀ H ₅₆ N ₈ O ₂ 860.40; found: 861.42 (M + H) ⁺ .





[0975] Compound F9, F10, and F11 was prepared in analogous fashion to the procedure used to synthesize Cap-3 first half procedure using acetaldehyde, propionaldehyde, and butyraldehyde respectively.

Compound F12

[0976] (Boc)₂O (2.295 g, 10.20 mmol) was added to a mixture of compound F9 (1.0 g, 4.636 mmol), hunig's base (1.78 mL, 10.20 mmol) in CH₂Cl₂ (12 mL), and the resulting mixture was stirred over night. The volatile component was removed in vacuo, and the residue was purified by a reverse

phase HPLC system (H₂O/methanol/TFA) to provide compound F12 as a clear wax (0.993 g).

[0977] LC (Cond. 3): RT=1.663 min; >95% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₅H₂₁NO₄: 279.33; found [M+Na]⁺ 302.30

[0978] Compound F13 was prepared in analogous fashion to the procedure used to synthesized example 1 from Compound 1e and F12.

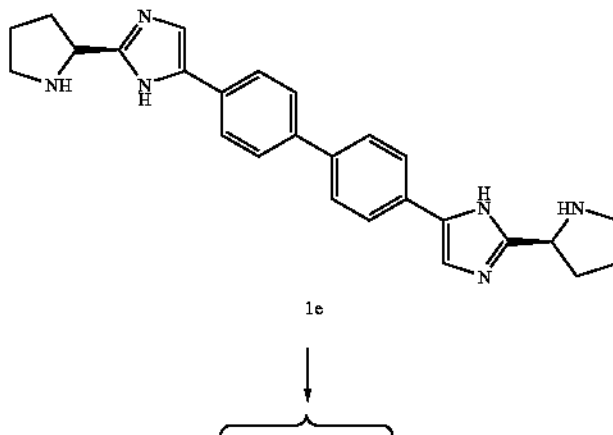
[0979] Compound F14 was prepared in analogous fashion to the procedure used to synthesized 132e.

[0980] Compound F15, F16, and F17 was prepared in analogous fashion to the procedure used to synthesize F14.

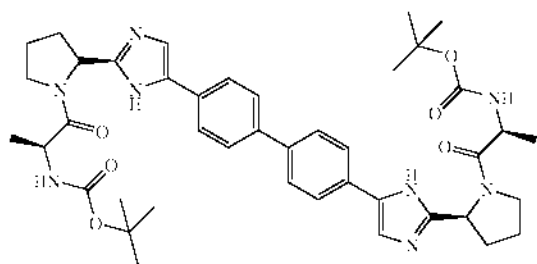
Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F9		RT = 0.580 minutes (condition 1, 94%); LRMS: Anal. Calcd. for C ₁₀ H ₁₃ NO ₂ 179.09; found: 180.26 (M + H) ⁺ .
F10		RT = 0.563 minutes (condition 3, 94%); LRMS: Anal. Calcd. for

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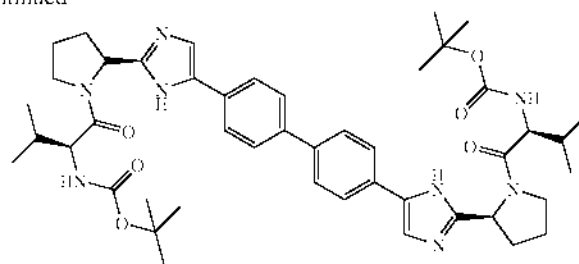
Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F11		C ₁₁ H ₁₅ NO ₂ 193.11; found: 194.26 (M + H) ⁺ . RT = 1.023 minutes (condition 3, 94%); LRMS: Anal. Calcd. for C ₁₂ H ₁₇ NO ₂ 207.13; found: 208.31 (M + H) ⁺ .
F12		RT = 1.663 minutes (condition 3, 95%); LRMS: Anal. Calcd. for C ₁₅ H ₂₁ NO ₄ 279.15; found: 302.30 (Na + H) ⁺ .
F13		RT = 2.595 minutes (condition 4, 94%); LRMS: Anal. Calcd. for C ₅₆ H ₆₆ N ₈ O ₆ 946.51; found: 947.64 (M + H) ⁺ .
F14	(1R)—N-ethyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(ethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	RT = 1.55 minutes (condition 5, 90%); LRMS: Anal. Calcd. for C ₄₆ H ₅₀ N ₈ O ₂ 746.41; found: 747.72 (M + H) ⁺ .
F15	(1R)—N-methyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(methylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	RT = 1.50 minutes (condition 5, 94%); LRMS: Anal. Calcd. for C ₄₄ H ₄₆ N ₈ O ₂ 718.37; found: 719.69 (M + H) ⁺ .
F16	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(propylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-propanamine	RT = 1.63 minutes (condition 5, 90%); LRMS: Anal. Calcd. for C ₄₈ H ₅₄ N ₈ O ₂ 774.43; found: 775.76 (M + H) ⁺ .
F17	N-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(butylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-1-butanamine	RT = 1.81 minutes (condition 5, 85%); LRMS: Anal. Calcd. for C ₅₀ H ₅₈ N ₈ O ₂ 802.47; found: 803.79 (M + H) ⁺ .



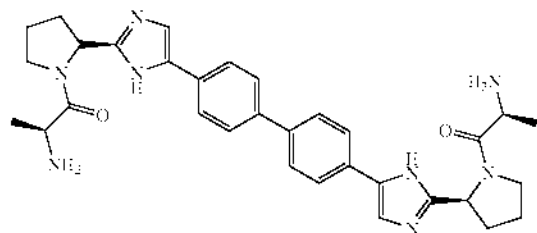
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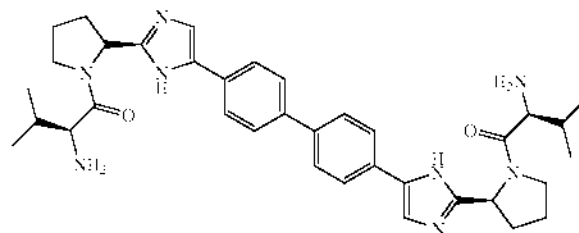
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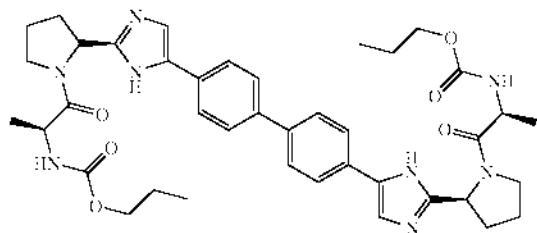
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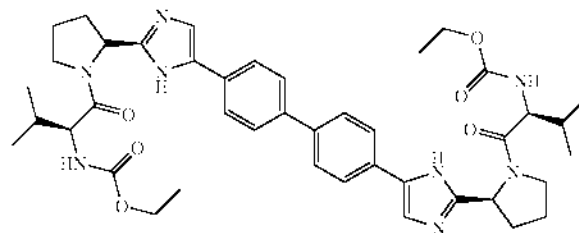
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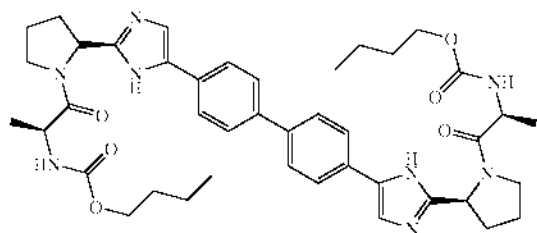
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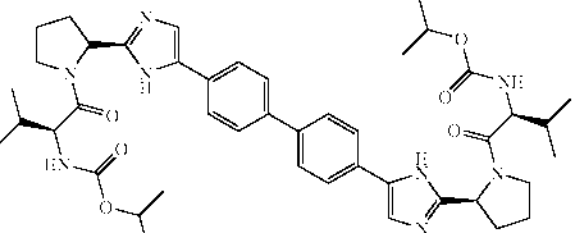
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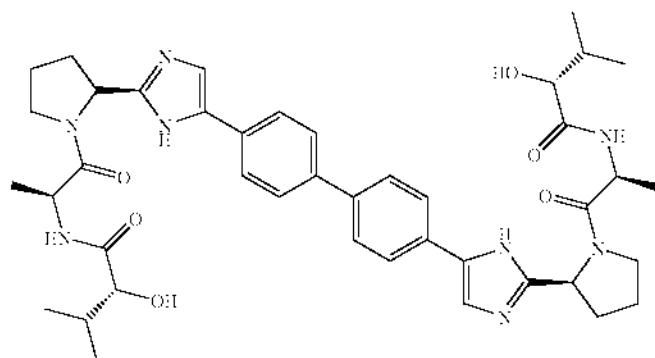
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126



127

[0981] Compound F18 and F23 was prepared in analogous fashion to the procedure used to synthesize example 1 with following modification: N-Boc-L-alanine and N-Boc-L-valine was used in place of N-Boc-L-proline respectively.

[0982] Compound F22 was prepared in analogous fashion to the procedure used to synthesize example 1 from Compound F19.

[0983] Compound F19, F24 was prepared in analogous fashion to the procedure used to synthesize 132e.

Compound F25

ethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[0984] To a solution of F24 (0.06 g, 0.074 mmol) in DMF (1 mL) was added Hunig's base (0.105 mL, 0.593 mmol) and ethyl carbonochloridate (0.016 mL, 0.163 mmol) then stirred

it at room temperature. Two hours later, checked it by LCMS. There were three major peaks which indicated desired compound, tri-coupled, and tetra-coupled compound. Stopped reaction and concentrated it by reduced pressure to get light brown oil which was treated with 10 mL of 2 M NH_3 in methanol for 20 minutes then concentrated it again to a yellow solid which was purified by preparative LC to provide compound F25 as a white TFA salt (57.6 mg).

[0985] LC (Cond. 6): RT=1.932 min, LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{42}\text{H}_{54}\text{N}_{10}\text{O}_6$: 766.42; found 767.55.

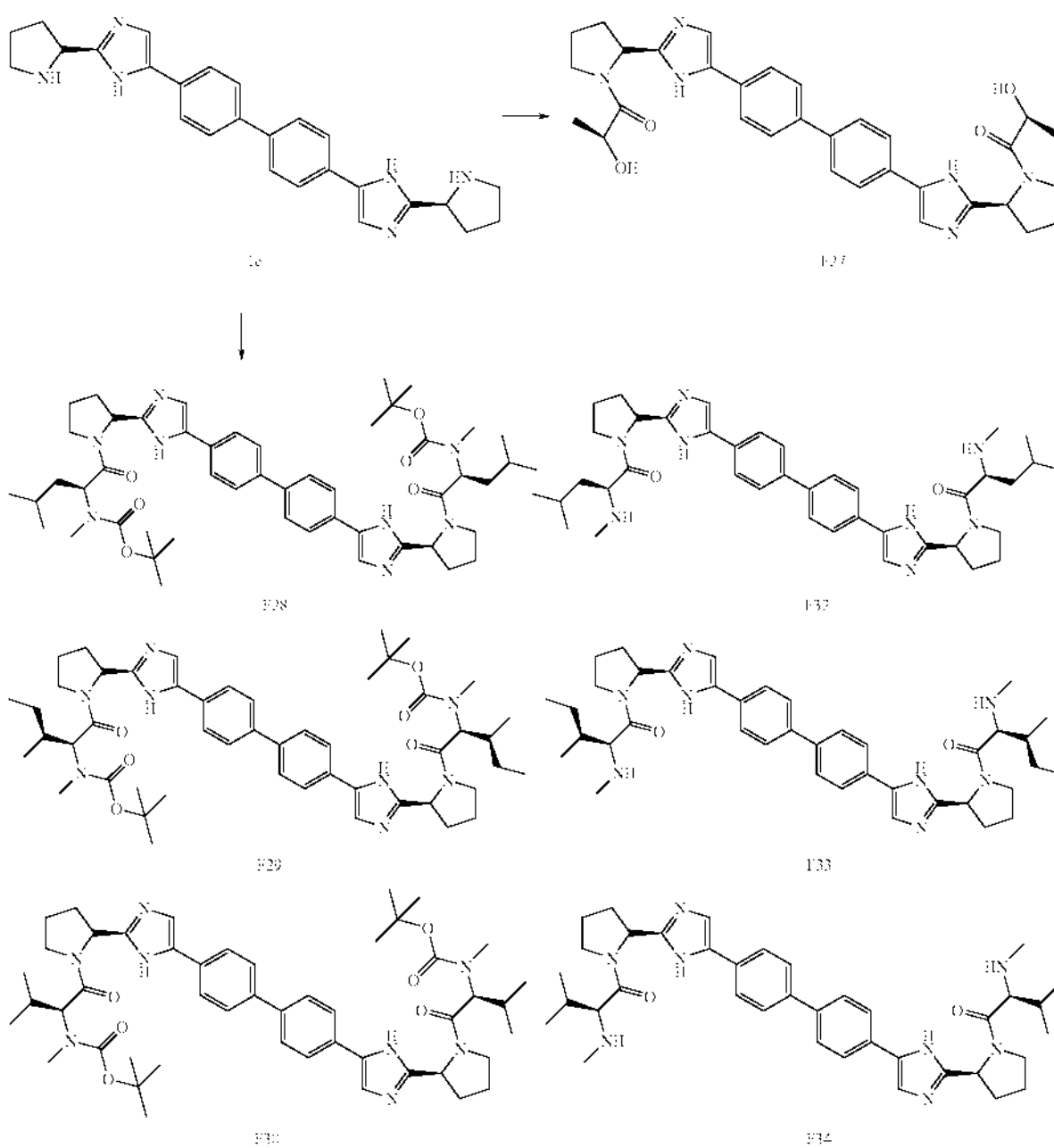
[0986] ^1H NMR (500 MHz, DMSO-d_6) δ ppm 0.69-0.94 (m, 12H) 1.16 (t, J=7.02 Hz, 6H) 1.90-2.26 (m, 8H) 2.40 (d, J=4.88 Hz, 2H) 3.73-3.92 (m, 4H) 3.94-4.08 (m, 4H) 4.12 (t, J=7.78 Hz, 2H) 5.15 (t, J=7.02 Hz, 2H) 7.26 (d, J=8.54 Hz, 2H) 7.85-7.93 (m, 4H) 7.93-8.01 (m, 4H) 8.13 (s, 2H) 14.68 (s, 2H)

[0987] Compound F20, F21, and F26 was prepared in analogous fashion to the procedure used to synthesize example 1.

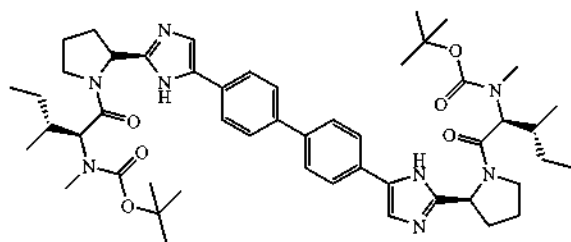
Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F18		RT = 2.257 minutes (condition 5, 96%); LRMS: Anal. Calcd. for $\text{C}_{42}\text{H}_{54}\text{N}_{10}\text{O}_6$ 766.42; found: 767.88 (M + H) ⁺ .
F19		RT = 1.462 minutes (condition 5, 95%); LRMS: Anal. Calcd. for $\text{C}_{32}\text{H}_{38}\text{N}_8\text{O}_2$ 566.31; found: 567.79 (M + H) ⁺ .
F20	propyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(propoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	RT = 1.338 minutes (condition 3, 89%); LRMS: Anal. Calcd. for $\text{C}_{40}\text{H}_{50}\text{N}_8\text{O}_6$ 738.39; found: 739.95 (M + H) ⁺ .
F21	butyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(butoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 1.447 minutes (condition 3, 96%); LRMS: Anal. Calcd. for $\text{C}_{42}\text{H}_{54}\text{N}_8\text{O}_6$ 766.93; found: 768.02 (M + H) ⁺ .
F22	(2S)-2-hydroxy-N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(2S)-2-hydroxy-3-methylbutanoyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-3-methylbutanamide	RT = 1.703 minutes (condition 4, 98%); LRMS: Anal. Calcd. for $\text{C}_{42}\text{H}_{54}\text{N}_8\text{O}$ 766.93; found: 768.02 (M + H) ⁺ .
F23		RT = 2.881 minutes (condition 7, 93%); LRMS: Anal. Calcd. for $\text{C}_{46}\text{H}_{62}\text{N}_8\text{O}_6$ 822.48; found: 823.95 (M + H) ⁺ .
F24		RT = 1.743 minutes (condition 7, 98%); LRMS: Anal. Calcd. for $\text{C}_{36}\text{H}_{46}\text{N}_8\text{O}_2$ 622.37; found: 624.07 (M + H) ⁺ .
F25	ethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 1.932 minutes (condition 6, 97%); LRMS: Anal. Calcd. for $\text{C}_{42}\text{H}_{54}\text{N}_8\text{O}_6$ 766.42; found: 767.55 (M + H) ⁺ .
F26	isopropyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((isopropoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-	RT = 2.122 minutes (condition 6, 98%); LRMS: Anal. Calcd. for $\text{C}_{44}\text{H}_{58}\text{N}_8\text{O}_6$ 794.45; found: 795.58 (M + H) ⁺ .

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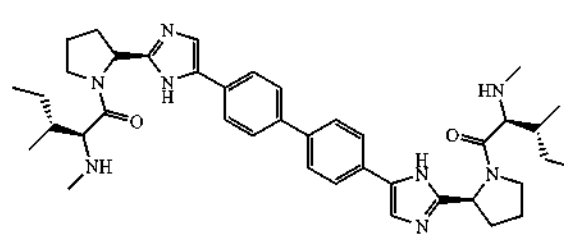
Entry	Compound Name	Retention time (LC Condition):	Homogeneity index MS data
	biphenyl-11-yl-1H-imidazol-2-yl)- 1-pyrrolidinylcarboxyl-2 methylpropylcarbamate		



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F31



F35

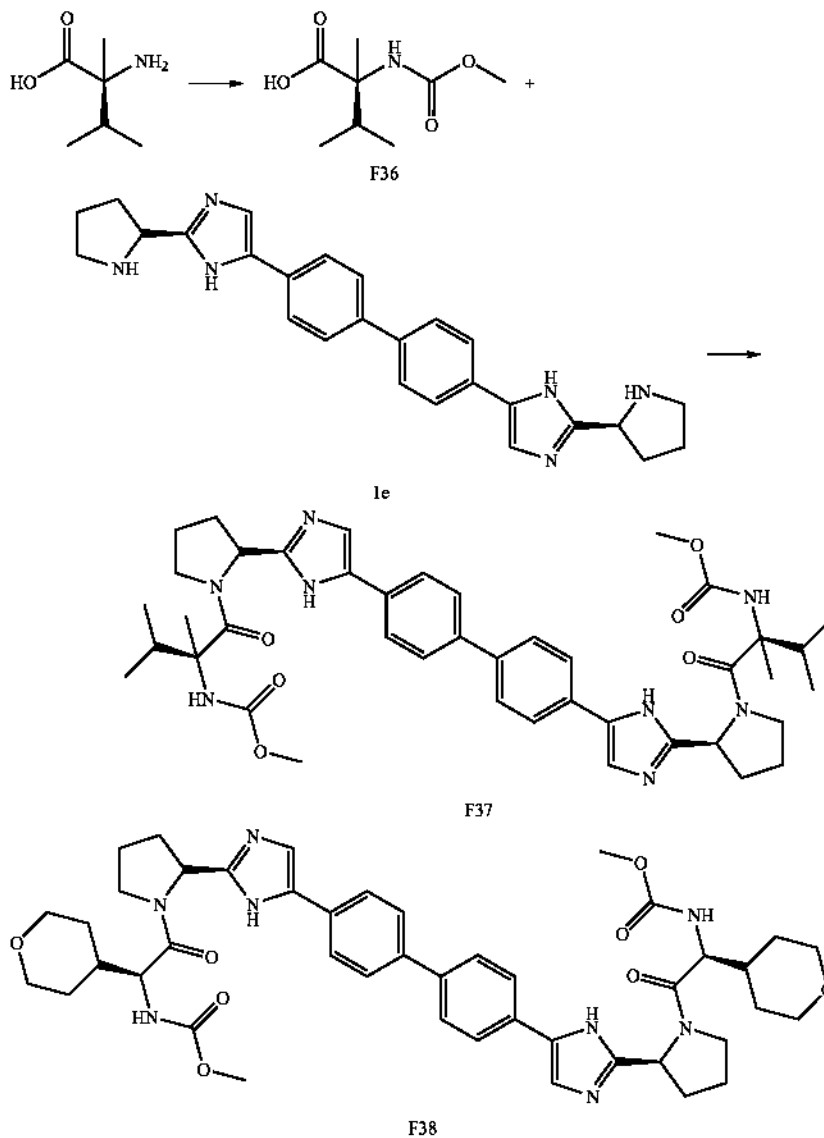
Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F27	(2S)-1-((2S)-2-(4-(2-((2S)-1-((2S)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol	RT = 1.03 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C ₃₂ H ₃₆ N ₆ O ₄ 568.28; found: 569.76 (M + H) ⁺ .
F28	tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)methylcarbamate	RT = 1.847 minutes (condition 3, 95%); LRMS: Anal. Calcd. for C ₅₀ H ₇₀ N ₈ O ₆ 878.54; found: 879.53 (M + H) ⁺ .
F29	tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylbutyl)methylcarbamate	RT = 2.202 minutes (condition 8, 98%); LRMS: Anal. Calcd. for C ₅₀ H ₇₀ N ₈ O ₆ 878.54; found: 879.57 (M + H) ⁺ .
F30	tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate	RT = 1.743 minutes (condition 8, 96%); LRMS: Anal. Calcd. for C ₄₈ H ₆₆ N ₈ O ₆ 850.51; found: 851.52 (M + H) ⁺ .
F31	tert-butyl ((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tert-butoxycarbonyl)-N-methyl-L-alloisoleucyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylbutyl)methylcarbamate	RT = 1.82 minutes (condition 8, 98%); LRMS: Anal. Calcd. for C ₅₀ H ₇₀ N ₈ O ₆ 878.54; found: 879.54 (M + H) ⁺ .
F32	(2S)-N,4-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-4-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine	RT = 3.715 minutes (condition 9, 98%); LRMS: Anal. Calcd. for C ₄₀ H ₅₄ N ₈ O ₂ 678.44; found: 679.46 (M + H) ⁺ .
F33	(2S)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine	RT = 3.058 minutes (condition 9, 99%); LRMS: Anal. Calcd. for C ₃₆ H ₄₆ N ₈ O ₂ 678.44; found: 679.61 (M + H) ⁺ .
F34	(2S)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(methylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine	RT = 3.206 minutes (condition 9, 99%); LRMS: Anal. Calcd. for C ₃₈ H ₅₀ N ₈ O ₂ 650.41; found: 651.41 (M + H) ⁺ .

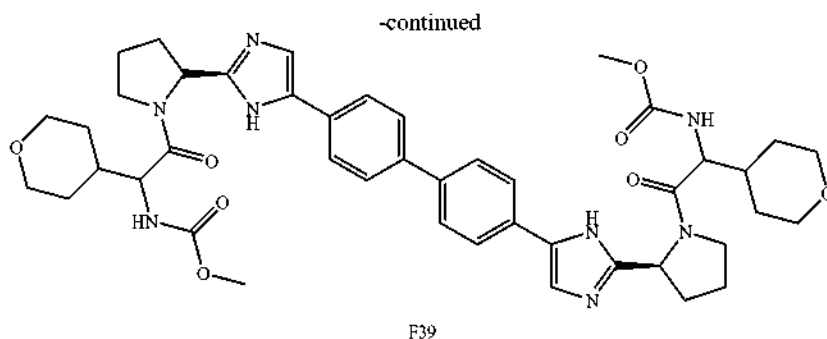
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Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F35	4-biphenyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-butanamine (2S,3R)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S,3R)-3-methyl-2-(methylanino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine	RT = 3.43 minutes (condition 9, 98%); LRMS: Anal. Calcd. for C ₄₀ H ₅₄ N ₈ O ₂ 678.44; found: 679.44 (M + H) ⁺ .

[0988] Compound F27 to F31 was prepared in analogous fashion to the procedure used to synthesize example 1.

[0989] Compound F32 to F35 was prepared in analogous fashion to the procedure used to synthesize 1e.





[0990] Compound F36 was prepared in analogous fashion to the procedure used to synthesize Cap-52.

[0991] Compound F37, F38, and F39 was prepared in analogous fashion to the procedure used to synthesize example 1 from Compound F36 and LS16 respectively.

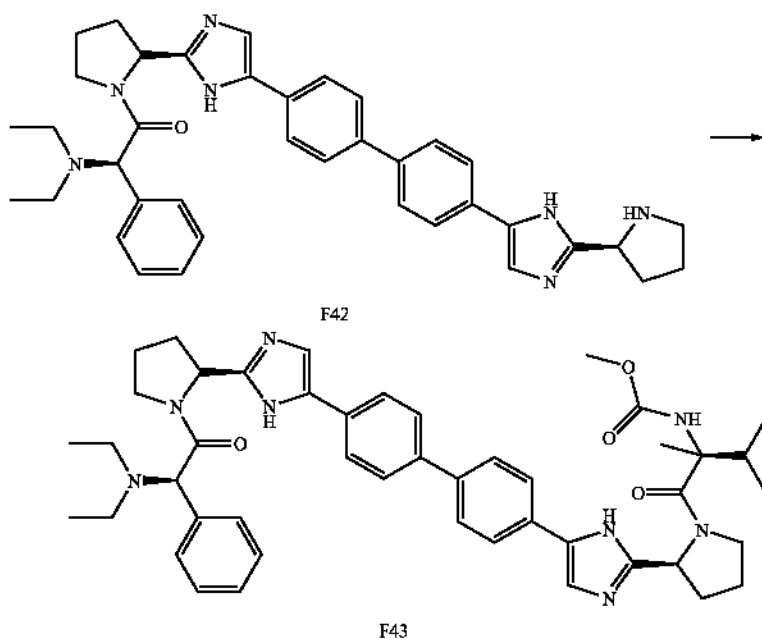
Entry	Compound	Retention time (LC-Condition); homogeneity index MS data
F36		RT = 1.55 minutes (condition 10); LRMS: Anal. Calcd. for C ₁₀ H ₁₃ NO ₂ 189.1; found: 190.13 (M + H) ⁺ . ¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 0.71-1.00 (m, 6H) 1.16-1.41 (m, 3H) 1.75-2.09 (m, 1H) 3.39-3.64 (m, 3H) 7.13 (s, 1H) 12.27 (s, 1H)
F37	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,2-dimethylpropyl)carbamate	RT = 2.572 minutes (condition 4, 98%); LRMS: Anal. Calcd. for C ₄₂ H ₅₄ N ₈ O ₆ 766.42; found: 767.48 (M + H) ⁺ .
F38	methyl ((1S)-2-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate	RT = 2.128 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C ₄₄ H ₅₄ N ₈ O ₈ 822.41; found: 823.45 (M + H) ⁺ .
F39	methyl (2-(((2S)-2-(4-(4'-(2-((2S)-1-(((methoxycarbonyl)amino)(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate	RT = 2.162 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C ₄₄ H ₅₄ N ₈ O ₈ 822.42; found: 823.49 (M + H) ⁺ .

Entry	Compound Name	Retention time (LC-Condition): homogeneity index MS data
	phenylacetyl)-2-pyrrolidinyl)- 1H-imidazol-5-yl)-4- biphenyl)-1H-imidazol- 2-yl)-1-pyrrolidinyl)-1-methyl- 2-oxoethyl)carbamate	Calcd. for C41H46N8O4 714.36; found: 715.84 (M + H) ⁺ .

US 2009/0068140 A1

Mar. 12, 2009

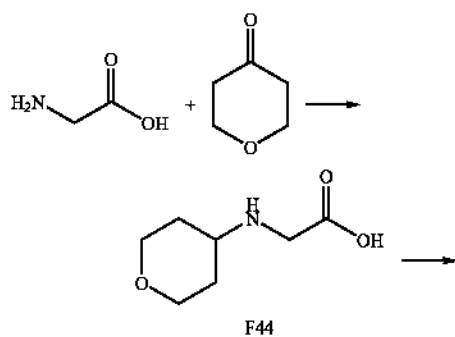
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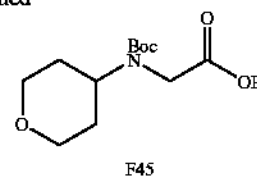
[0994] Compound F42 was prepared in analogous fashion to the procedure used to synthesize example 28f employing Cap-2 in place of Cap-4.

[0995] Compound F43 was prepared in analogous fashion to the procedure used to synthesize 2 from Compound F42.

Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F42		RT = 2.0 minutes (condition 10, 95%); LRMS: Anal. Calcd. for C ₃₈ H ₄₃ N ₇ O 613.35; found: 614.40 (M + H) ⁺ .
F43	methyl ((1S)-1-(((2S)-2-(5-(4'-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,2-dimethylpropyl)carbamate	RT = 2.308 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C ₅₀ H ₇₀ N ₈ O ₆ 784.44; found: 785.49 (M + H) ⁺ .



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[0996] Compound F44 was prepared following below paper with following modification: glycine was used in place of leucine.

[0997] A simple method for preparation of N-mono- and N,N-di-alkylated α-amino acids

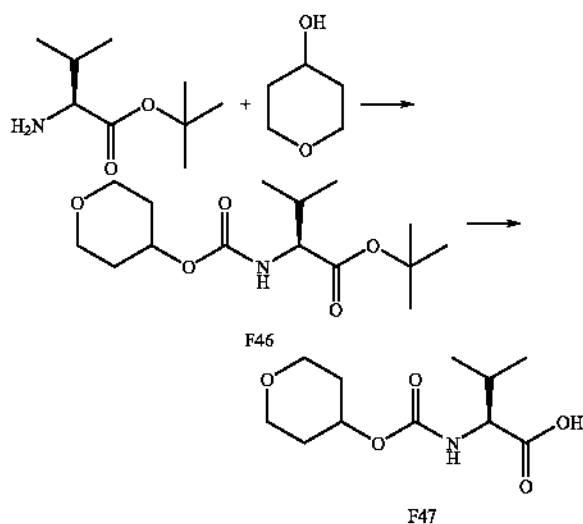
[0998] Yuntao Song et al., *Tetrahedron Lett.* 41, October 2000, Pages 8225-8230.

[0999] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 1.37-1.62 (m, 2H) 1.86 (dd, $J=12.36$, 1.98 Hz, 2H) 3.01-3.12 (m, 1H) 3.15 (s, 2H) 3.25 (t, $J=11.75$ Hz, 2H) 3.86 (dd, $J=11.44$, 4.12 Hz, 2H) 7.67-8.48 (m, 1H).

Compound F45

[1000] 2-(tetrahydro-2H-pyran-4-ylamino)acetic acid (0.2 g, 1.256 mmol) F44 was dissolved in DMF (22.5 mL) and Et_3N (2.5 mL, 17.94 mmol). After 5 minutes BOC_2O (0.583 mL, 2.51 mmol) was added and the reaction solution was heated to 60°C . for 1 h. The reaction was concentrated by reduced pressure providing a light yellow oil to which was added 20 mL HCl H_2O which was adjusted to pH 3 at 0°C . and stirred for 10 minutes. The reaction mixture was extracted by ethyl acetate 3×20 mL, dried (MgSO_4), filtered, and concentrated to dryness. Ether was added and the mixture was sonicated and filtered providing a white solid F45 2-(tert-butoxycarbonyl(tetrahydro-2H-pyran-4-yl)amino)acetic acid (0.14 g, 0.540 mmol, 43.0% yield).

[1001] ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 1.27-1.44 (m, 9H) 1.43-1.69 (m, 4H) 3.19-3.39 (m, 2H) 3.74 (s, 2H) 3.79-3.92 (m, 2H) 3.97-4.16 (m, 1H) 12.46 (s, 1H).



[1002] Compound F46 was prepared following the below referenced procedure with following modification: (S)-tert-butyl 2-amino-3-methylbutanoate was used in place of (S)-methyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-methylbutanoate.

[1003] Hans-Joachim Knolker, et al. *Synlett* 1997; 925-928

[1004] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 0.77-0.97 (m, 6H) 1.32-1.45 (m, 9H) 1.45-1.56 (m, 2H) 1.74-1.91 (m, 2H) 1.94-2.11 (m, 1H) 3.36-3.53 (m, 2H) 3.76 (dd, $J=8.09$, 6.26 Hz, 1H) 3.77-3.90 (m, 2H) 4.69 (dd, $J=9.00$, 4.73 Hz, 1H) 7.35 (d, $J=8.24$ Hz, 1H)

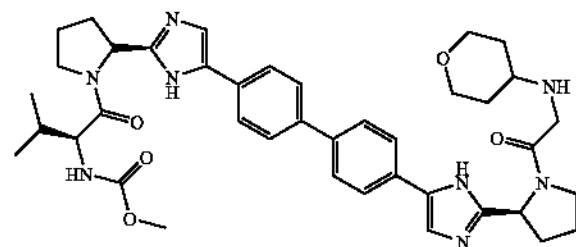
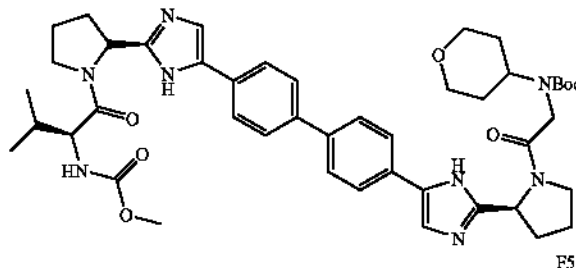
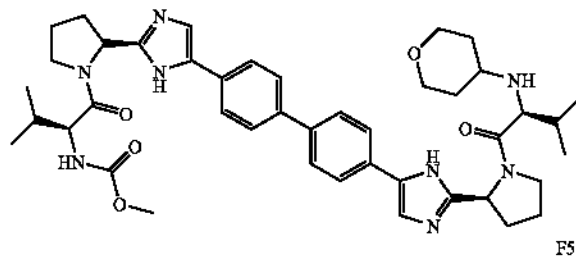
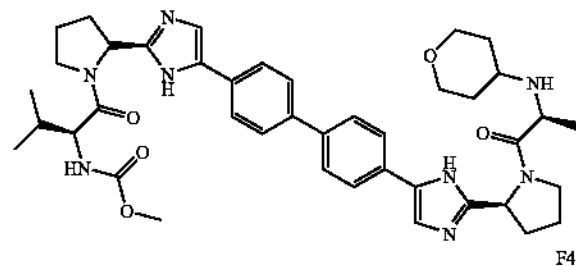
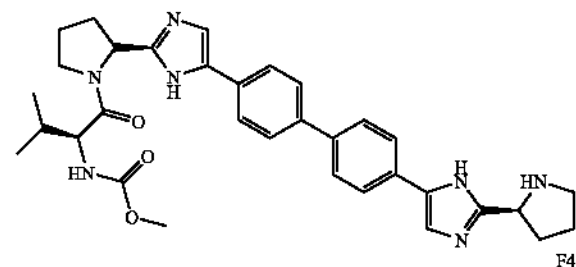
Compound F47

[1005] To a Compound 46 (S)-tert-butyl 3-methyl-2-((tetrahydro-2H-pyran-4-yloxy)carbonylamino)butanoate (0.21 g, 0.697 mmol) was added HCl in dioxane (15 mL, 60.0 mmol) and the mixture was stirred at room temperature under nitrogen for three hours. The reaction was done and concen-

trated under reduced pressure to provide F47(S)-3-methyl-2-((tetrahydro-2H-pyran-4-yloxy)carbonylamino)butanoic acid (0.1694 g, 0.691 mmol, 100% yield) as a clear wax.

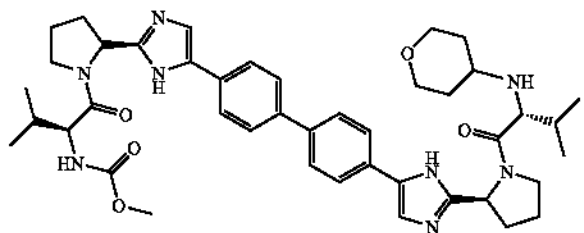
[1006] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 0.88 (t, $J=6.71$ Hz, 6H) 1.41-1.60 (m, 2H) 1.85 (d, $J=12.21$ Hz, 2H) 1.97-2.08 (m, 1H) 3.41 (t, $J=10.68$ Hz, 1H) 3.45-3.52 (m, 1H) 3.64-3.74 (m, 1H) 3.77-3.89 (m, 2H) 4.63-4.72 (m, 1H) 7.32 (d, $J=8.55$ Hz, 1H) 12.52 (s, 1H)

LS18

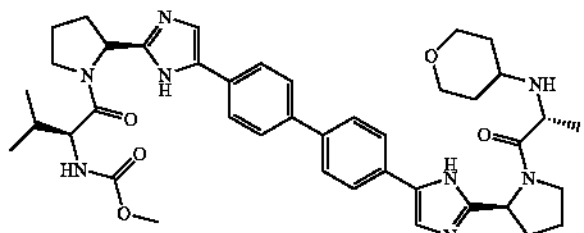


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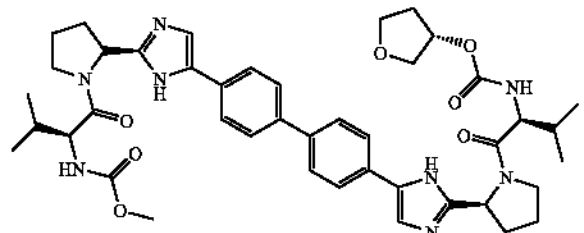
F52



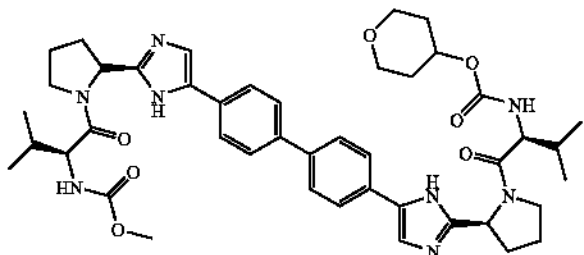
F53



F54

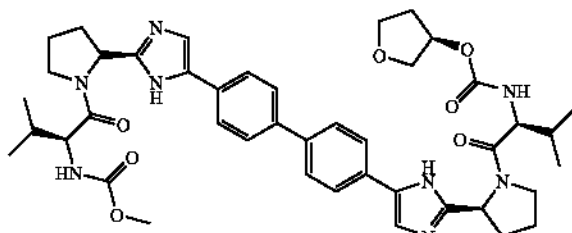


F55

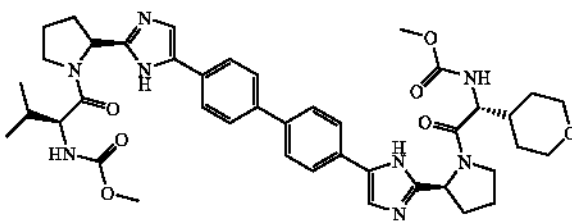


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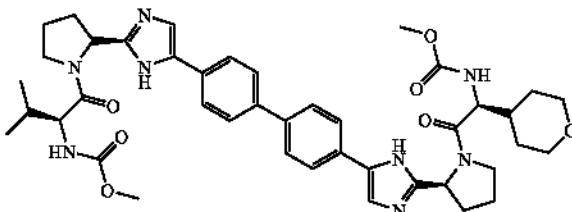
F56



F57



F58



[1007] Compound F48 to F58 except F51 was prepared in analogous fashion to the procedure used to synthesize example 1 from LS18.

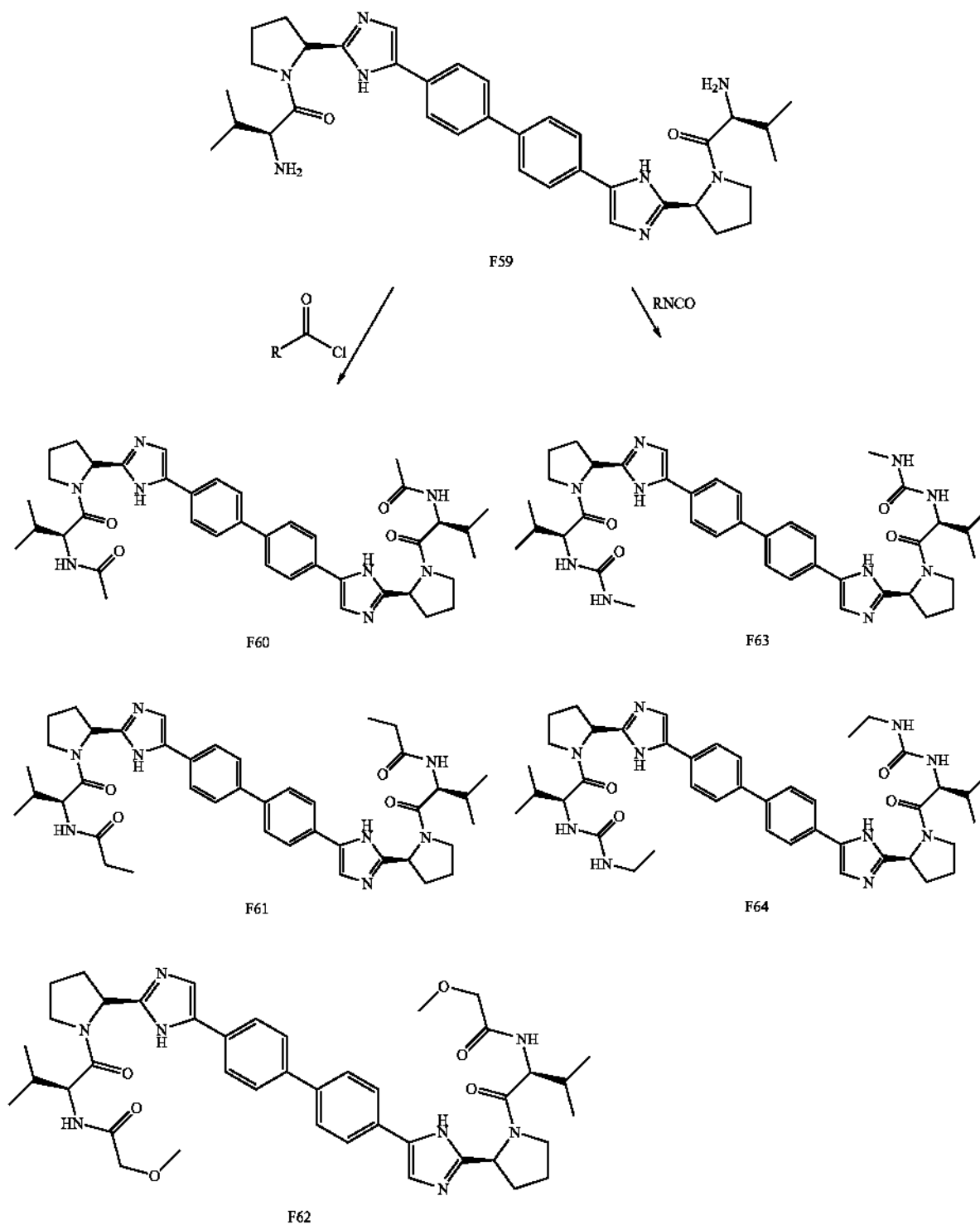
[1008] Compound F51 was prepared in analogous fashion to the procedure used to synthesize 1e from F50.

Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F48	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.103 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C41H52N8O5 736.41; found: 737.07 (M + H) ⁺ .
F49	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.117 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C43H56N8O5 764.44; found: 765.75 (M + H) ⁺ .
F50		RT = 2.547 minutes (condition 7, 98%); LRMS: Anal. Calcd.

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Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
		for C ₄₅ H ₅₈ N ₈ O ₇ 822.44; found: 823.17 (M + H) ⁺ .
F51	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)glycyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.138 minutes (condition 7, 96%); LRMS: Anal. Calcd. for C ₄₀ H ₅₀ N ₈ O ₅ 722.39; found: 723.63 (M + H) ⁺ .
F52	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.083 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C ₄₃ H ₅₆ N ₈ O ₅ 764.44; found: 765.78 (M + H) ⁺ .
F53	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 0.963 minutes (condition 11, 95%); LRMS: Anal. Calcd. for C ₄₃ H ₅₄ N ₈ O ₇ 736.41; found: 737.54 (M + H) ⁺ .
F54	(3S)-tetrahydro-3-furanyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.378 minutes (condition 7, 95%); LRMS: Anal. Calcd. for C ₄₃ H ₅₄ N ₈ O ₇ 794.41; found: 795.94 (M + H) ⁺ .
F55	tetrahydro-2H-pyran-4-yl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.447 minutes (condition 7, 99%); LRMS: Anal. Calcd. for C ₄₄ H ₅₆ N ₈ O ₇ 808.43; found: 809.42 (M + H) ⁺ .
F56	(3R)-tetrahydro-3-furanyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.398 minutes (condition 7, 96%); LRMS: Anal. Calcd. for C ₄₃ H ₅₄ N ₈ O ₇ 794.41; found: 795.36 (M + H) ⁺ .
F57	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(2R)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.272 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C ₄₂ H ₅₂ N ₈ O ₇ 780.40; found: 781.34 (M + H) ⁺ .
F58	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.225 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C ₄₂ H ₅₂ N ₈ O ₇ 780.40; found: 781.27 (M + H) ⁺ .

250



Compound F59

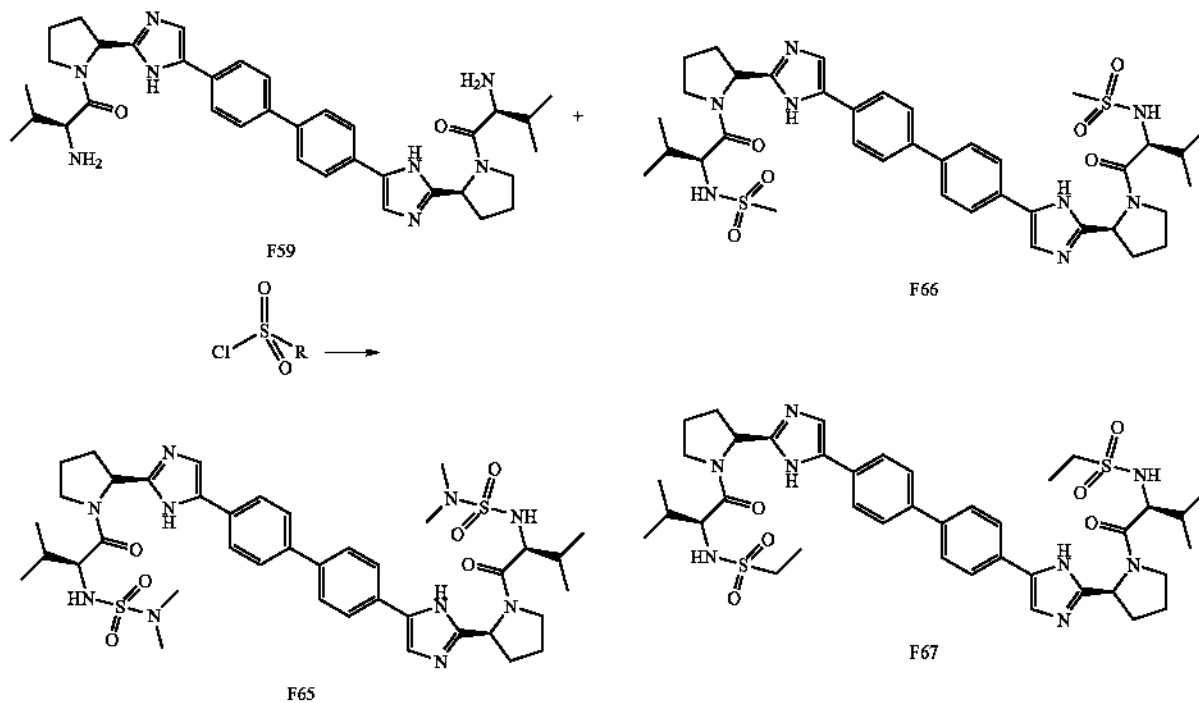
[1009] Compound F59 was prepared in analogous fashion to the procedure used to synthesize 26a with following modification: Boc-L-val-OH was used in place of Boc-D-val-OH.

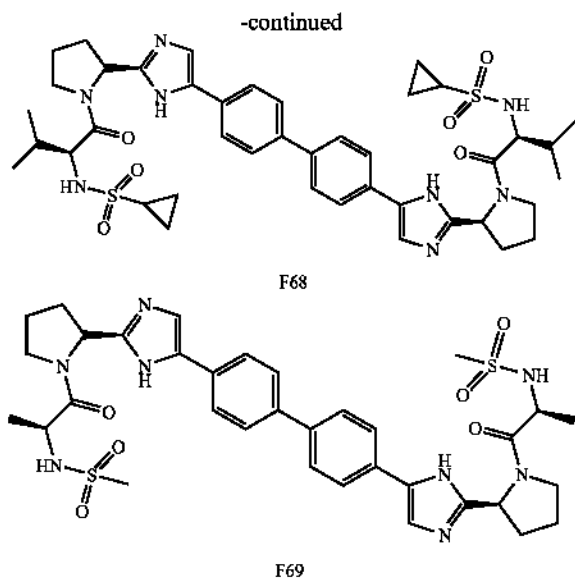
[1010] Compound F60 to F62 were prepared in analogous fashion to the procedure used to synthesize example 29 from F59.

[1011] Compound F63 and F64 were prepared in analogous fashion to the procedure used to synthesize Cap45.

Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F59		RT = 1.743 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C ₃₆ H ₄₆ N ₈ O ₂ 622.37; found: 624.07 (M + H) ⁺ .
F60	N-((1S)-1-(((2S)-2-(4-(4'-(2-(2S)-1-((2S)-2-acetamido-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide	RT = 2.047 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C ₄₀ H ₅₀ N ₈ O ₄ 706.44; found: 707.77 (M + H) ⁺ .
F61	N-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-(2S)-1-((2S)-3-methyl-2-(propionylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)propanamide	RT = 2.215 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C ₄₂ H ₅₄ N ₈ O ₄ 734.43; found: 735.87 (M + H) ⁺ .
F62	2-methoxy-N-((1S)-1-(((2S)-2-(4-(4'-(2-(2S)-1-((2S)-2-(methoxyacetyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide	RT = 2.232 minutes (condition 10, 99%); LRMS: Anal. Calcd. for C ₄₂ H ₅₄ N ₈ O ₆ 766.93; found: 768.05 (M + H) ⁺ .
F63	1-methyl-3-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-(2S)-1-((N-(methylcarbamoyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)urea	RT = 2.082 minutes (condition 10, 95%); LRMS: Anal. Calcd. for C ₄₀ H ₅₂ N ₁₀ O ₄ 736.42; found: 737.86 (M + H) ⁺ .
F64	1-ethyl-3-((1S)-1-(((2S)-2-(4-(4'-(2-(2S)-1-((2S)-2-(ethylcarbamoyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)urea	RT = 1.617 minutes (condition 12, 93%); LRMS: Anal. Calcd. for C ₄₂ H ₅₆ N ₁₀ O ₄ 764.45; found: 765.57 (M + H) ⁺ .

-continued





Compound F65

[1012] To a solution of F59 (0.06 g, 0.074 mmol in DMF (1 mL) was added dimethylsulfonyl chloride (0.016 mL, 0.148 mmol) and Hunig's Base (0.078 mL, 0.445 mmol) then stirred it at room temperature for 3 h. Solvent was removed by reduced pressure to get light brown oil which was purified by PreHPLC providing F65 N-((S)-1-((S)-2-(5-(4'-((S)-1-((S)-2-(N,N-dimethylsulfonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)propane-2-sulfonamide (19.0 mg, 0.018 mmol, 24.08% yield)

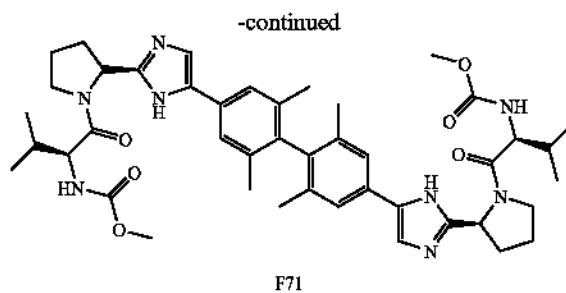
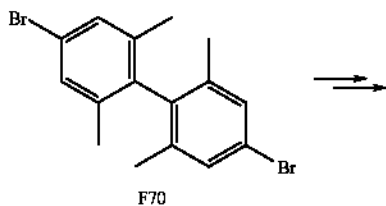
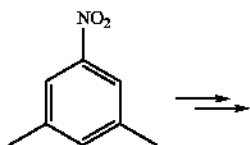
[1013] ^1H NMR (500 MHz, DMSO- d_6) δ ppm 0.65-1.03 (m, 12H) 1.87-2.08 (m, 4H) 2.06-2.27 (m, 4H) 2.37-2.46 (m, 2H) 2.56-2.69 (m, 12H) 3.66-3.92 (m, 6H) 5.14 (t, $J=7.63$ Hz, 2H) 7.49 (d, $J=9.16$ Hz, 2H) 7.89 (d, $J=8.24$ Hz, 4H) 7.96 (s, 4H) 8.14 (s, 2H) 14.72 (s, 2H)

[1014] RT=2.047 minutes (condition 10, 98%); LRMS: Anal. Calcd. for $\text{C}_{40}\text{H}_{50}\text{N}_8\text{O}_4$ 706.38; found: 707.77 (M+H) $^+$.

[1015] 1b Fret (EC50, μM)=0.21

[1016] Compound F66 to F69 was prepared in analogous fashion to the procedure used to synthesize F65 from Compound F59.

Entry	Compound Name	Retention time (LC-Condition); homogeneity index MS data
F66	N-((1S)-2-methyl-1-(((2S)-2-(4-(4'-((2S)-1-((2S)-3-methyl-2-((methylsulfonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)methanesulfonamide	RT = 2.02 minutes (condition 10, 98%); LRMS: Anal. Calcd. for $\text{C}_{38}\text{H}_{50}\text{N}_8\text{O}_6\text{S}_2$ 778.38; found: 779.60 (M + H) $^+$.
F67	N-((1S)-1-(((2S)-2-(4-(4'-((2S)-1-((2S)-2-((ethylsulfonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)ethanesulfonamide	RT = 2.172 minutes (condition 10 98%); LRMS: Anal. Calcd. for $\text{C}_{40}\text{H}_{54}\text{N}_8\text{O}_6\text{S}_2$ 807.04; found: 808.42 (M + H) $^+$.
F68	N-((1S)-1-(((2S)-2-(4-(4'-((2S)-1-((2S)-2-((cyclopropylsulfonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)cyclopropanesulfonamide	RT = 2.217 minutes (condition 10, 93%); LRMS: Anal. Calcd. for $\text{C}_{42}\text{H}_{54}\text{N}_8\text{O}_6\text{S}_2$ 831.06; found: 832.49 (M + H) $^+$.
F69	N-((1S)-1-methyl-2-(((2S)-2-(5-(4'-((2S)-1-((N-(methylsulfonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)methanesulfonamide	RT = 1.983 minutes (condition 10, 95%); LRMS: Anal. Calcd. for $\text{C}_{34}\text{H}_{42}\text{N}_8\text{O}_6\text{S}_2$ 722.27; found: 723.68 (M + H) $^+$.



[1017] Compound F70 was prepared following the procedure described in Anna Helms et al., *J. Am. Chem. Soc.* 1992 114(15) pp 6227-6238.

[1018] Compound F71 was prepared in analogous fashion to the procedure used to synthesize Example 1.

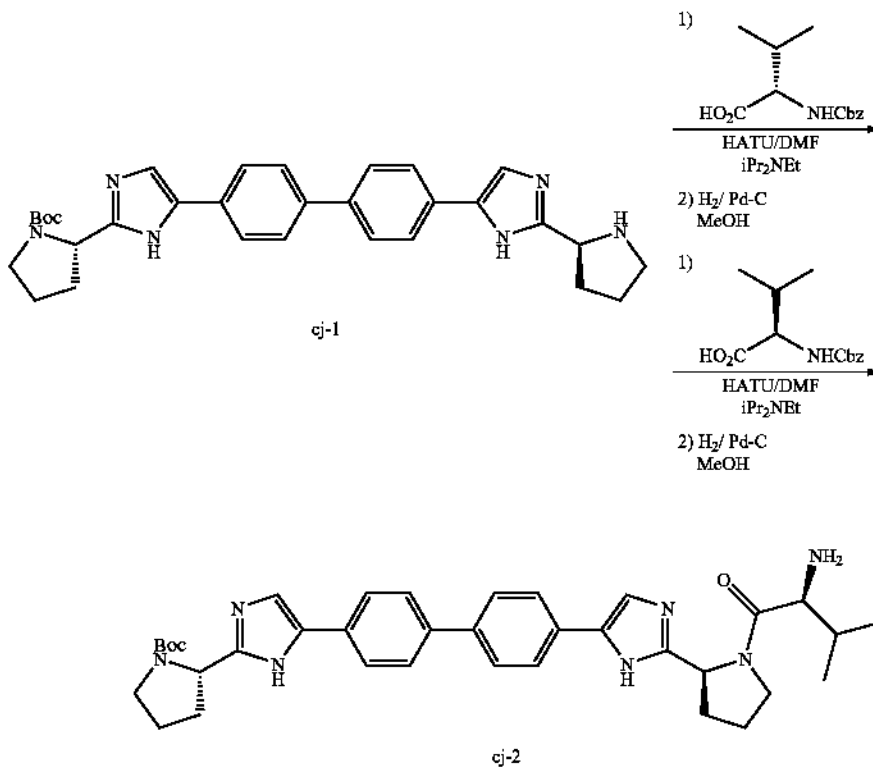
[1019] ^1H NMR (500 MHz, DMSO- d_6) δ ppm 0.69-0.95 (m, 12H) 1.92 (s, 12H) 1.97-2.27 (m, 8H) 2.40 (s, 2H) 3.55 (s, 6H) 3.73-3.97 (m, 4H) 4.12 (t, $J=7.78$ Hz, 2H) 5.14 (t, $J=7.02$ Hz, 2H) 7.34 (d, $J=8.24$ Hz, 2H) 7.49-7.70 (m, 4H) 8.04 (s, 2H) 14.59 (s, 2H) RT=2.523 minutes (condition 7, 96%); LRMS: Anal. Calcd. for $\text{C}_{44}\text{H}_{58}\text{N}_8\text{O}_6$ 794.45; found: 795.48 (M+H) $^+$.

Section cj

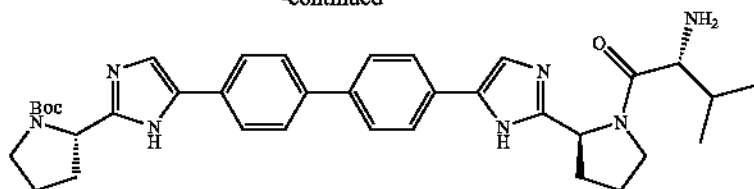
Synthesis of Carbamate Replacements

Example cj-2 and cj-3

[1020]



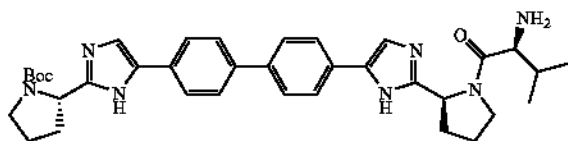
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cj-3

Preparation of (S)-tert-Butyl 2-(5-(4'-(2-((S)-1-((S)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-2)

[1021]



[1022] To a solution of (S)-tert-butyl 2-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-1) (1.00 g, 1.91 mmol), iPr_2NEt (1.60 mL, 9.19 mmol) and N-Z-valine (0.62 g, 2.47 mmol) in DMF (10 mL) was added HATU (0.92 g, 2.42 mmol). The solution was allowed to stir at rt for 1 h and then it was poured into ice water (ca. 250 mL) and allowed to stand for 20 min. The mixture was filtered and the solid washed with water and then dried in vacuo overnight to afford a colorless solid (1.78 g) which was used as such in the next step. LCMS: Anal. Calcd. for $C_{44}H_{51}N_7O_5$: 757; found: 758 (M+H)⁺. A mixture of this material (1.70 g) and 10% Pd—C (0.37 g) in MeOH (100 mL) was hydrogenated (balloon pressure) for 12 h. The mixture was then filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (Biotage system/0-10% MeOH—CH₂Cl₂) to afford the title compound as a light yellow foam (0.90 g, 76%).

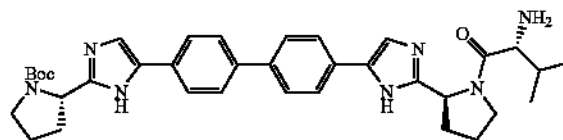
[1023] ¹HNMR (400 MHz, DMSO-d₆) δ 12.18 (s, 0.35H), 11.73 (s, 0.65H), 11.89 (s, 0.65H), 11.82 (s, 0.35H), 7.77-7.81 (m, 3H), 7.57-7.71 (m, 5H), 7.50-7.52 (m, 2H), 5.17 (dd, J=3.6, 6.5 Hz, 0.3H), 5.08 (dd, J=3.6, 6.5 Hz, 0.7H), 4.84 (m, 0.3H), 4.76 (m, 0.7H), 3.67-3.69 (m, 1H), 3.50-3.62 (m, 1H),

3.34-3.47 (m, 2H), 2.22-2.28 (m, 2H), 2.10-2.17 (m, 2H), 1.74-2.05 (m, 6H), 1.40 (s, 4H), 1.15 (s, 5H), 0.85-0.91 (m, 4H), 0.79 (d, J=6.5 Hz, 2H).

[1024] LCMS: Anal. Calcd. for $C_{36}H_{45}N_7O_3$: 623; found: 624 (M+H)⁺.

Preparation of (S)-tert-Butyl 2-(5-(4'-(2-((S)-1-((R)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-3)

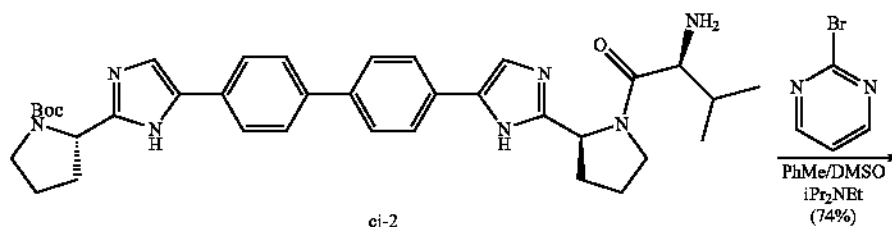
[1025]



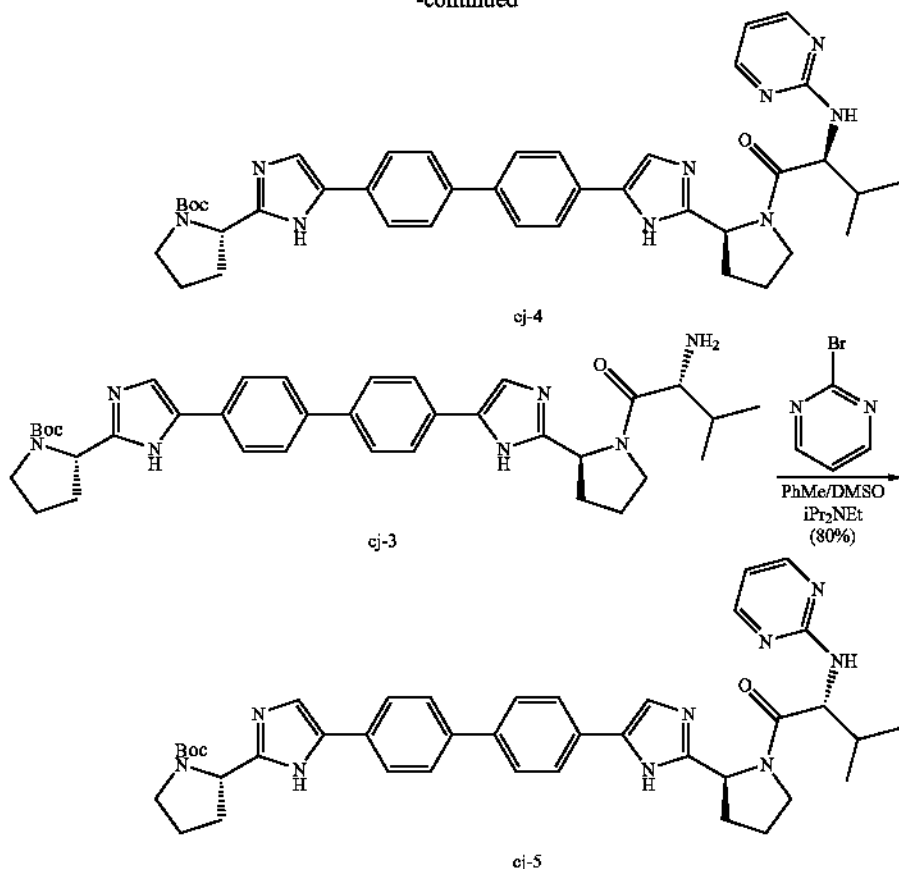
[1026] (S)-tert-Butyl 2-(5-(4'-(2-((S)-1-((R)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-3) was prepared using the same method used to prepare cj-2 to give a colorless foam (1.15 g, 76%). ¹HNMR (400 MHz, DMSO-d₆) δ 12.17 (s, 0.35H), 12.04 (s, 0.65H), 11.89 (s, 0.65H), 11.81 (s, 0.35H), 7.78-7.83 (m, 3H), 7.60-7.71 (m, 5H), 7.43-7.52 (m, 2H), 5.22-5.25 (m, 0.4H), 5.05-5.07 (m, 0.6H), 4.83-4.86 (m, 0.5H), 4.72-4.78 (m, 0.5H), 3.78-3.84 (m, 1H), 3.49-3.64 (m, 2H), 3.35-3.43 (m, 2H), 2.19-2.32 (m, 1H), 2.04-2.17 (m, 3H), 1.95-2.04 (m, 2H), 1.76-1.90 (m, 3H), 1.40 (s, 4H), 1.15 (s, 5H), 0.85-0.91 (m, 4H), 0.67 (d, J=6.5 Hz, 1H), 0.35 (d, J=6.5 Hz, 1H). LCMS: Anal. Calcd. for $C_{36}H_{45}N_7O_3$: 623; found: 624 (M+H)⁺.

Example cj-4 and cj-5

[1027]

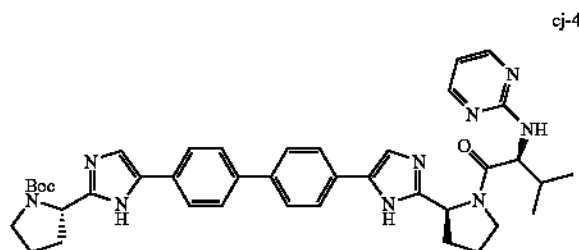


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Preparation of (S)-tert-Butyl 2-(5-(4'-(2-((S)-1-((S)-3-methyl-2-(pyrimidin-2-ylamino)butanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-4)

[1028]



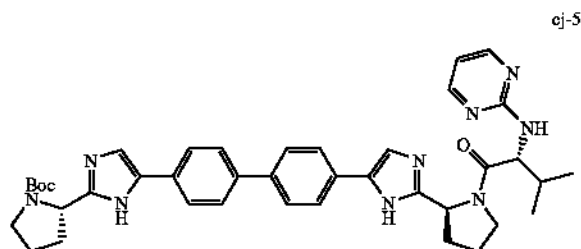
[1030] ¹HNMR (400 MHz, DMSO-d₆) δ 14.56 (br s, 2H), 8.28 (d, J=5.0 Hz, 1H), 8.12-8.20 (m, 2H), 7.94-7.97 (m, 3H), 7.83-7.91 (m, 5H), 7.06 (d, J=8.1 Hz, 1H), 6.62 (app t, J=5.0 Hz, 1H), 4.99-5.10 (m, 2H), 4.50 (app t, J=7.7 Hz, 1H), 4.07-4.12 (m, 2H), 3.83-3.87 (m, 1H), 3.56-3.62 (m, 1H), 3.40-3.47 (m, 2H), 2.36-2.41 (m, 1H), 1.94-2.22 (m, 6H), 1.40 (s, 4H), 1.17 (s, 5H), 0.88 (app t, J=6.5 Hz, 6H).

[1031] LCMS: Anal. Calcd. for C₄₀H₄₇N₉O₃: 701; found: 702 (M+H)⁺.

Preparation of (S)-tert-Butyl 2-(5-(4'-(2-((S)-1-((R)-3-methyl-2-(pyrimidin-2-ylamino)butanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-5)

[1032]

[1029] A mixture of (S)-tert-butyl 2-(5-(4'-(2-((S)-1-((S)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-2) (0.45 g, 0.72 mmol), 2-bromopyrimidine (0.37 g, 2.34 mmol) and iPr₂NEt (0.20 mL, 1.18 mmol) in toluene-DMSO (4:1, 5 mL) was heated at 90° C. overnight. The volatiles were removed in vacuo and the residue was purified by preparative HPLC (YMC Pack C-1 8, 30×100 mm/MeCN—H₂O-TFA). The title compound (0.56 g, 74%), as its TFA salt, was obtained as a yellow-orange glass.



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[1033] The TFA salt of the title compound was prepared following the same method used to prepare cj-4 to give a light yellow solid (0.375 g, 59%).

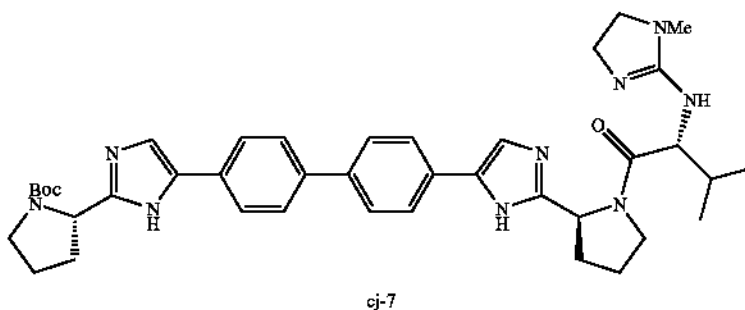
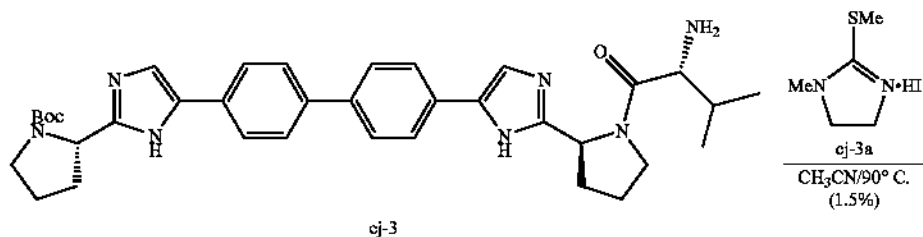
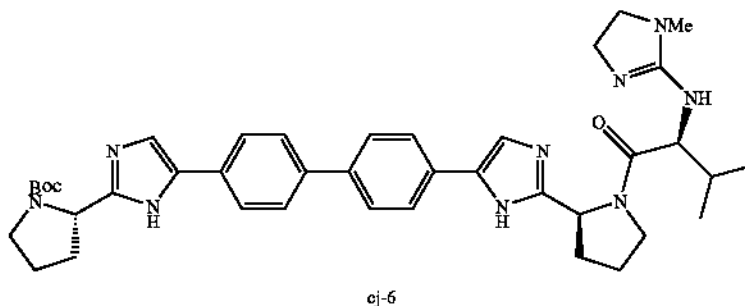
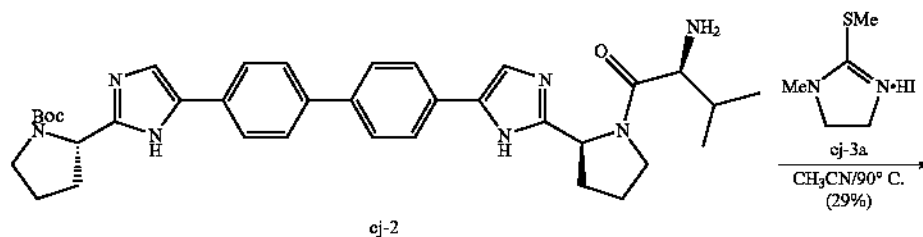
[1034] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.67 (br s, 2H), 8.30 (d, $J=4.3$ Hz, 1H), 8.04-8.19 (m, 2H), 7.84-7.96 (m, 8H), 6.88 (d, $J=8.6$ Hz, 1H), 6.61 (app t, $J=4.5$ Hz, 1H), 5.17 (dd, $J=4.4, 8.0$ Hz, 1H), 5.00-5.07 (m, 1H), 4.67 (dd, $J=7.3, 8.1$ Hz, 1H), 3.91-3.96 (m, 1H), 3.70-3.75 (m, 1H), 3.56-3.62 (m, 1H), 3.42-3.45 (m, 1H), 2.39-2.43 (m, 2H), 2.04-2.16 (m,

5H), 1.94-1.97 (m, 2H), 1.40 (s, 4H), 1.17 (s, 5H), 0.95 (d, $J=6.6$ Hz, 2.5H), 0.91 (d, $J=6.6$ Hz, 2.5H), 0.86 (d, $J=6.6$ Hz, 0.5H), 0.81 (d, $J=6.6$ Hz, 0.5H).

[1035] LCMS: Anal. Calcd. for $\text{C}_{40}\text{H}_{47}\text{N}_9\text{O}_3$: 701; found: 702 ($\text{M}+\text{H}$) $^+$.

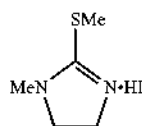
Example cj-6 and cj-7

[1036]



Preparation of
1-Methyl-2-(methylthio)-4,5-dihydro-1H-imidazole
hydroiodide

[1037]



cj-3a

[1038] The title compound was prepared according to: Kister, J.; Assef, G.; Dou, H. J.-M.; Metzger, J. *Tetrahedron* 1976, 32, 1395. Thus, a solution of N-methylethylenediamine (10.8 g, 146 mmol) in EtOH—H₂O (1:1, 90 mL) was preheated to 60° C. and CS₂ (9.0 mL, 150 mmol) was added dropwise. The resulting mixture was heated at 60° C. for 3 h and then conc. HCl (4.7 mL) was slowly added. The temperature was raised to 90° C. and stirring was continued for 6 h. After the cooled mixture had been stored at -20° C., it was filtered and the resulting solid dried in vacuo to afford 1-methylimidazolidine-2-thione (8.43 g, 50%) as a beige solid.

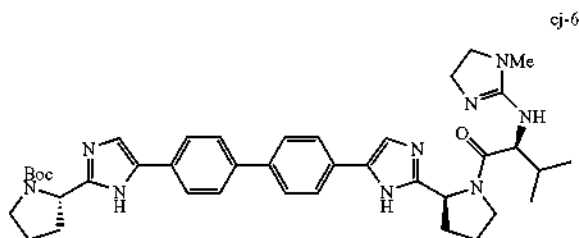
[1039] ¹HNMR (400 MHz, CDCl₃) δ 5.15 (s, br, 1H), 3.67-3.70 (m, 2H), 3.53-3.58 (m, 2H), 3.11 (s, 3H).

[1040] To a suspension of 1-methylimidazolidine-2-thione (5.17 g, 44.5 mmol) in acetone (50 mL) was added MeI (2.9 mL, 46.6 mmol). The solution was allowed to stir at room temperature for 4 h and the resulting solid was quickly filtered and then dried in vacuo to give 1-methyl-2-(methylthio)-4,5-dihydro-1H-imidazole hydroiodide (8.79 g, 77%) as beige solid.

[1041] ¹HNMR (400 MHz, CDCl₃) δ 9.83 (s, br, 1H), 3.99-4.12 (m, 4H), 3.10 (s, 3H), 2.99 (s, 3H).

Preparation of (S)-tert-Butyl 2-(5-(4'-(2-((S)-1-((S)-3-methyl-2-(1-methyl-4,5-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-6)

[1042]



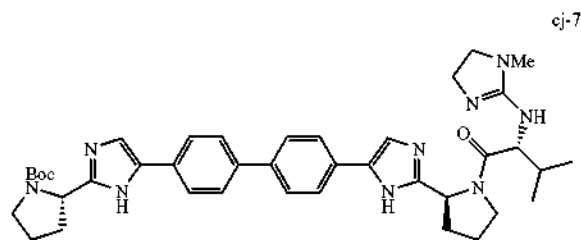
cj-6

[1043] A mixture of (S)-tert-butyl 2-(5-(4'-(2-((S)-1-((S)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)-pyrrolidine-1-carboxylate (cj-2) (0.280 g, 0.448 mmol) and 1-methyl-2-(methylthio)-4,5-dihydro-1H-imidazole hydroiodide (cj-3a) (0.121 g, 0.468 mmol) in CH₃CN (5 mL) was heated at 90° C. for 12 h. Another 0.030 g of 1-methyl-2-(methylthio)-4,5-dihydro-1H-imidazole hydroiodide (cj-3a) was added and heating continued for a further 12 h. The crude reaction mixture was directly purified by prep HPLC (Luna C—18/MeCN—H₂O—TFA) to give the TFA salt of the title compound (0.089 g) as a light yellow solid which was used as such in the subsequent steps.

[1044] LCMS: Anal. Calcd. for C₄₀H₅₁N₉O₃: 705; found: 706 (M+H)⁺.

Preparation of (S)-tert-Butyl 2-(5-(4'-(2-((S)-1-((R)-3-methyl-2-(1-methyl-4,5-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-7)

[1045]



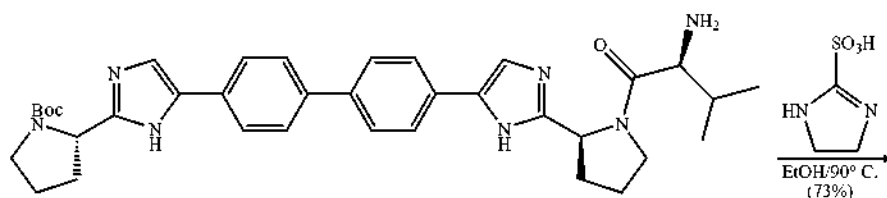
cj-7

[1046] The title compound was prepared from cj-3 according to the method described for the synthesis of cj-6, except that the reaction mixture was initially purified by prep HPLC (YMC-Pack 25x250 mm/MeCN—H₂O—NH₄OAc) and then repurified by prep HPLC (Luna Phenyl-hexyl/MeCN—H₂O—NH₄OAc). This gave the desired product (0.005 g) as a foam which was used as such in the subsequent steps.

[1047] LCMS: Anal. Calcd. for C₄₀H₅₁N₉O₃: 705; found: 706 (M+H)⁺.

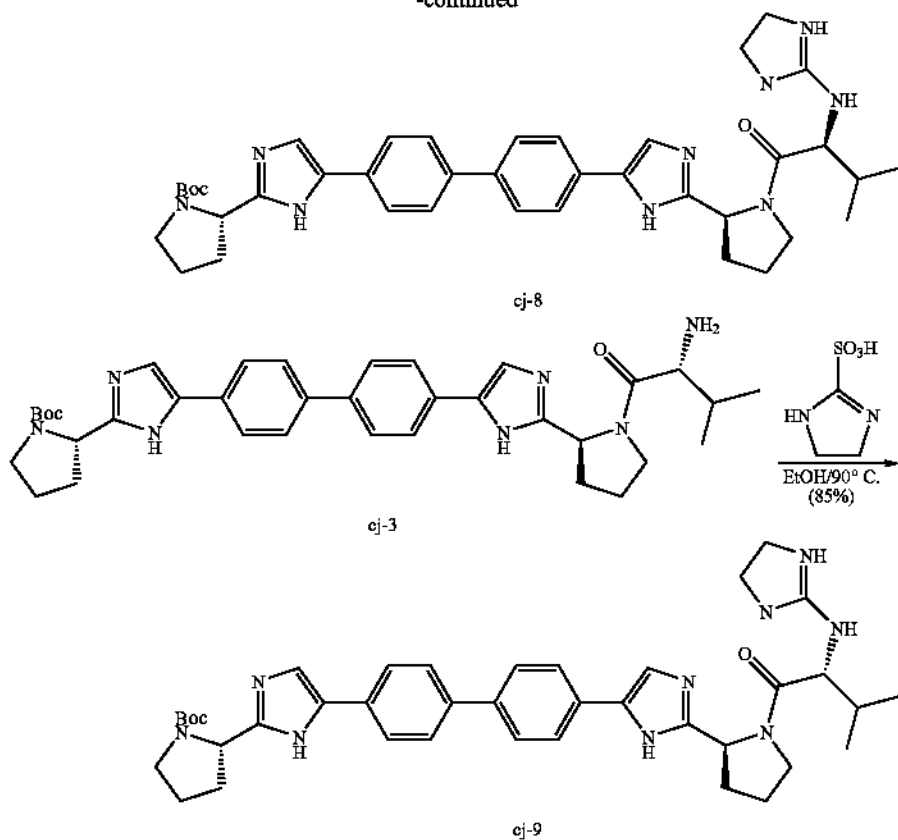
Example cj-8 and cj-9

[1048]



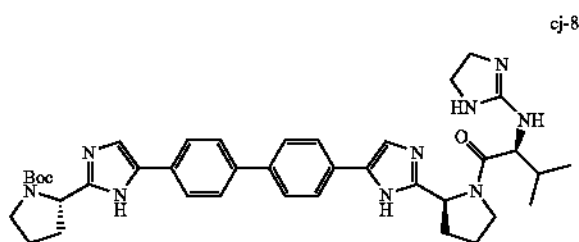
cj-2

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Preparation of (S)-tert-Butyl 2-(5-(4'-(2-((S)-1-((S)-3-methyl-2-(3,4-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-8)

[1049]



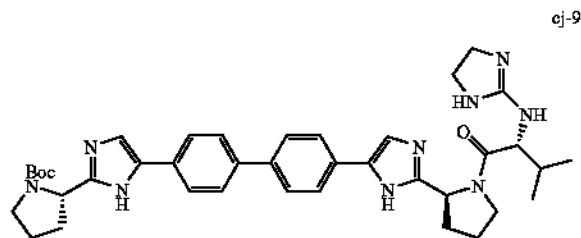
[1050] A mixture of (s)-tert-butyl 2-(5-(4'-(2-((S)-1-((s)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-2) (0.298 g, 0.480 mmol), 4,5-dihydro-1H-imidazole-2-sulfonic acid (AstaTech) (0.090 g, 0.60 mmol) and $i\text{Pr}_2\text{NEt}$ (0.083 mL, 0.48 mmol) in EtOH (4 mL) was heated at 100° C. for 12 h. The cooled mixture was evaporated to dryness and the residue was purified by prep HPLC (Luna 5u C18/MeCN—H₂O—TFA, $\times 2$) to afford the TFA salt of the title compound (0.390 g, 73%) as a light yellow solid.

[1051] ¹HNMR (400 MHz, DMSO- d_6) δ 14.66 (br s, 2H), 8.51 (br s, 1H), 8.20 (d, $J=10.1$ Hz, 2H), 8.10 (br s, 1H), 7.82-7.91 (m, 7H), 7.30 (br s, 1H), 5.12 (t, $J=7.1$ Hz, 1H), 4.97-5.05 (m, 2H), 4.37 (dd, $J=4.3, 10.1$ Hz, 2H), 3.82-3.86 (m, 2H), 3.73-3.77 (m, 2H), 3.59 (s, 4H), 3.39-3.48 (m, 2H), 2.15-2.25 (m, 2H), 1.93-2.07 (m, 5H), 1.40 (s, 4H), 1.17 (s, 5H), 0.93 (d, $J=6.6$ Hz, 3H), 0.69 (br s, 3H).

[1052] LCMS: Anal. Calcd. for C₃₉H₄₉N₉O₃: 691; found: 692 (M+H)⁺.

Preparation of (S)-tert-Butyl 2-(5-(4'-(2-((S)-1-((R)-3-methyl-2-(3,4-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-9)

[1053]



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[1054] The title compound was prepared from cj-3 according to the same method used to prepare cj-8 to afford the TFA salt (0.199 g, 57%) as a yellow glass.

[1055] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.58 (br s, 4H), 8.23 (d, $J=9.6$ Hz, 1H), 8.11 (s, 1H), 7.87-7.89 (m, 6H), 7.25 (br s, 1H), 5.17-5.20 (m, 1H), 4.96-5.04 (m, 1H), 4.37 (dd, $J=5.5, 9.6$ Hz, 1H), 3.91-3.95 (m, 2H), 3.37-3.46 (m, partially obscured by H_2O , 4H), 2.39-2.42 (m, partially obscured by solvent, 2H), 2.01-2.09 (m, 4H), 1.94-1.98 (m, 2H), 1.40 (s, 3H), 1.17 (s, 6H), 0.95 (d, $J=6.5$ Hz, 2.5H), 0.85 (d, $J=6.5$ Hz, 2.5H), 0.66 (d, $J=7.0$ Hz, 0.5H), 0.54 (d, $J=6.5$ Hz, 0.5H).

[1056] LCMS: Anal. Calcd. for $\text{C}_{39}\text{H}_{49}\text{N}_9\text{O}_3$: 691; found: 692 ($\text{M}+\text{H}$) $^+$.

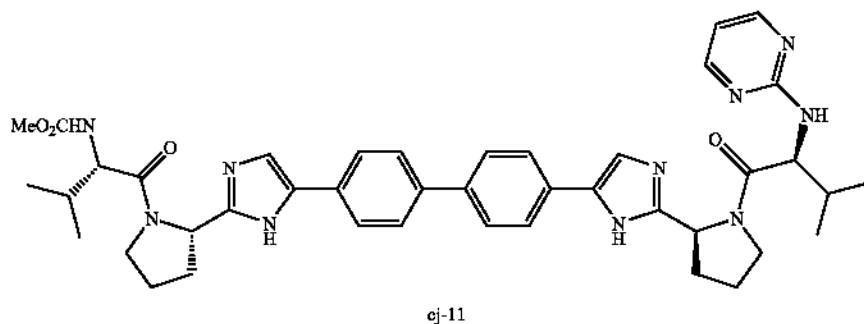
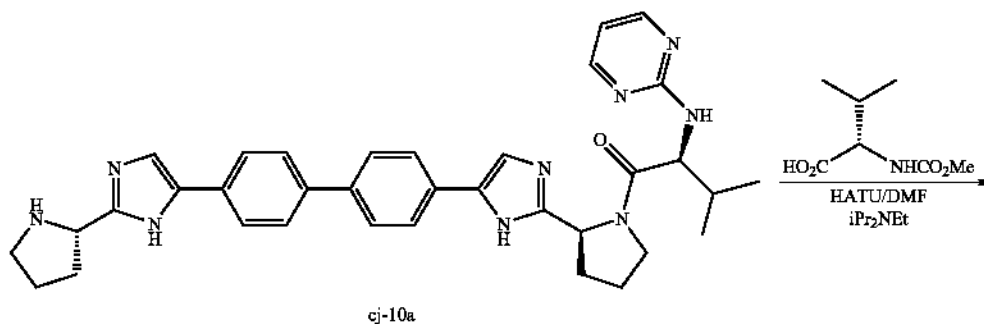
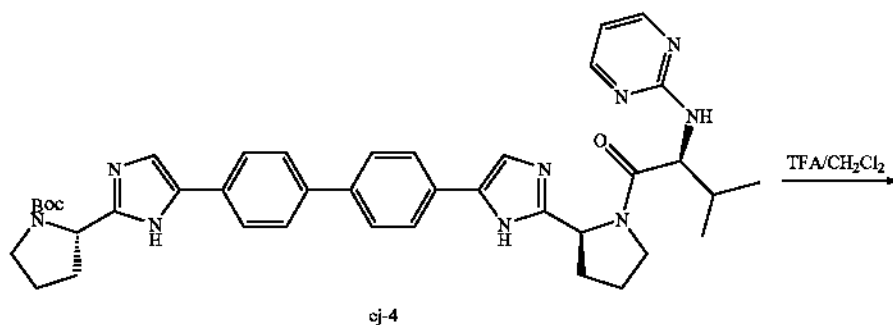
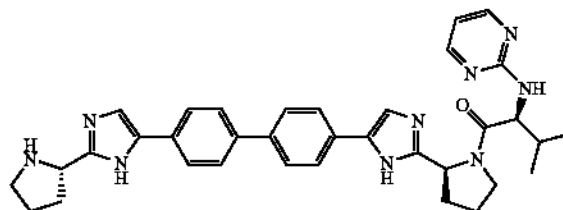
Example cj-1

[1057]

Preparation of (S)-3-Methyl-2-(pyrimidin-2-ylamino)-1-((S)-2-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)butan-1-one (cj-10a)

[1058]

cj-10



[1059] Step 1: A solution of the TFA salt of (S)-tert-butyl 2-(5-(4'-(2-((S)-1-((S)-3-methyl-2-(pyrimidin-2-ylamino)butanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-4) (0.208 g, 0.199 mmol) in a mixture CH_2Cl_2 (4 mL) and TFA (3 mL) was stirred at room temperature for 1.5 h. The solvents were then removed in vacuo and the residue was purified by prep HPLC (Luna 5u C18/MeCN— H_2O -TFA) to give the TFA salt of the title compound (0.391 g) as an orange gum.

[1060] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.53 (br s, 3H), 9.52-9.57 (m, 2H), 8.98-9.04 (m, 2H), 8.28 (d, $J=4.6$ Hz, 2H),

8.13 (br s, 1H), 7.79-7.91 (m, 7H), 7.07 (d, $J=8.1$ Hz, 1H), 6.62 (app t, $J=4.8$ Hz, 1H), 5.07 (t, $J=7.1$ Hz, 1H), 4.72-4.78 (m, 2H), 4.48-4.51 (m, 1H), 4.08-4.12 (m, 2H), 3.28-3.36 (m, 2H), 2.37-2.42 (m, 2H), 1.97-2.22 (m, 6H), 0.88 (app t, $J=4.5$ Hz, 6H).

[1061] LCMS: Anal. Calcd. for $\text{C}_{35}\text{H}_{39}\text{N}_9\text{O}$: 601; found: 602 ($M+H$) $^+$.

[1062] Similarly, the following examples were prepared according to the representative method above;

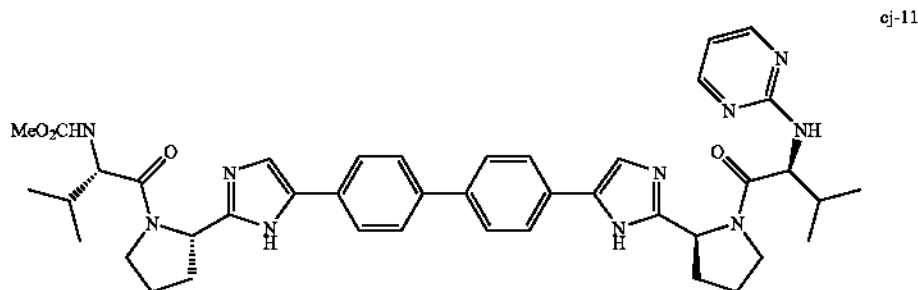
Example	Structure	LCMS
cj-10a (from cj-3)		LCMS: Anal. Calcd. for $\text{C}_{35}\text{H}_{39}\text{N}_9\text{O}$: 601; found: 602 ($M+H$) $^+$.
cj-10b (from cj-2)		LCMS: Anal. Calcd. for $\text{C}_{35}\text{H}_{43}\text{N}_9\text{O}$: 605; found: 606 ($M+H$) $^+$.
cj-10c (from cj-3)		LCMS: Anal. Calcd. for $\text{C}_{35}\text{H}_{43}\text{N}_9\text{O}$: 605; found: 606 ($M+H$) $^+$.
cj-10d (from cj-2)		LCMS: Anal. Calcd. for $\text{C}_{34}\text{H}_{41}\text{N}_9\text{O}$: 591; found: 592 ($M+H$) $^+$.

-continued

Example	Structure	LCMS
cj-10e (from cj-3)		LCMS: Anal. Calcd. for $C_{34}H_{41}N_9O$: 591; found: 592 $(M + H)^+$

Preparation of methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate (cj-11)

[1063]



methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

[1064] Step 2: To a solution of the TFA salt of (S)-3-methyl-2-(pyrimidin-2-ylamino)-1-((S)-2-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)butan-1-one (cj-10) (0.208 g, 0.197 mmol) in DMF (4 mL) was added iPr_2NEt (0.20 mL, 1.15 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.049 g, 0.28 mmol) and HATU (0.105 g, 0.276 mmol). The solution was stirred for 1.5 h at room temperature, diluted with MeOH (2 mL) and purified directly by prep HPLC (Luna 5u C18/MeCN—H₂O—NH₄OAc). This material was repu-

rified by flash chromatography (SiO₂/2-10% MeOH—CH₂Cl₂) to give a solid which was lyophilized from CH₃CN—H₂O to give the title compound (48.6 mg, 32%) as a colourless solid.

[1065] ¹HNMR (400 MHz, DMSO-d₆) δ 11.78 (br s, 1H), 8.28 (d, J=4.5 Hz, 1H), 7.76-7.79 (m, 4H), 7.66-7.69 (m, 4H), 7.48-7.51 (m, 2H), 7.29 (d, J=8.6 Hz, 1H), 6.93 (d, J=8.1 Hz, 1H), 6.60 (app t, J=4.5 Hz, 1H), 5.03-5.09 (m, 2H), 4.48 (t, J=8.1 Hz, 1H), 3.99-4.08 (m, 2H), 3.78-3.85 (m, 2H), 3.53 (s, 3H), 2.12-2.21 (m, 4H), 1.87-2.05 (m, 7H), 0.83-0.97 (m, 12H).

[1066] LCMS: Anal. Calcd. for C₄₂H₅₀N₁₀O₄: 758; found: 759 (M+H)⁺.

[1067] Similarly, the following examples were prepared according to the representative method above;

Example	Compound Name	Structure	LCMS
cj-11a (from cj-10 and Cap-52)	methyl ((1S)-1- methyl-2-oxo-2- ((2S)-2-(5-(4'- (2-((2S)-1-(N-2- pyrimidinyl-L- valyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)- 1- pyrrolidinyl) ethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{46}N_{10}O_4$: 730; found: 731 (M + H) ⁺ .
cj-11b (from cj-10 and Cap-4)	methyl ((1R)-2- oxo-1-phenyl-2- ((2S)-2-(5-(4'- (2-((2S)-1-(N-2- pyrimidinyl-L- valyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)- 1- pyrrolidinyl) ethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{48}N_{10}O_4$: 792; found: 793 (M + H) ⁺ .
cj-11c (from cj-10 and Cap-2)	N-((1S)-1- ((2S)-2-(5-(4'- (2-((2S)-1-((2R)- 2- (diethylamino)- 2-phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)- 1- pyrrolidinyl) carbonyl)-2- methylpropyl)- 2- pyrimidinamine		LCMS: Anal. Calcd. for $C_{47}H_{54}N_{10}O_2$: 790; found: 791 (M + H) ⁺ .
cj-11d (from cj-10b and Cap-51)	methyl ((1S)-2- methyl-1-(((2S)- 2-(5-(4'- (2-((2S)-1-(N-(1- methyl-4,5- dihydro-1H- imidazol-2-yl)- L-valyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)- 1- pyrrolidinyl) carbonyl)propyl) carbamate		LCMS: Anal. Calcd. for $C_{42}H_{54}N_{10}O_4$: 762; found: 763 (M + H) ⁺ .

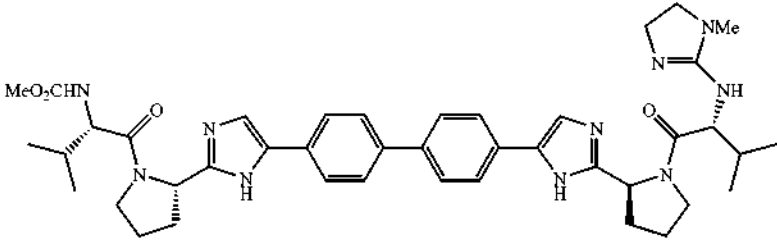
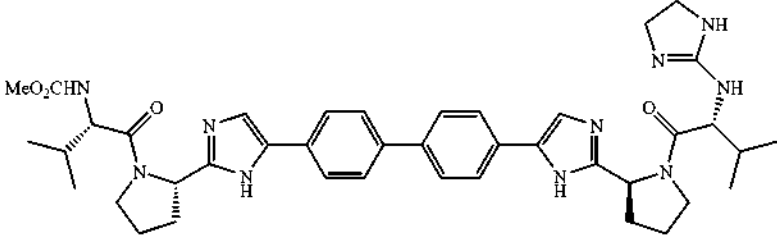
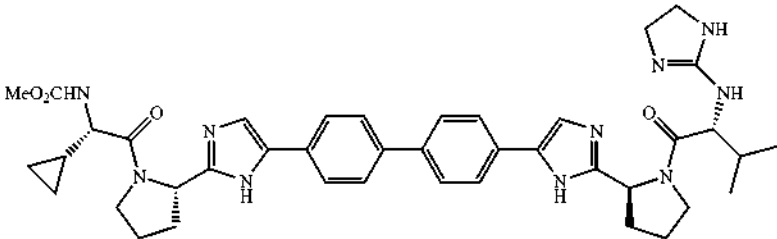
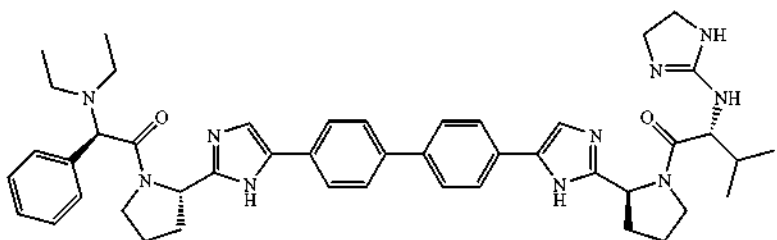
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Example	Compound Name	Structure	LCMS
cj-11e (from cj-10d and Cap-51)	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₅₂ N ₁₀ O ₄ : 748; found: 749 (M + H) ⁺ .
cj-11f (from cj-10d and Cap-52)	methyl ((1S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for C ₃₉ H ₄₈ N ₁₀ O ₄ : 720; found: 721 (M + H) ⁺ .
cj-11g (from cj-10d and Cap-2)	N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-4,5-dihydro-1H-imidazol-2-yl)amine		LCMS: Anal. Calcd. for C ₄₆ H ₅₆ N ₁₀ O ₂ : 780; found: 781 (M + H) ⁺ .
cj-11h (from cj-10d and Cap-4)	methyl ((1R)-2-oxo-1-phenyl-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₅₀ N ₁₀ O ₄ : 782; found: 783 (M + H) ⁺ .

-continued

Example	Compound Name	Structure	LCMS
cj-11i (from cj-10a and Cap-51)	methyl ((1S)-2- methyl-1-(((2S)- 2-(5-(4'- (2-((2S)-1-(N-2- pyrimidinyl-D- valyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)- 1- pyrrolidinyl) carbonyl)propyl) carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$: 758; found: 759 (M + H) ⁺ .
cj-11j (from cj-10a and Cap-52)	methyl ((1S)-1- methyl-2-oxo-2- ((2S)-2-(5-(4'- (2-((2S)-1-(N-2- pyrimidinyl-D- valyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)- 1- pyrrolidinyl) ethyl) carbamate		LCMS: Anal. Calcd. for $C_{40}H_{46}N_{10}O_4$: 730; found: 731 (M + H) ⁺ .
cj-11k (from cj-10a and Cap-2)	N-((1R)-1- ((2S)-2-(5-(4'- 2-((2S)-1-((2R)- 2- (diethylamino)- 2-phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)- 1- pyrrolidinyl) carbonyl)-2- methylpropyl)- 2- pyrimidinamine		LCMS: Anal. Calcd. for $C_{47}H_{54}N_{10}O_2$: 790; found: 791 (M + H) ⁺ .
cj-11l (from cj-10a and Cap-4)			LCMS: Anal. Calcd. for $C_{45}H_{48}N_{10}O_4$: 792; found: 793 (M + H) ⁺ .

-continued

Example	Compound Name	Structure	LCMS
cf-11m (from cj-10c and Cap-51)	methyl ((1S)-2-methyl-1-((2S)-2-(5-(4'-(2-(2S)-1-(N-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl) propyl) carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₅₄ N ₁₀ O ₄ : 762; found: 763 (M + H) ⁺ .
cj-11n (from cj-10e and Cap-51)	methyl ((1S)-1-((2S)-2-(5-(4'-(2-(2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl) carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₅₂ N ₁₀ O ₄ : 748; found: 749 (M + H) ⁺ .
cj-11o (from cj-10e and Cap-54b)	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-(2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₅₀ N ₁₀ O ₄ : 746; found: 747 (M + H) ⁺ .
cj-11p (from cj-10e and Cap-2)	N-((1R)-1-((2S)-2-(5-(4'-(2-(2S)-1-(2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl)-4,5-dihydro-1H-imidazol-2-amine		LCMS: Anal. Calcd. for C ₄₆ H ₅₆ N ₁₀ O ₂ : 780; found: 781 (M + H) ⁺ .

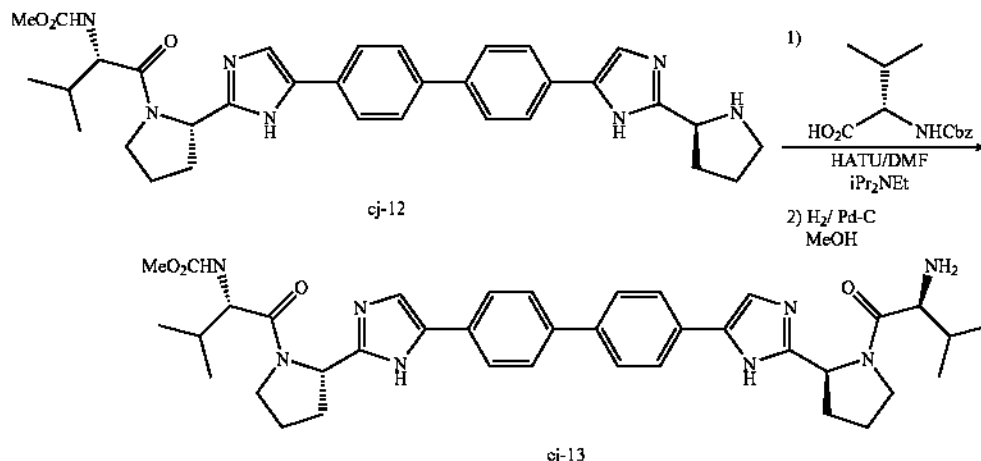
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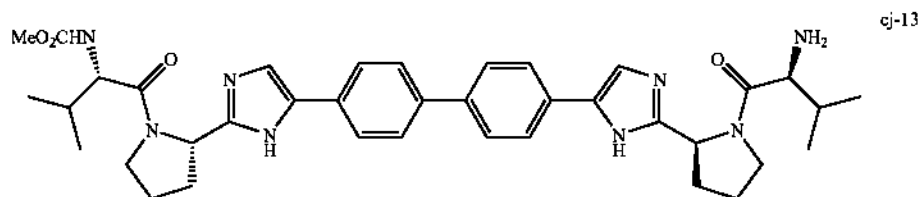
Example-cj-13

[1068]



Preparation of Methyl (S)-1-((S)-2-(5-(4'-(2-((S)-1-(2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-13)

[1069]



[1070] To a solution of methyl (S)-3-methyl-1-oxo-1-((S)-2-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-12) (1.16 g, 1.99 mmol), Z-Val-OH (0.712 g, 2.83 mmol) and $i\text{Pr}_2\text{NEt}$ (0.70 mL, 5.42 mmol) in DMF (40 mL) was added HATU (1.10 g, 2.89 mmol) portionwise. The mixture was allowed to stir at room temperature for 1 h and was then poured into ice-water (400 mL) and allowed to stand for 20 min. The mixture was filtered and the solid washed with cold water and allowed to air dry overnight to give the Z-protected intermediate. LCMS: Anal. Calcd. for $\text{C}_{46}\text{H}_{54}\text{N}_8\text{O}_6$: 814; found: 815 ($\text{M}+\text{H}$)⁺.

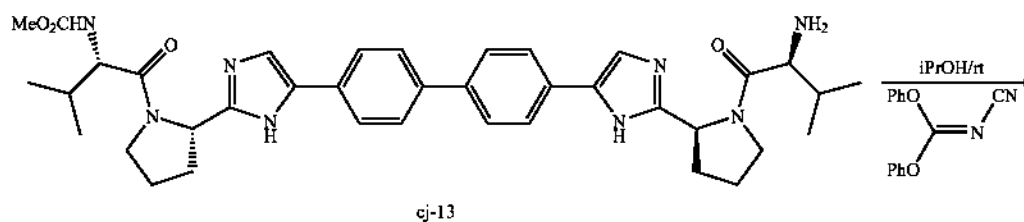
[1071] The obtained solid was dissolved in MeOH (80 mL), 10% Pd—C (1.0 g) was added and the mixture was hydroge-

nated at room temperature and atmospheric pressure for 3 h. The mixture was then filtered and the filtrate concentrated in vacuo. The resulting residue was purified by flash chromatography (SiO_2 /5-20% MeOH— CH_2Cl_2) to afford the title compound (1.05 g, 77%) as a colorless foam. ¹HNMR (400 MHz, $\text{DMSO}-d_6$) δ 11.75 (s, 1H), 7.75-7.79 (m, 3H), 7.61-7.67 (m, 5H), 7.49 (s, 1H), 7.26-7.28 (m, 1H), 5.05-5.09 (m, 2H), 4.03-4.09 (m, 2H), 3.77-3.80 (m, 1H), 3.66-3.70 (m, 1H), 3.52 (s, 3H), 3.40-3.47 (m, 2H), 2.21-2.26 (m, 1H), 2.10-2.17 (m, 3H), 1.81-2.02 (m, 6H), 0.77-0.92 (m, 12H).

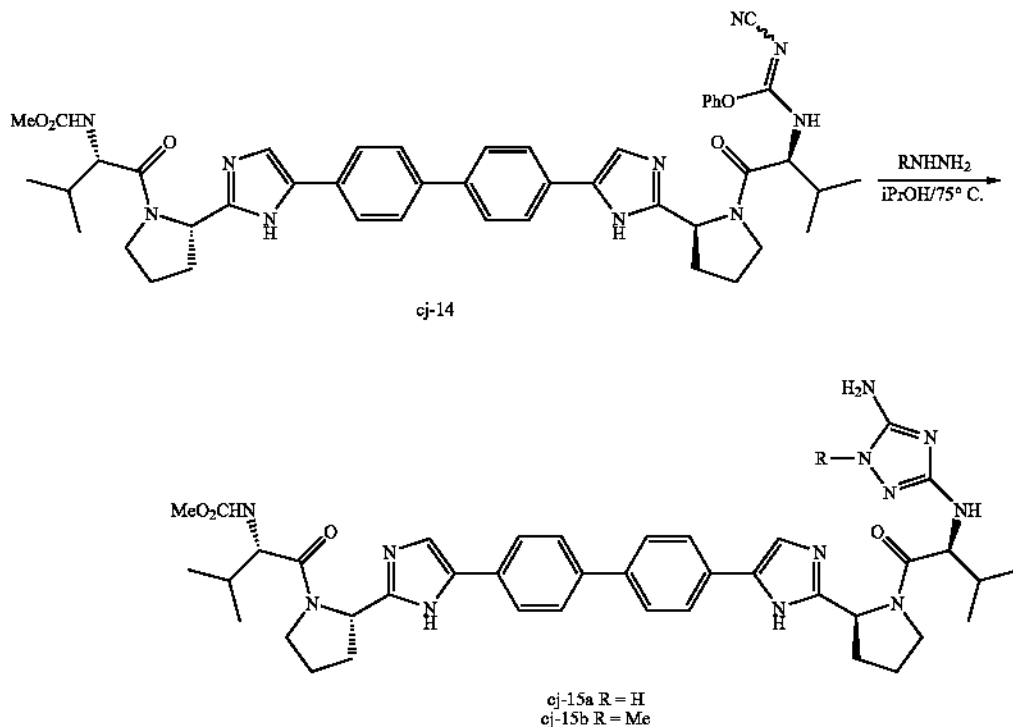
[1072] LCMS: Anal. Calcd. for $\text{C}_{38}\text{H}_{48}\text{N}_8\text{O}_4$: 680; found: 681 ($\text{M}+\text{H}$)⁺.

Example cj-15

[1073]

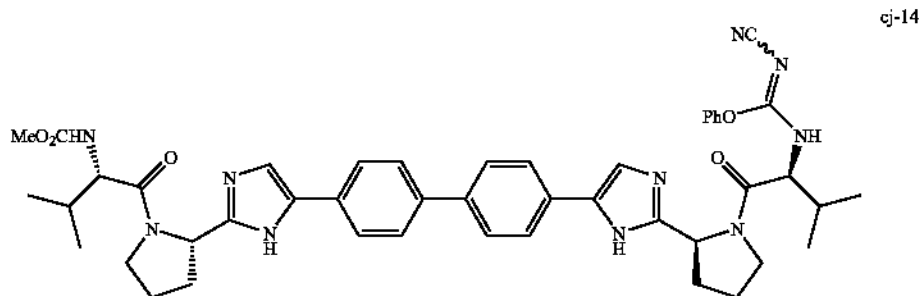


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Preparation of Methyl (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-((Z/E)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14)

[1074]



[1075] A mixture of methyl (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-13) (0.329 g, 0.527 mmol) and diphenyl cyanocarbonimide (0.128 g, 0.537 mmol) in iPrOH (10 mL) was stirred at room temperature for

12 h. The resulting solid was filtered and air-dried to give the title compound (0.187 g, 43%) as a cream-colored solid. This material was used as such in the next step without further purification.

[1076] LCMS: Anal. Calcd. for $C_{46}H_{52}N_{10}O_5$: 824; found: 825 (M+H)⁺.

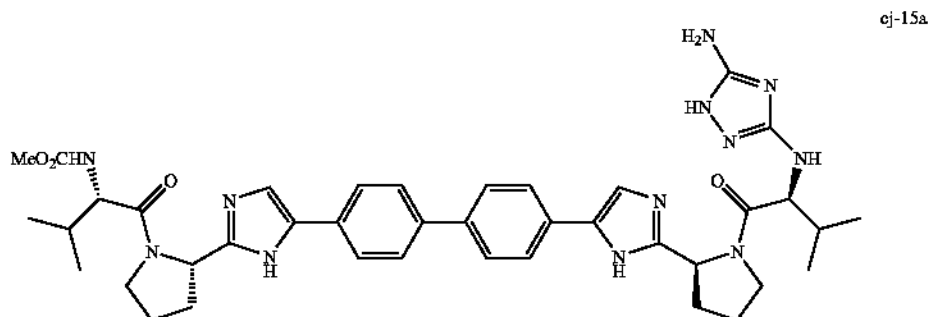
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Preparation of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1-methyl-1H-1,2,4-triazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (cj-15a, R=H)

[1077]



[1078] A solution of methyl (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-((Z/E)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.074 g, 0.090 mmol) and hydrazine hydrate (0.05 mL, 0.88 mmol) in iPrOH (2 mL) was heated at 75° C. for 7 h. The solvent was then removed in vacuo and the residue was purified by prep HPLC (Luna 5u C18/MeCN—H₂O—NH₄OAc) to give foam which was lyophilized from CH₃CN—H₂O to give the title compound (0.032 g, 46%) as a colorless solid.

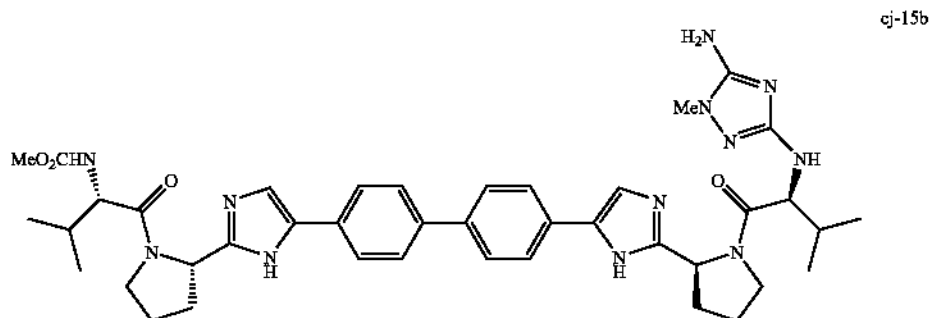
[1079] ¹HNMR (400 MHz, DMSO-d₆) δ 12.17 (s, 1H), 11.75 (m, 2H), 10.66-10.84 (m, 2H), 7.76-7.79 (m, 3H), 7.62-7.74 (m, 4H), 7.49-7.51 (m, 1H), 7.24-7.29 (m, 2H),

5.28-5.32 (m, 1H), 5.05-5.08 (m, 2H), 4.04-4.09 (m, 3H), 3.87-3.94 (m, 2H), 3.72-3.81 (m, 2H), 3.53 (s, 3H), 2.09-2.17 (m, 2H), 1.90-2.02 (m, 6H), 0.81-0.99 (m, 12H).

[1080] LCMS: Anal. Calcd. for C₄₀H₅₀N₁₂O₄: 762; found: 763 (M+H)⁺.

Preparation of Methyl (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-(5-amino-1-methyl-1H-1,2,4-triazol-3-ylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-15b, R=Me)

[1081]



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[1082] A solution of methyl (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-((Z/E)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.105 g, 0.128 mmol) and N-methylhydrazine (0.010 mL, 0.188 mmol) in iPrOH (2 mL) was heated at 75° C. for 3 h. A second portion of N-methylhydrazine (0.010 mL, 0.188 mmol) was added and heating was continued for 7 h. The volatiles were then removed in vacuo and the residue was purified by prep HPLC (Luna 5u C18/MeCN—H₂O—NH₄OAc) to give a foam which was further purified by flash chromatography (SiO₂/0-20% MeOH—CH₂Cl₂). The resulting material was lyophilized from CH₃CN—H₂O to give the title compound (0.029 g, 29%) as a colorless solid.

[1083] ¹HNMR (400 MHz, DMSO-d₆) δ 13.79 (s, 0.4H), 12.19 (s, 1H), 11.76 (m, 1.6H), 7.77-7.85 (m, 4H), 7.62-7.71

(m, 4H), 7.49-7.51 (m, 1H), 7.24-7.29 (m, 1H), 6.31 (d, J=9.1 Hz, 0.5H), 6.09 (d, J=9.1 Hz, 1.5H), 5.87 (s, 1H), 5.34-5.36 (m, 1H), 5.04-5.08 (m, 2H), 4.89 (s, 1H), 4.75 (s, 2H), 3.53 (s, 3H), 2.10-2.17 (s, 3H), 1.94-2.02 (m, 6H), 0.81-0.98 (m, 12H).

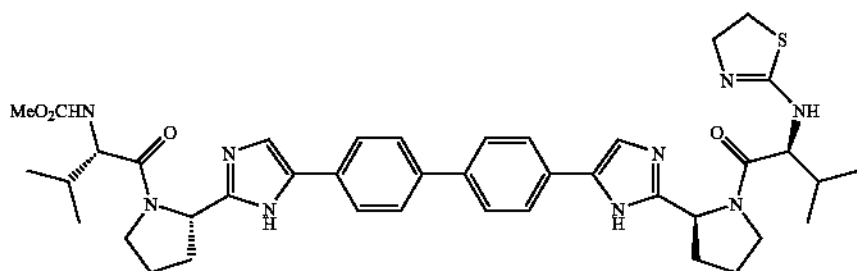
[1084] LCMS: Anal. Calcd. for C₄₁H₅₂N₁₂O₄: 776; found: 777 (M+H)⁺.

[1085] HRMS: Anal. Calcd. for C₄₁H₅₂N₁₂O₄: 776.4234; found: 777.4305 (M+H)⁺.

Example cj-15c

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1,3-thiazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1086]



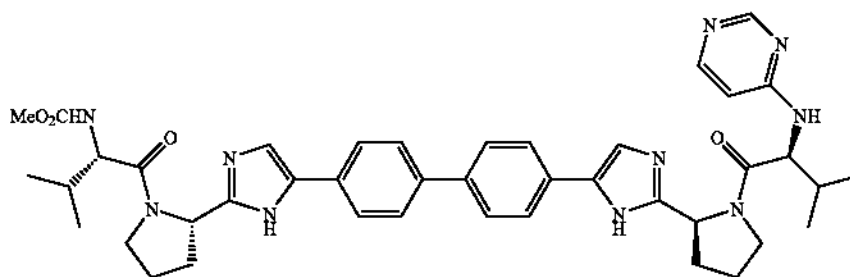
cj-15c

[1087] Example cj-15c was prepared by the condensation of Intermediate cj-13 with 2-(methylthio)-4,5-dihydrothiazole (Aldrich) using conditions analogous to those in the preparation of Intermediate cj-4. LCMS: Anal. Calcd. for C₄₁H₅₁N₉O₄S: 765; found: 766 (M+H)⁺.

Example 15-d

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-4-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

[1088]

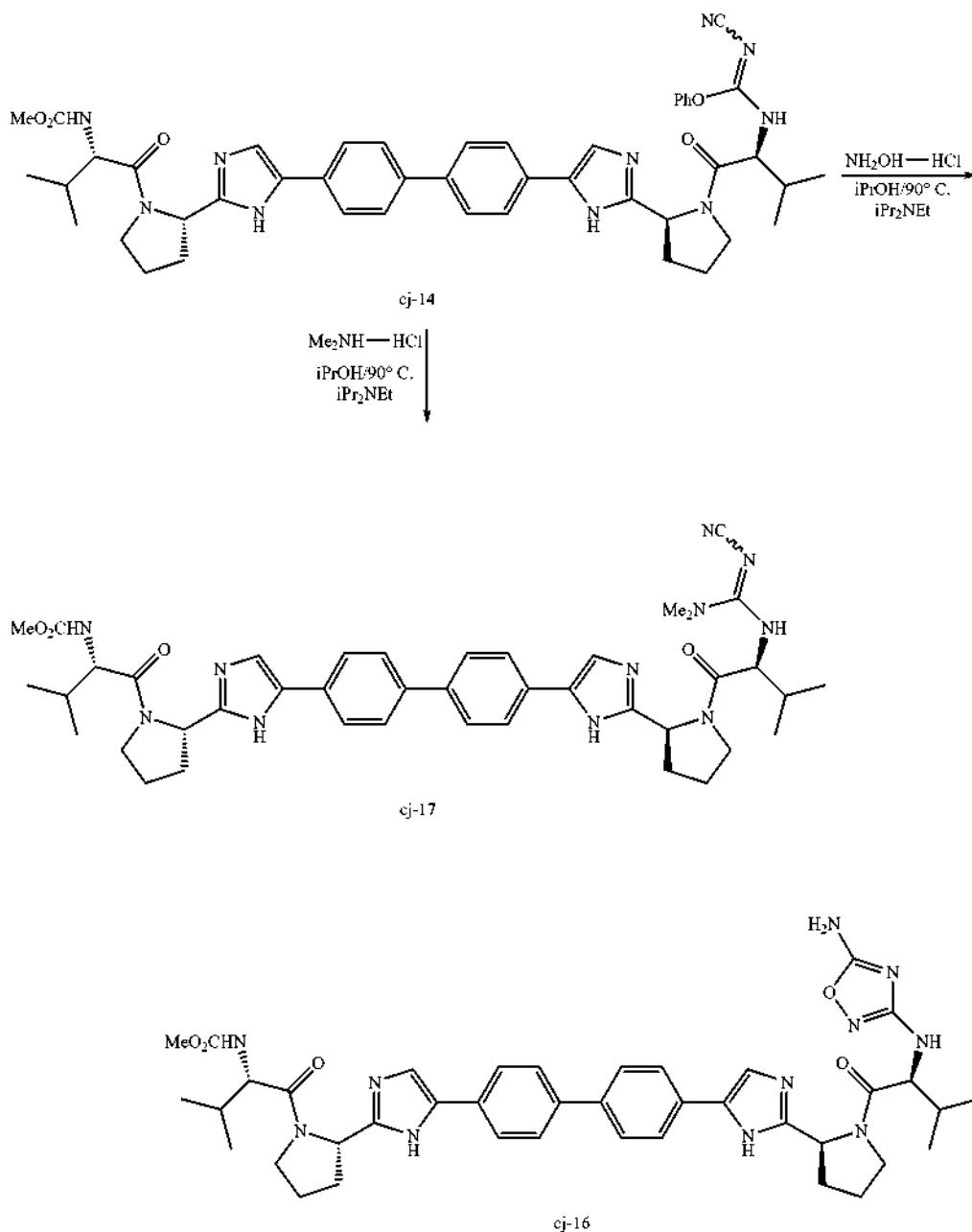


15d

[1089] Example cj-15d was prepared by the condensation of Intermediate cj-13 with 4,6-dichloropyrimidine (Aldrich) using conditions analogous to those in the preparation of Intermediate cj-4, followed by hydrogenation with 10%Pd—C. LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$: 758; found: 759 (M+H)⁺.

Example cj-16 and cj-17

[1090]



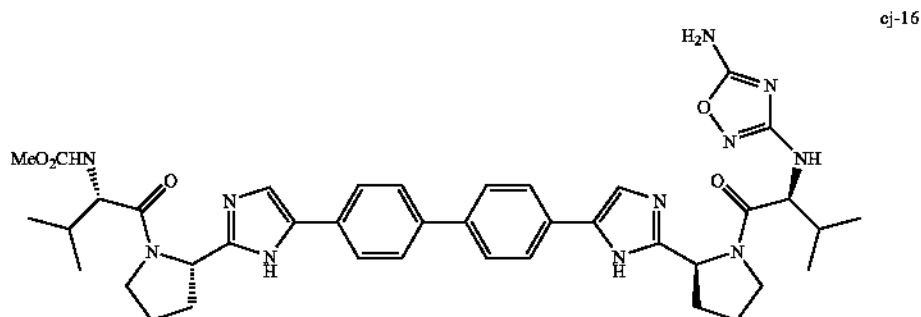
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Preparation of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1,2,4-oxadiazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (cj-16)

[1091]



cj-16

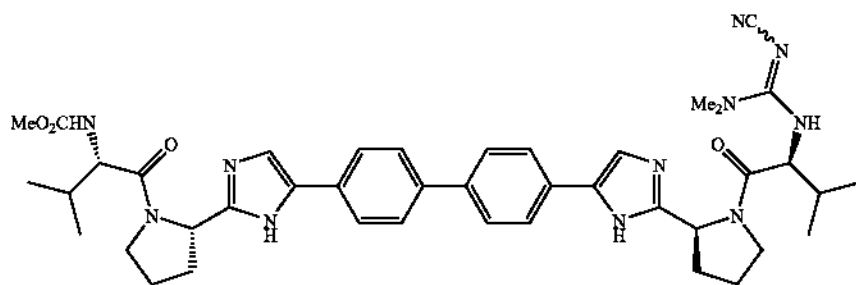
[1092] A solution of methyl (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-((Z/E)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.120 g, 0.205 mmol) and hydroxylamine hydrochloride (0.0213 g, 0.307 mmol) in iPrOH (5 mL) was heated at 75° C. for 3 h. A second portion of hydroxylamine hydrochloride (0.0213 g, 0.307 mmol) was added and heating continued for 7 h. The volatiles were then removed in vacuo and the residue was purified by prep HPLC (Luna 5u C18/MeCN—H₂O—NH₄OAc) to give a foam which was further purified by flash chromatography (SiO₂/5% MeOH—CH₂Cl₂). The resulting colorless wax was lyophilized from CH₃CN—H₂O to give the title compound (0.0344 g, 22%) as a colorless solid.

[1093] ¹HNMR (400 MHz, DMSO-d₆) δ 12.18-12.22 (m, 1H), 11.80 (s, 1H), 11.75 (s, 1H), 8.03-8.06 (m, 1H), 7.77 (app d, J=8.1 Hz, 2H), 7.62-7.73 (m, 4H), 7.50 (dd, J=2.0, 5.5 Hz, 1H), 7.24-7.29 (m, 2H), 5.69 (s, 1H), 5.06-5.11 (m, 2H), 4.14 (t, J=8.6 Hz, 1H), 4.06 (unresolved dd, J=8.0, 8.6 Hz, 1H), 3.78-3.90 (m, 3H), 3.53 (s, 3H), 3.01 (br s, 2H), 2.10-2.19 (m, 3H), 1.90-2.04 (m, 5H), 0.81-0.96 (m, 12H).

[1094] LCMS: Anal. Calcd. for C₄₀H₄₉N₁₁O₅: 763; found: 764 (M+H)⁺.

Preparation of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(cyano(dimethyl)carbamimidoyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (cj-17)

[1095]



cj-17

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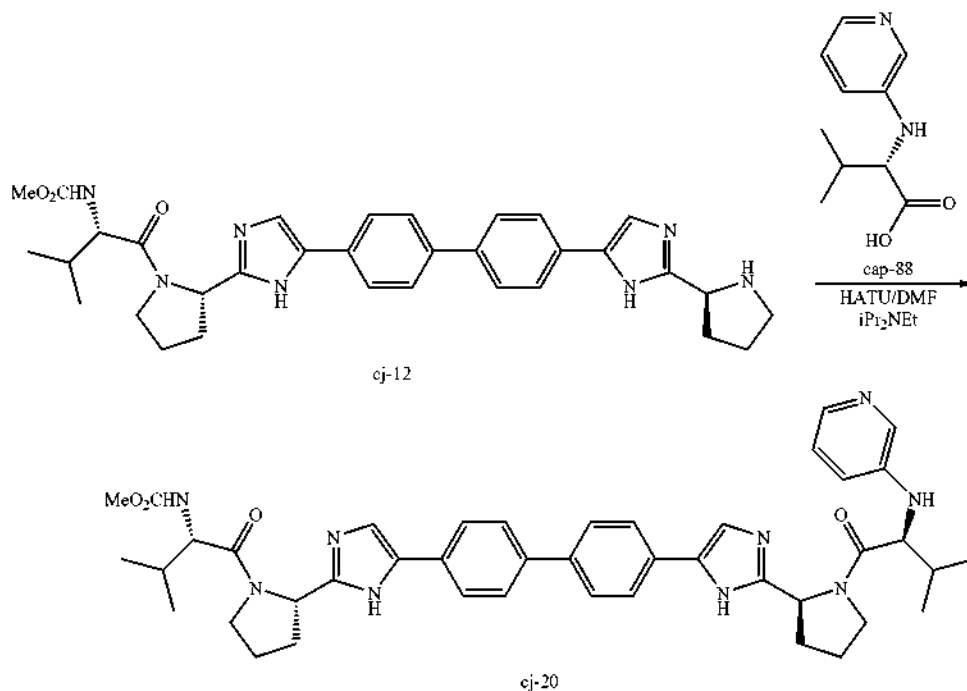
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[1096] A solution of methyl (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-((Z/E)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.115 g, 0.198 mmol) and dimethylamine hydrochloride (0.0257 g, 0.315 mmol) in iPrOH (5 mL) was heated at 90° C. for 12 h. A second portion of dimethylamine hydrochloride (0.0257 g, 0.315 mmol) was added and heating was continued for 48 h. The volatiles were then removed in vacuo and the residue was purified by prep HPLC (Luna 5u C18/MeCN—H₂O—NH₄OAc) and then repurified by flash chromatography (SiO₂/5% MeOH—CH₂Cl₂). The resulting colorless wax was lyophilized from CH₃CN—H₂O to give the title compound (0.0318 g, 21%) as a colorless solid.

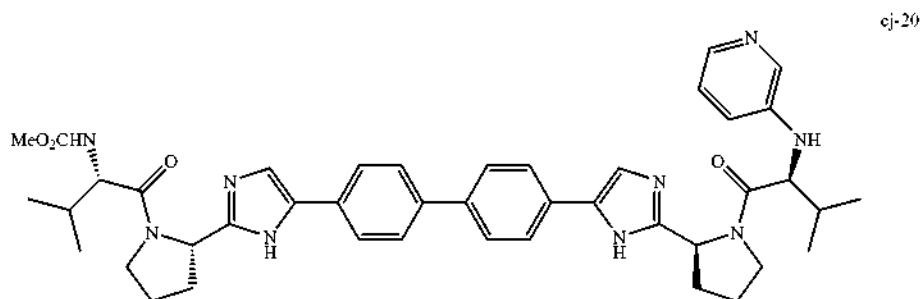
[1097] ¹HNMR (400 MHz, DMSO-d₆) δ 12.22 (m, 0.6H), 11.81 (s, 1H), 11.75 (s, 1H), 12.17-12.22 (m, 0.5H), 11.99-12.04 (m, 0.5H), 11.75-11.81 (m, 1H), 7.76-7.79 (m, 3H), 7.62-7.73 (m, 5H), 7.50 (t, J=2.0 Hz, 1H), 7.23-7.29 (m, 1H), 6.64 (d, J=8.1 Hz, 1H), 5.06-5.08 (m, 2H), 4.47 (t, J=8.1 Hz, 2H), 4.06 (unresolved dd, J=8.0, 8.6 Hz, 1H), 3.84-3.90 (m, 2H), 3.76-3.82 (m, 3H), 3.53 (s, 3H), 3.00 (s, 6H), 2.11-2.20 (m, 3H), 1.90-2.04 (m, 5H), 0.97 (d, J=6.5 Hz, 3H), 0.89-0.91 (m, 6H), 0.84 (d, J=6.5 Hz, 3H).

[1098] LCMS: Anal. Calcd. for C₄₂H₅₃N₁₁O₄: 775; found: 776 (M+H)⁺

Example cj-20

[1099]

Preparation of methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate (cj-20)

[1100]

[1101] To a solution of methyl (S)-3-methyl-1-oxo-1-((S)-2-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-13) (0.060 g, 0.103 mmol) in DMF (2 mL) was added $i\text{Pr}_2\text{NEt}$ (0.18 mL, 1.02 mmol), (S)-3-methyl-2-(pyridin-3-ylamino)butanoic acid (Cap-88) (0.040 g, 0.206 mmol) and HATU (0.078 g, 0.205 mmol). The reaction mixture was stirred for 1.5 h at room temperature and then it was directly purified by prep HPLC (Luna 5u C18/MeCN—H₂O—NH₄OAc). The resulting solid was repurified by flash chromatography (SiO₂/0-10% MeOH—CH₂Cl₂) and the obtained product was lyophilized from CH₃CN—H₂O to give the title compound (0.044 g, 56%) as a solid.

[1102] ¹HNMR (400 MHz, DMSO-*d*₆) δ 12.19 (s, 1H), 11.76 (s, 1H), 8.07 (d, *J*=2.6 Hz, 1H), 7.62-7.85 (m, 8H), 7.49-7.51 (m, 2H), 7.24-7.29 (m, 1H), 6.99-7.06 (m, 2H), 6.46-6.49 (m, 0.5H), 5.97-5.99 (m, 0.5H), 5.71 (d, *J*=9.0 Hz, 1H), 5.55 (d, *J*=10.6 Hz, 1H), 5.22-5.44 (m, 1H), 5.03-5.09 (m, 2H), 4.04-4.13 (m, 2H), 3.78-3.90 (m, 3H), 3.66-3.71 (m, 1H), 3.53 (s, 3H), 2.03-2.19 (m, 2H), 1.84-2.01 (m, 4H), 0.81-1.01 (m, 12H).

[1103] LCMS: Anal. Calcd. for C₄₃H₅₁N₉O₄: 757; found: 758 (M+H)⁺.

[1104] Similarly, the following examples were prepared according to the representative method above;

Example	Compound Name	Structure	LCMS
ej-20a (from ej-22 and Cap-88)	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-(2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₄₇ N ₉ O ₄ : 729; found: 730 (M+H) ⁺ .
ej-20b (from ej-23 and Cap-88)	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-(2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl) carbamate		LCMS: Anal. Calcd. for C ₄₃ H ₅₁ N ₉ O ₅ : 773; found: 774 (M+H) ⁺ .
ej-20c (from ej-24 and Cap-88)	N-((1S)-1-(((2S)-2-(5-(4'-(2-(2S)-1-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-3-pyridinamine		LCMS: Anal. Calcd. for C ₄₉ H ₅₃ N ₉ O ₂ : 789; found: 790 (M+H) ⁺ .
ej-20d (from ej-12 and Cap-88)	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-(2S)-1-(N-5-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl) carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₅₀ N ₁₀ O ₄ : 758; found: 759 (M+H) ⁺ .

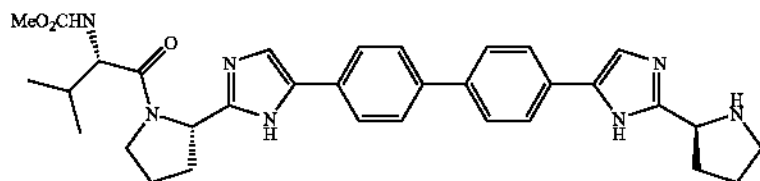
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Preparation of Methyl (S)-3-methyl-1-oxo-1-((S)-2-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-12)

[1105]



cj-12

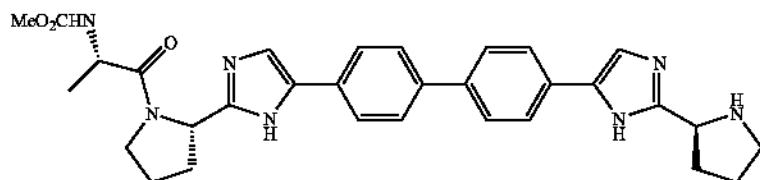
[1106] Synthesized from Intermediate-28d and Cap-51 as in Example 28e, followed by Boc removal with TFA/CH₂Cl₂ and free base formation with MCX resin.

[1107] ¹HNMR (400 MHz, MeOH-d₄) δ 7.79-7.82 (m, 3H), 7.65-7.75 (m, 5H), 7.48 (s, 1H), 7.32 (s, 1H), 5.19 (dd, J=5.5, 5.7 Hz, 1H), 4.75 (t, J=7.8 Hz, 1H), 4.25 (d, J=7.3 Hz, 1H), 3.88-4.04 (m, 2H), 3.67 (s, 3H), 3.35-3.51 (m, 3H), 2.43-2.51 (m, 1H), 2.02-2.38 (m, 7H), 0.97 (d, J=6.5 Hz, 3H), 0.92 (d, J=6.9 Hz, 3H).

[1108] LCMS: Anal. Calcd. for C₃₃H₃₉N₇O₃: 581; found: 582 (M+H)⁺.

Preparation of Methyl (S)-1-oxo-1-((S)-2-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)propan-2-ylcarbamate (cj-22)

[1109]



cj-22

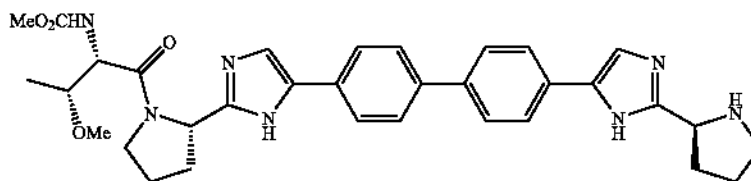
[1110] Synthesized from Intermediate-28d and Cap-52 as in Example 28e, followed by Boc removal with TFA/CH₂Cl₂ and free base formation with MCX resin.

[1111] ¹HNMR (400 MHz, MeOH-d₄) δ 7.68-7.79 (m, 4H), 7.59-7.65 (m, 4H), 7.44 (d, J=6.6 Hz, 1H), 7.37 (s, 0.3H), 7.27 (s, 0.7H), 5.18 (dd, J=4.0, 7.6 Hz, 1H), 4.74 (t, J=8.0 Hz, 1H), 4.46 (dd, J=6.8, 13.9 Hz, 1H), 3.84 (unresolved dd, J=6.1, 6.5 Hz, 1H), 3.62 (s, 3H), 3.54 (s, 1H), 3.32-3.46 (m, 3H), 2.40-2.46 (m, 1H), 2.26-2.39 (m, 2H), 2.14-2.24 (m, 2H), 2.01-2.12 (m, 2H), 0.32 (d, J=7.1 Hz, 3H).

[1112] LCMS: Anal. Calcd. for C₃₁H₃₅N₇O₃: 553; found: 554 (M+H)⁺.

Preparation of Methyl (2S,3R)-3-methoxy-1-oxo-1-((S)-2-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-23)

[1113]



cj-23

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[1114] Synthesized from Intermediate-28d and Cap-86 as in Example 28e, followed by Boc removal with TFA/CH₂Cl₂ and free base formation with MCX resin.

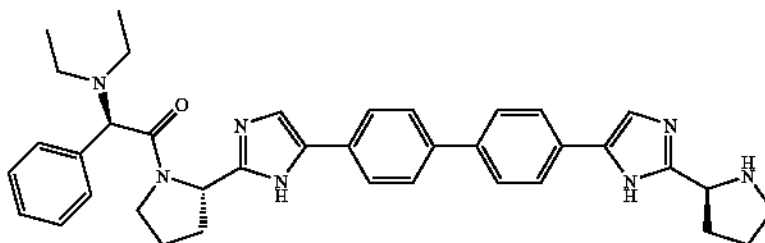
[1115] ¹HNMR (400 MHz, MeOH-d₄) δ 7.72 (m, 4H), 7.64-7.69 (m, 4H), 7.48 (d, J=4.1 Hz, 1H), 7.38 (s, 0.3H), 7.33 (s, 0.7H), 5.51-5.54 (m, 0.2H), 5.22 (dd, J=4.9, 7.6 Hz, 0.8H), 4.76 (t, J=8.0 Hz, 1H), 4.48 (d, J=5.1 Hz, 0.8H), 4.35-4.36 (m, 0.2H), 3.90-3.99 (m, 1H), 3.68 (s, 3H), 3.54 (s, 1H), 3.35-3.48 (m, 4H), 3.29 (s, 3H), 2.42-2.50 (m, 1H), 2.30-2.37 (m, 2H), 2.19-2.26 (m, 2H), 2.05-2.15 (m, 2H), 1.19 (d, J=6.1 Hz, 3H).

[1116] LCMS: Anal. Calcd. for C₃₃H₃₉N₇O₄: 597; found: 598 (M+H)⁺.

Preparation of (R)-2-(Diethylamino)-2-phenyl-1-((S)-2-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)ethanone (cj-24)

[1117]

cj-24



[1118] Synthesized from Intermediate-28d and Cap-2 as in Example 28e, followed by Boc removal with TFA/CH₂Cl₂ and free base formation with MCX resin.

[1119] ¹HNMR (400 MHz, MeOH-d₄) δ 7.59-7.82 (m, 10H), 7.36-7.51 (m, 4H), 7.01-7.15 (m, 1H), 5.09-5.13 (m, 2H), 4.77 (t, J=8.5 Hz, 1H), 4.03-4.05 (m, 1H), 3.67-3.93 (m, 1H), 3.35-3.47 (m, 2H), 3.18-3.23 (m, 1H), 2.91-3.07 (m, 2H), 2.70-2.84 (m, 2H), 2.34-2.60 (m, 2H), 1.97-2.24 (m, 5H), 1.07-1.17 (m, 6H).

[1120] LCMS: Anal. Calcd. for C₃₈H₄₃N₇O: 613; found: 614 (M+H)⁺.

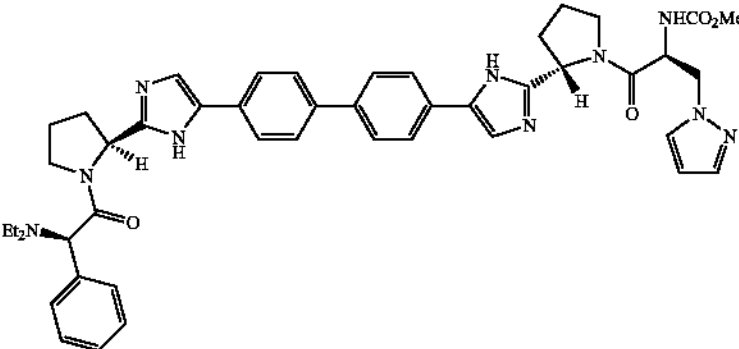
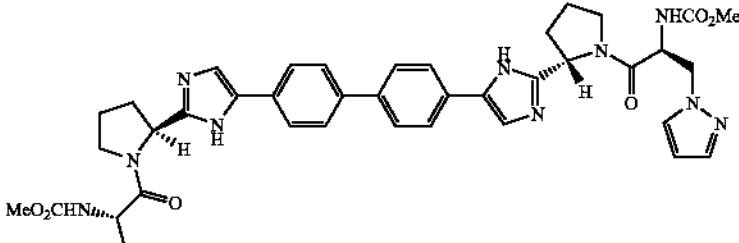
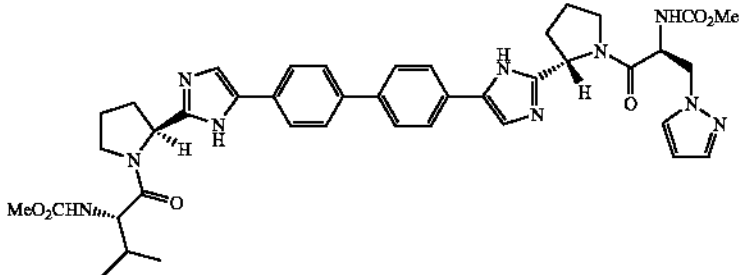
[1121] The following were prepared according to the procedure in example 28 starting with 28d. The caps are given in the table in the order they were appended to 28d. Where a cap number is not given the corresponding carboxylic acid is commercially available.

Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj-32	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenyl-acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-yl)methyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₅₁ N ₁₁ O ₄ : 809; found: 810 (M+H) ⁺ .	2/ 128

-continued

Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 33	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₃₈ H ₄₃ N ₁₁ O ₆ : 749; found: 750 (M + H) ⁺ .	52/ 128
cj- 34	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((methoxycarbonyl)amino)-3-(1H-1,2,3-triazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl) carbamate		LCMS: Anal. Calcd. for C ₄₀ H ₄₇ N ₁₁ O ₆ : 777; found: 777 (M + H) ⁺ .	51/ 128
cj- 35	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₀ H ₄₇ N ₁₁ O ₇ : 793; found: 794 (M + H) ⁺ .	86/ 128

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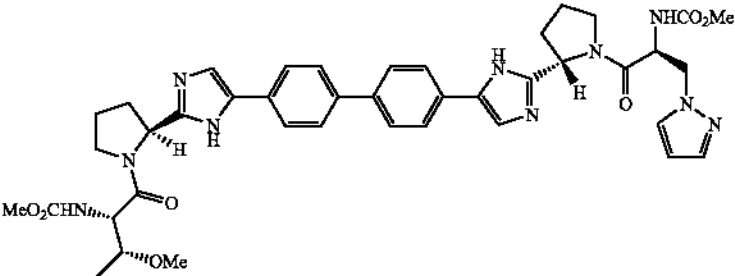
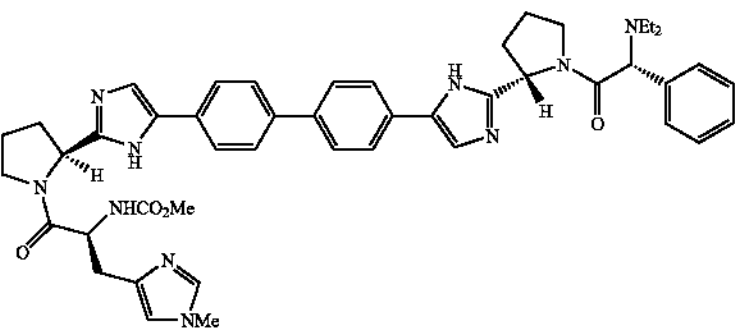
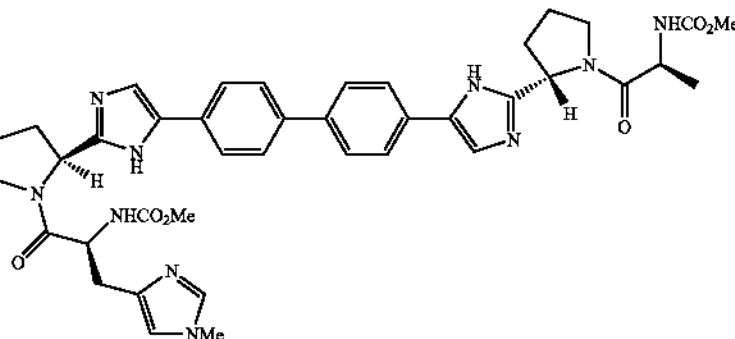
Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 36	methyl ((1S)-2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(diethyl-amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)-ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₅₂ N ₁₀ O ₄ : 808; found: 809 (M + H) ⁺ .	2/ 129
cj- 37	methyl ((1S)-2-((2S)-2-(5-(4'-((2S)-1-(N-(methoxy-carbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl) ethyl) carbamate		LCMS: Anal. Calcd. for C ₃₉ H ₄₄ N ₁₀ O ₆ : 748; found: 749 (M + H) ⁺ .	52/ 129
cj- 38	methyl ((1S)-1-(((2S)-2-(5-(4'-((2S)-2-((methoxy-carbonyl) amino)-3-(1H-pyrazol-1-yl) propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methyl-propyl) carbamate		LCMS: Anal. Calcd. for C ₄₀ H ₄₇ N ₁₁ O ₇ : 776; found: 777 (M + H) ⁺ .	51/ 129

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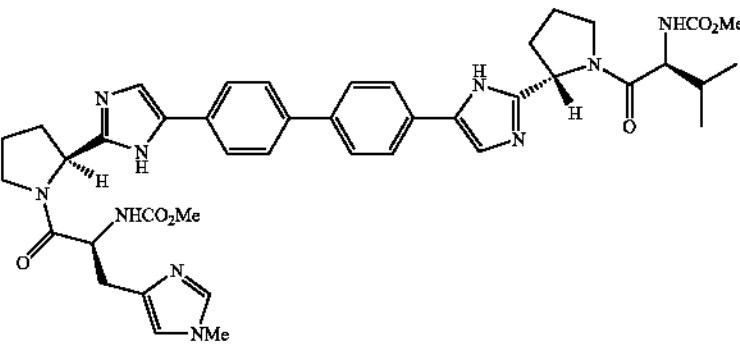
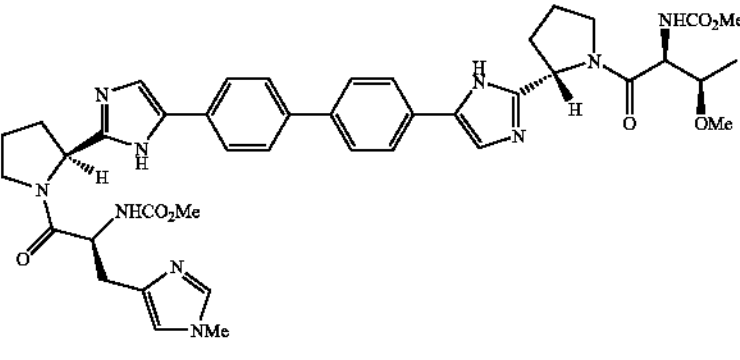
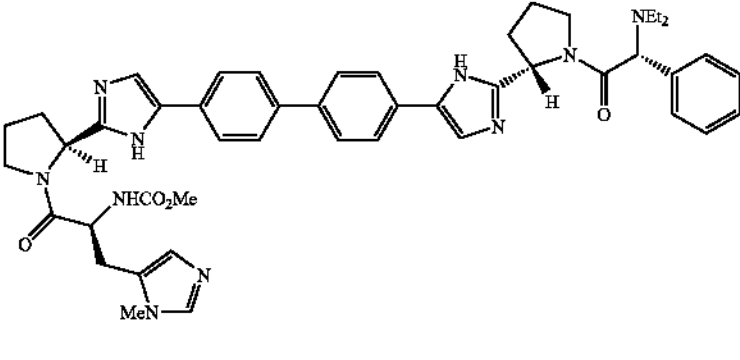
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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 39	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-yl)methyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₄₈ N ₁₀ O ₇ : 792; found: 793 (M + H) ⁺ .	86/ 129
cj- 40	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₅₄ N ₁₀ O ₄ : 822; found: 823 (M + H) ⁺ .	2/ 127
cj- 41	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₀ H ₄₆ N ₁₀ O ₆ : 762; found: 763 (M + H) ⁺ .	52/ 127

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Bx- am- ple	Compound Name	Structure	LCMS	Cap
cj- 42	methyl ((1S)-1- (((2S)-2-(5-(4'- (2-((2S)-1- (2S)- 2-((methoxy- carbonyl) amino)-3-(1- methyl-1H- imidazol-4- yl)propanoyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4-biphenyl)- 1H-imidazol-2-yl)- 1-pyrrolidinyl) carbonyl)-2- methylpropyl) carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₅₀ N ₁₀ O ₆ : 790; found: 791 (M + H) ⁺ .	51/ 127
cj- 43	methyl ((1S)-2- ((2S)-2-(5-(4'- (2-((2S)-1- (2S,3R)-3- methoxy-2- ((methoxy- carbonyl) amino)butanoyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)-1- ((1-methyl-1H- imidazol-4- yl)methyl)-2- oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₅₀ N ₁₀ O ₇ : 806; found: 806 (M + H) ⁺ .	86/ 127
cj- 44	methyl ((1S)-2- ((2S)-2-(5-(4'- (2-((2S)-1-((2R)- 2- (diethylamino)- 2-phenyl- acetyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)-1- ((1-methyl-1H- imidazol-5- yl)methyl)-2- oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₅₄ N ₁₀ O ₄ : 822; found: 823 (M + H) ⁺ .	2/ 126

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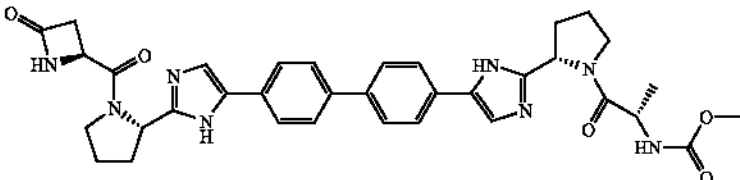
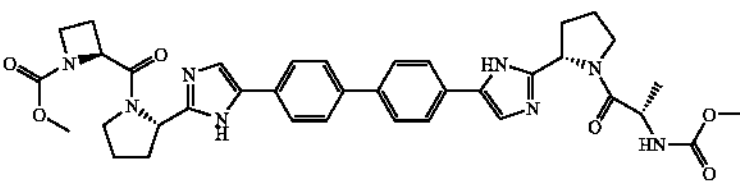
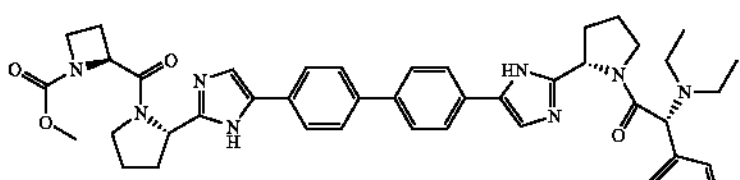
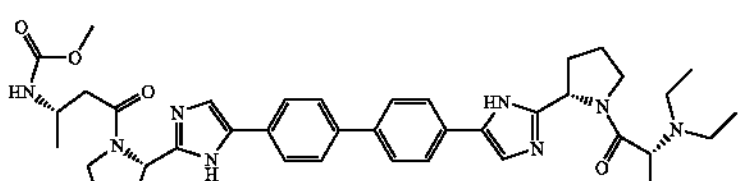
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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 45	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for C ₄₀ H ₄₆ N ₁₀ O ₈ : 762; found: 763 (M + H) ⁺ .	52/ 126
cj- 46	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(2S)-2-((methoxycarbonyl)amino)-3-(1-methyl-1H-imidazol-5-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₅₀ N ₁₀ O ₈ : 790; found: 791	51/ 126
cj- 47	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₅₀ N ₁₀ O ₇ : 806; found: 807 (M + H) ⁺ .	86/ 126

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 48	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(((2S)-4-oxo-2-azetidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₃₅ H ₃₈ N ₈ O ₅ 650; found: 651 (M + H) ⁺ .	52/ —
cj- 49	methyl (2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidine-carboxylate		LCMS: Anal. Calcd. for C ₃₇ H ₄₂ N ₈ O ₆ 694; found: 695 (M + H) ⁺ .	52/ 114
cj- 50	methyl (2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidine-carboxylate		LCMS: Anal. Calcd. for C ₄₄ H ₅₀ N ₈ O ₄ 754; found: 755 (M + H) ⁺ .	2/ 114
cj- 51	methyl ((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-3-oxopropyl)carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₅₂ N ₈ O ₄ 756; found: 757 (M + H) ⁺ .	2/ 115

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 52	methyl ((1R)-3- ((2S)-2-(5-(4'- (2-((2S)-1-((2R)- 2-(diethyl- amino)- 2-phenyl- acetyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)-1- pyrrolidinyl)- 1-isopropyl-3- oxopropyl) carbamate		LCMS: Ansl. Calcd. for C ₄₆ H ₅₆ N ₈ O ₄ 784; found: 785 (M + H) ⁺ .	2/ 116
cj- 53	methyl ((1S)-1- benzyl-3- ((2S)-2-(5-(4'- (2-((2S)-1-((2R)- 2-(diethyl- amino)- 2-phenyl- acetyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)-1- pyrrolidinyl)- 3-oxopropyl) carbamate		LCMS: Ansl. Calcd. for C ₅₀ H ₅₆ N ₈ O ₄ 833; found: 834 (M + H) ⁺ .	2/ 96
cj- 54	methyl ((1R)-3- ((2S)-2-(5-(4'- (2-((2S)-1-((2R)- 2-(diethyl- amino)- 2-phenyl- acetyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)-1- pyrrolidinyl)- 3-oxo-1-(2- thienylmethyl) propyl) carbamate		LCMS: Ansl. Calcd. for C ₄₈ H ₅₄ N ₈ O ₄ S 838; found: 839 (M + H) ⁺ .	2/ 119
cj- 55	methyl ((1R)-3- ((2S)-2-(5-(4'- (2-((2S)-1-((2R)- 2-(diethyl- amino)- 2-phenyl- acetyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)-1- pyrrolidinyl)- 3-oxo-1-(3- thienylmethyl) propyl) carbamate		LCMS: Ansl. Calcd. for C ₄₈ H ₅₄ N ₈ O ₄ S 838; found: 839 (M + H) ⁺ .	2/ 120

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 56	methyl ((1S)-3- ((2S)-2-(5-(4'- 2-((2S)-1-((2R)- 2-(diethyl- amino)- 2-phenyl- acetyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)-1- pyrrolidinyl)- 3-oxo-1-(2- thienylmethyl) propyl) carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₄ N ₈ O ₄ S 838; found: 839 (M + H) ⁺ .	2/ 118
cj- 57	methyl ((1S,3R)- 3-(((2S)-2-(5-(4'- 2-((2S)-1-((2R)- 2-(diethyl- amino)-2- phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5-yl)- 4-biphenyl)- 1H-imidazol- 2-yl)-1- pyrrolidinyl) carbonyl) cyclopentyl) carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₅₄ N ₈ O ₄ 782; found: 783 (M + H) ⁺ .	2/ 99a
cj- 58	methyl ((1R)-1- benzyl-3-((2S)- 2-(5-(4'-2- ((2S)-1-((2R)-2- (diethyl- amino)-2- phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5-yl)- 4-biphenyl)- 1H-imidazol-2-yl)- 1-pyrrolidinyl)- 3-oxopropyl) carbamate		LCMS: Anal. Calcd. for C ₅₀ H ₅₆ N ₈ O ₄ 832; found: 833 (M + H) ⁺ .	2/ 117
cj- 59	methyl ((1R)-3- ((2S)-2-(5-(4'- 2-((2S)-1-((2R)-2- (diethyl- amino)-2- phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4-biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- 1-(2-fluoro- benzyl)-3- oxopropyl) carbamate		LCMS: Anal. Calcd. for C ₅₀ H ₅₅ N ₈ O ₄ F 850; found: 851 (M + H) ⁺ .	2/ 100

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 60	methyl (((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl) cyclopentyl) carbamate		LCMS: Ansl. Calcd. for C ₄₆ H ₅₄ N ₈ O ₄ 782; found: 783 (M + H) ⁺ .	2/ 99
cj- 61	methyl (((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-(methoxycarbonyl) amino) cyclopentyl) carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl) carbamate		LCMS: Ansl. Calcd. for C ₄₁ H ₅₀ N ₈ O ₆ 750; found: 751 (M + H) ⁺ .	52/ 99a
cj- 62	methyl (((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-(methoxycarbonyl) amino) cyclopentyl) carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl) carbamate		LCMS: Ansl. Calcd. for C ₄₁ H ₅₀ N ₈ O ₆ 750; found: 751 (M + H) ⁺ .	52/ 99

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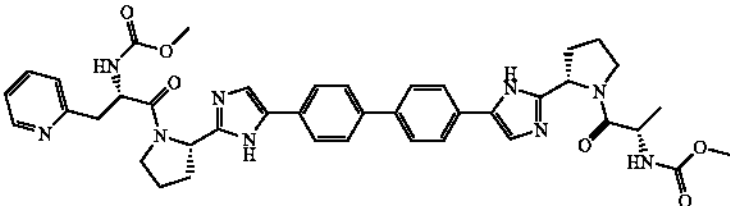
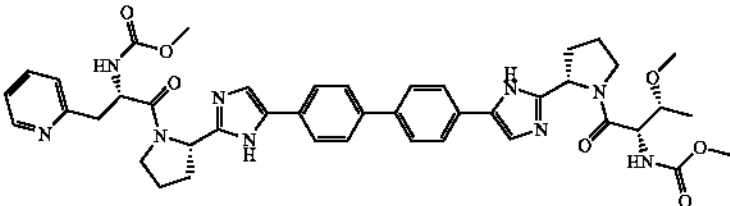
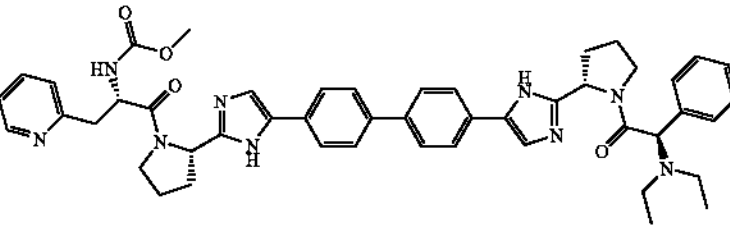
Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 63	methyl ((1R)-2- ((2S)-2-(5-(4'- 2-((2S)-1- (((1R,3S)-3- ((methoxy- carbonyl) amino) cyclopentyl) carbonyl)-2- pyrrolidinyl)- 1H-imidazol- 5-yl)-4- biphenyl)-1- H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxo-1- phenylethyl) carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₈ N ₈ O ₆ 748; found: 785 (M + H) ⁺ .	4/ 99a
cj- 64	methyl ((1R)-2- ((2S)-2-(5-(4'- 2-((2S)-1- (((1S,3R)-3- ((methoxy- carbonyl) amino) cyclopentyl) carbonyl)-2- pyrrolidinyl)- 1H-imidazol- 5-yl)-4- biphenyl)-1- H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxo-1- phenylethyl) carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₈ N ₈ O ₆ 748; found: 785 (M + H) ⁺ .	4/ 99
cj- 65	methyl ((1S)-1- (((2S)-2-(5-(4'- 2-((2S)-1- ((2S)-2- ((methoxy- carbonyl) amino)-3-(2- pyridinyl) propanoyl)-2- pyrrolidinyl)- 1H-imidazol- 5-yl)-4- biphenyl)-1- H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl)-2- methylpropyl) carbamate		LCMS: Anal. Calcd. for C ₄₃ H ₄₉ N ₉ O ₆ 787; found: 788 (M + H) ⁺ .	51/ 93

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 66	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₄₅ N ₉ O ₆ 759; found: 760 (M + H) ⁺ .	52/ 93
cj- 67	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₃ H ₄₉ N ₉ O ₇ 803; found: 804 (M + H) ⁺ .	86/ 93
cj- 68	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₅₃ N ₉ O ₄ 819; found: 820 (M + H) ⁺ .	2/ 93

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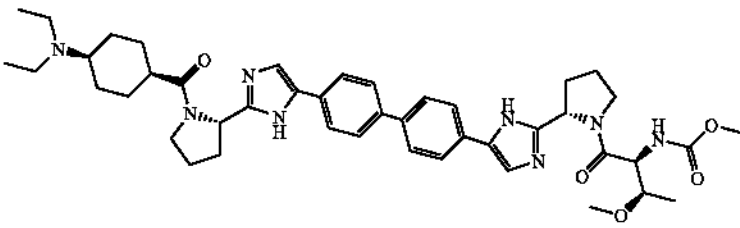
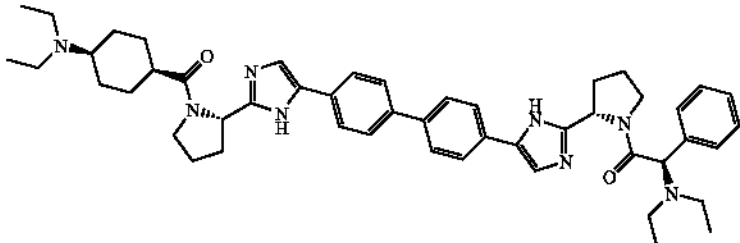
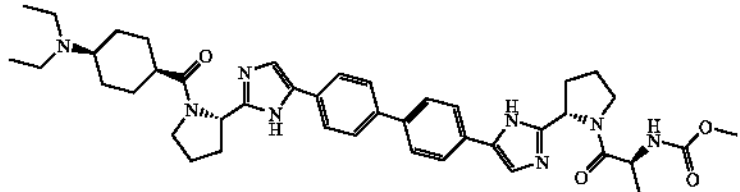
Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 69	methyl ((1S)-1- (((2S)-2-(5-(4'- (2-((2S)-1- ((cis- 4-((methoxy- carbonyl) amino) cyclohexyl) carbonyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl)- 2-methyl- propyl) carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₅₂ N ₈ O ₆ 764; found: 765 (M + H) ⁺ .	51/ 104
cj- 70	methyl ((1S)-1- (((2S)-2-(5-(4'- (2-((2S)-1- ((trans- 4-((methoxy- carbonyl) amino) cyclohexyl) carbonyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl)- 2-methyl- propyl) carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₅₂ N ₈ O ₆ 764; found: 765 (M + H) ⁺ .	51/ 105
cj- 71	methyl ((1S)-1- (((2S)-2-(5-(4'- (2-((2S)-1- ((cis-4- (diethylamino) cyclohexyl) carbonyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl)-2- methylpropyl) carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₅₈ N ₈ O ₄ 762; found: 763 (M + H) ⁺ .	51/ 106

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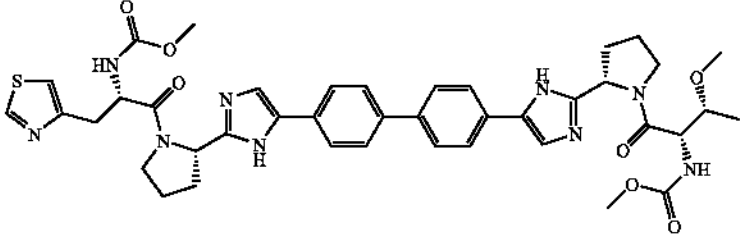
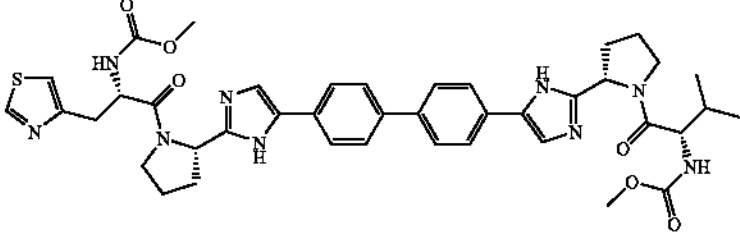
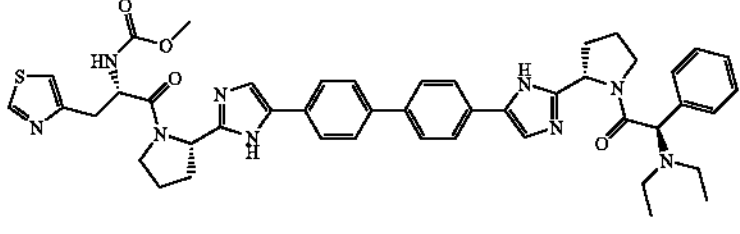
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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 72	methyl ((1S,2R)-1- (((2S)-2-(5-(4'- 2-((2S)-1- (cis-4- (diethyl- amino) cyclohexyl) carbonyl)- 2-pyrrolidinyl)- 1H-imidazol- 5-yl)-4- biphenyl)- 1H-imidazol- 2-yl)-1- pyrrolidinyl) carbonyl)-2- methoxy- propyl) carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₅₈ N ₈ O ₅ 778; found: 779 (M + H) ⁺ .	86/ 106
cj- 73	cis-4-(((2S)- 2-(5-(4'-2- ((2S)-1-((2R)-2- (diethyl- amino)-2- phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl)-N,N- diethyl- cyclo- hexanamine		LCMS: Anal. Calcd. for C ₄₉ H ₆₂ N ₈ O ₂ 794; found: 795 (M + H) ⁺ .	2/ 106
cj- 74	methyl ((1S)- 2-((2S)-2-(5-(4'- (2-((2S)-1- (cis-4- (diethyl- amino) cyclohexyl) carbonyl)- 2-pyrrolidinyl)- 1H-imidazol- 5-yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- 1-methyl-2- oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₅₄ N ₈ O ₄ 734; found: 735 (M + H) ⁺ .	52/ 106

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 75	methyl ((1S)-1- ((1-benzyl- 1H-imidazol-4- yl)methyl)-2- (2S)-2-(5-(4'- (2-((2S)-1- ((2S,3R)-3- methoxy- 2-((methoxy- carbonyl) amino) butanoyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)- 1-pyrrolidinyl)- 2- oxoethyl) carbamate		LCMS: Anal. Calcd. for $C_{48}H_{54}N_{10}O_7$ 882; found: 883 (M + H) ⁺ .	86/ 108
cj- 76	methyl ((1S)-1- (((2S)-2-(5-(4'- (2-((2S)-1-((2S)- 3-(1-benzyl- 1H-imidazol-4- yl)-2- ((methoxy- carbonyl) amino) propanoyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1H- imidazol-2-yl)- 1-pyrrolidinyl) carbonyl)-2- methylpropyl) carbamate		LCMS: Anal. Calcd. for $C_{48}H_{54}N_{10}O_6$ 866; found: 867 (M + H) ⁺ .	51/ 108
cj- 77	methyl ((1S)-2- ((2S)-2-(5-(4'- (2-((2S)-1- ((2S)-3-(1- benzyl-1H- imidazol-4- yl)-2- ((methoxy- carbonyl) amino) propanoyl)- 2-pyrrolidinyl)- 1H-imidazol-5-yl)-4- biphenyl)-1H- imidazol-2-yl)- 1-pyrrolidinyl)- methyl-2- oxoethyl) carbamate		LCMS: Anal. Calcd. for $C_{46}H_{50}N_{10}O_6$ 838; found: 839 (M + H) ⁺ .	52/ 108

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 78	methyl ((1S)-2- ((2S)-2-(5-(4'- (2-(2S)-1- (2S,3R)-3- methoxy-2- ((methoxy- carbonyl) amino) butanoyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)-2- oxo-1-(1,3- thiazol-4- yl(methyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₄₇ N ₉ O ₇ S 809; found: 810 (M + H) ⁺ .	86/ 107
cj- 79	methyl ((1S)-1- (((2S)-2-(5-(4'- (2-(2S)-1- (2S)-2-((methoxy- carbonyl) amino)-3-(1,3- thiazol-4- yl)propanoyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl)-2- methylpropyl) carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₄₇ N ₉ O ₆ S 793; found: 794 (M + H) ⁺ .	51/ 107
cj- 80	methyl ((1S)-2- ((2)-2-(5-(4'- (2-(2S)-1- (2R)-2- (diethyl- amino)-2- phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxo-1-(1,3- thiazol-4- yl(methyl) ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₅₁ N ₉ O ₄ S 825; found: 826 (M + H) ⁺ .	2/ 107

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
ej- 81	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-yl)methyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₃₉ H ₄₃ N ₉ O ₈ S 765; found: 766 (M + H) ⁺ .	51/ 107
ej- 82	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₃ H ₄₉ N ₉ O ₇ 803; found: 804 (M + H) ⁺ .	86/ 109
ej- 83	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₃ H ₄₉ N ₉ O ₆ 787; found: 788 (M + H) ⁺ .	51/ 109

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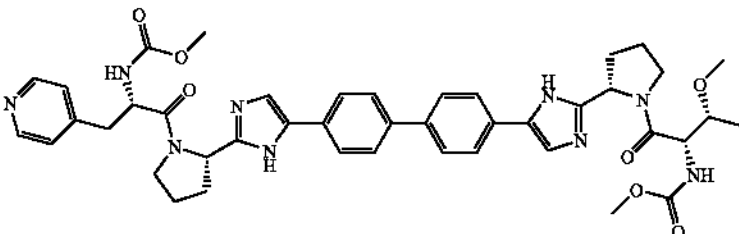
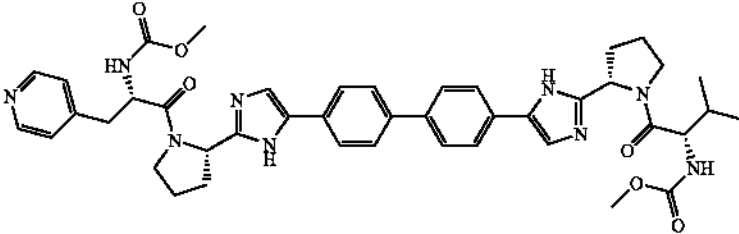
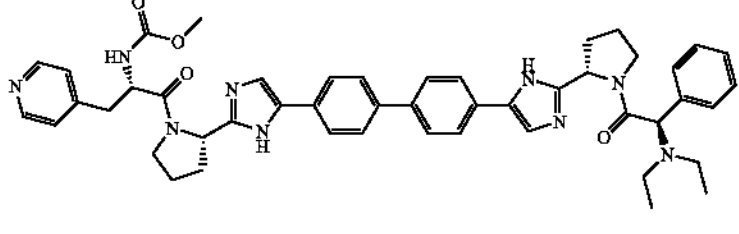
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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 84	methyl ((1S)-2- ((2S)-2-(5-(4'- 2-((2S)-1- ((2R)-2- (diethyl- amino)-2- phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5-yl)- 4-biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxo-1-(3- pyridinyl- methyl)ethyl) carbamate		LCMS: Anal. Calcd. for $C_{48}H_{53}N_9O_4$ 819; found: 820 (M + H) ⁺ .	2/ 109
cj- 85	methyl ((1S)-2- ((2S)-2-(5-(4'- 2-((2S)-1-N- (methoxy- carbonyl)- L-alanyl)-2- pyrrolidinyl)- 1H-imidazol-5-yl)- 4-biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxo-1-(3- pyridinyl- methyl)ethyl) carbamate		LCMS: Anal. Calcd. for $C_{41}H_{45}N_9O_6$ 759; found: 760 (M + H) ⁺ .	52/ 109
cj- 86	methyl ((1R,3S)-3- (((2S)-2-(5-(4'- 2-((2S)-1- ((2S)-3- methoxy-2- (methoxy- carbonyl) amino) butanoyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- carbonyl) cyclopentyl) carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_8O_7$ 766; found: 767 (M + H) ⁺ .	86/ 99

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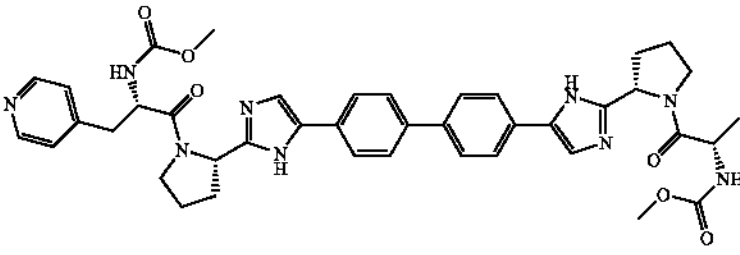
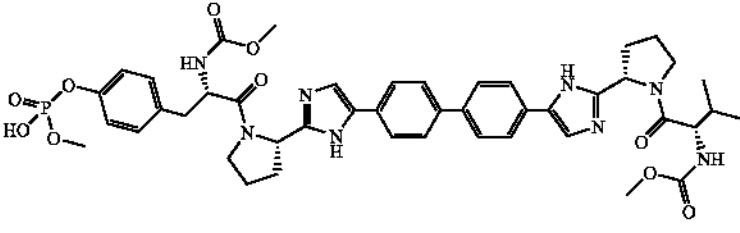
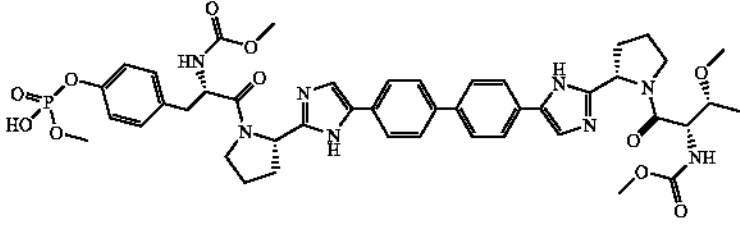
Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 87	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₃ H ₄₉ N ₉ O ₇ 803; found: 804 (M + H) ⁺ .	86/ 110
cj- 88	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₃ H ₄₉ N ₉ O ₆ 787; found: 788 (M + H) ⁺ .	51/ 110
cj- 89	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for C ₄₈ H ₅₃ N ₉ O ₄ 819; found: 820 (M + H) ⁺ .	2/ 110

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-continued

Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 90	methyl ((1S)-2- ((2S)-2-(5-(4'- (2-((2S)-1-(N- (methoxy- carbonyl)- L-alanyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxo-1-(4- pyridinyl- methyl)ethyl) carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₄₅ N ₉ O ₆ 759; found: 760 (M + H) ⁺ .	52/ 110
cj- 91	methyl ((1S)-1- (((2S)-2-(5-(4'- (2-((2S)-1-((O-hydroxy- (methoxy- phosphoryl)-N- (methoxy- carbonyl)- L-tyrosyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl)-2- methylpropyl) carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₅₃ N ₉ O ₁₀ P 896; found: 897 (M + H) ⁺ .	51/ 111
cj- 92	methyl ((1S,2R)-1- (((2S)-2-(5-(4'- (2-((2S)-1-((O-hydroxy(methoxy- phosphoryl)-N- (methoxy-carbonyl)- L-tyrosyl)-2- pyrrolidinyl)-1H- imidazol-5-yl)-4- biphenyl)-1H- imidazol-2-yl)-1- pyrrolidinyl) carbonyl)-2- methoxy-propyl) carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₅₃ N ₉ O ₁₁ P 912; found: 913 (M + H) ⁺ .	86/ 111

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 93	methyl ((1S)-1- (((2S)-2-(5-(4'- 2-((2S)-1- (((1S,2R)-2- (methoxy- carbonyl) amino) cyclohexyl) carbonyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1- H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl)-2- methyl- propyl) carbamate		LCMS: Anal. Calcd. for C ₄₂ H ₅₂ N ₈ O ₆ 764; found: 765 (M + H) ⁺ .	98/ 51
cj- 94	methyl ((1R,2S)-2- (((2S)-2-(5-(4'- 2-((2S)-1- (2R)-2- (diethyl- amino)-2- phenyl- acetyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1- H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl) cyclohexyl) carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₅₆ N ₈ O ₄ 796; found: 797 (M + H) ⁺ .	98/ 2
cj- 95	methyl ((1R)-2- ((2S)-2-(5-(4'- 2-((2S)-1- (((1S,2R)-2- (methoxy- carbonyl) amino) cyclohexyl) carbonyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)-1- H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxo-1- phenylethyl) carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₅₀ N ₈ O ₆ 798; found: 799 (M + H) ⁺ .	98/ 4

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Bx- am- ple	Compound Name	Structure	LCMS	Cap
cj- 96	methyl ((1R,2S)-2- (((2S)-2-(5-(4'- (2-((2S)-1-N- (methoxy- carbonyl)- L-alanyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl) cyclohexyl) carbamate		LCMS: Anal. Calcd. for $C_{46}H_{48}N_8O_6$ 736; found: 737 (M + H) ⁺ .	98/ 51
cj- 97	methyl ((1R,2S)-2- (((2S)-2-(5-(4'- (2-((2S)-1- (cis-4- (diethyl- amino) cyclohexyl) carbonyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl) cyclohexyl) carbamate		LCMS: Anal. Calcd. for $C_{46}H_{60}N_8O_4$ 788; found: 789 (M + H) ⁺ .	98/ 106
cj- 98	methyl ((1R,2S)-2- (((2S)-2-(5-(4'- (2-((2S)-1- (2R)-2- acetamido-2- phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl) cyclohexyl) carbamate		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_5$ 782; found: 783 (M + H) ⁺ .	98/ 130

-continued

Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 99	methyl ((1S)-1- (((2S)-2-(5-(4'- 2-((2S)-1- ((2S)-3-(1H- indol-3-yl)-2- (methoxy- carbonyl) amino) propanoyl)- 2-pyrrolidiny)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidiny)- carbonyl)-2- methylpropyl)- carbamate		LCMS: Anal. Calcd. for $C_{56}H_{51}N_9O_6$ 825; found: 826 (M + H) ⁺ .	51/ 112
cj- 100	methyl ((1S)-1-(1H- indol-3-ylmethyl)-2- ((2S)-2-(5-(4'- (2S)-1-((2S,3R)-3- methoxyl-2- (methoxy-carbonyl) amino)butanoyl)-2- pyrrolidiny)-1H- imidazol-5-yl)-4- biphenyl)-1H- imidazol-2-yl)-1- pyrrolidiny)-2- oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{51}N_9O_7$ 841; found: 842 (M + H) ⁺ .	86/ 112
cj- 101	methyl ((1S)-2- ((2S)-2-(5-(4'- (2S)-1- (2R)-2- (diethyl- amino)-2- phenyl- acetyl)-2- pyrrolidiny)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidiny)- 1-(1H-indol- 3-ylmethyl)- 2-oxoethyl) carbamate		LCMS: Anal. Calcd. for $C_{51}H_{55}N_9O_4$ 857; found: 858 (M + H) ⁺ .	2/ 112

-continued

Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 102	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-yl)-2-((methoxy-carbonyl) amino) propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₇ N ₉ O ₆ 797; found: 798 (M + H) ⁺ .	52/ 112
cj- 103	methyl ((1S)-1-(4-(amino-methyl) benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxy-carbonyl) amino)-3-methyl) butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₅ H ₅₃ N ₉ O ₆ 815; found: 816 (M + H) ⁺ .	see text
cj- 104	methyl (((2S)-2-(5-(4'-(2-((2S)-1-(O-benzyl-N-(methoxy-carbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methyl-propyl) carbamate		LCMS: Anal. Calcd. for C ₅₁ H ₅₆ N ₈ O ₇ 892; found: 893 (M + H) ⁺ .	51/ 113

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 105	methyl ((1S,2R)-1- (((2S)-2-(5-(4'- 2-((2S)-1-(O- benzyl-N- (methoxy- carbonyl)- L-tyrosyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl)- 2-methoxypropyl) carbamate		LCMS: Anal. Calcd. for C ₅₁ H ₅₆ N ₈ O ₈ 908; found: 909 (M + H) ⁺ .	86/ 113
cj- 106	methyl ((1S)-1- (4-(benzyloxy) benzyl)-2- ((2S)-2-(5-(4'- 2-((2S)-1- (2R)-2- (diethyl- amino)-2- phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₅₆ H ₆₀ N ₈ O ₅ 924; found: 925 (M + H) ⁺ .	2/ 113
cj- 107	methyl ((1S)-1- (4-(benzyloxy) benzyl)-2- ((2S)-2-(5-(4'- 2-((2S)-1- (N- (methoxy- carbonyl)- L-alanyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₉ H ₅₂ N ₈ O ₇ 864; found: 865 (M + H) ⁺ .	52/ 113
cj- 108	methyl ((1R,2R)-2- (((2S)-2-(5-(4'- 2-((2S)-1-(N- (methoxy- carbonyl)- L-alanyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl) cyclopentyl) carbamate		LCMS: Anal. Calcd. for C ₃₉ H ₄₆ N ₈ O ₆ 722; found: 723 (M + H) ⁺ .	122/ 52

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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 109	methyl ((1R,2R)-2- (((2S)-2-(5-(4'- 2-((2S)-1- (2R)-2- (diethyl- amino)-2- phenylacetyl)- 2-pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl) cyclopentyl) carbamate		LCMS: Anal. Calcd. for C ₄₆ H ₅₄ N ₈ O ₄ 782; found: 783 (M + H) ⁺ .	122/ 2
cj- 110	methyl ((1R)-2- ((2S)-2-(5-(4'- 2-((2S)-1- (((1R,2R)-2- ((methoxy- carbonyl) amino) cyclopentyl) carbonyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxo-1- phenylethyl) carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₄₈ N ₈ O ₆ 784; found: 785 (M + H) ⁺ .	122/ 4
cj- 111	methyl ((1S)-1- (4-hydroxy- benzyl)-2- ((2S)-2-(5-(4'- 2-((2S)-1- (2S)-2- ((methoxy- carbonyl) amino)-3- methyl- butanoyl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl)- 2-oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₄ H ₅₀ N ₈ O ₇ 802; found: 803 (M + H) ⁺ .	see text

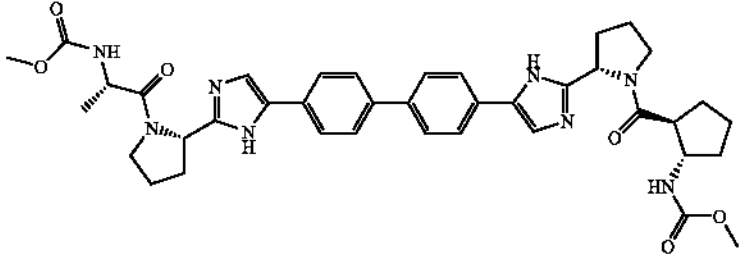
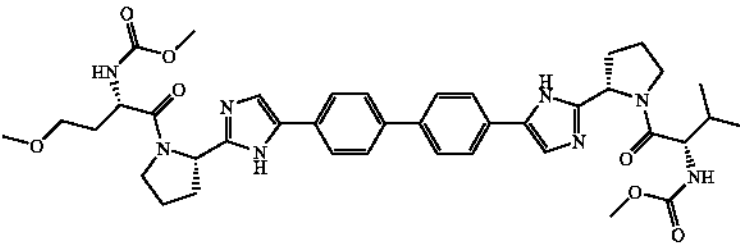
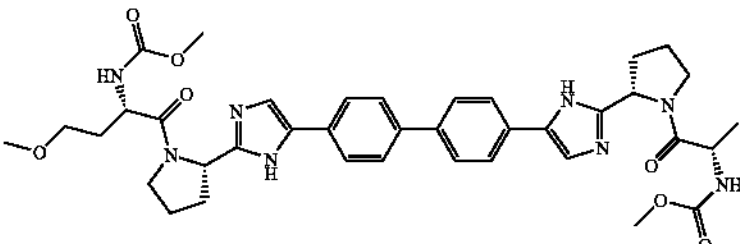
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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 112	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethyl-amino)-2-phenylacetyl)-2-pyrrolidiny)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidiny)-1-(4-hydroxybenzyl)-2-oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₉ H ₅₄ N ₈ O ₅ 834; found: 835 (M + H) ⁺ .	see text
cj- 113	methyl ((1S)-1-(4-hydroxybenzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxy-carbonyl)-L-alanyl)-2-pyrrolidiny)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidiny)-2-oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₅₄ N ₈ O ₇ 774; found: 775 (M + H) ⁺ .	see text
cj- 114	methyl ((1S)-1-(4-(acetamido-methyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(methoxy-carbonyl)amino)-3-methyl-butanoyl)-2-pyrrolidiny)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidiny)-2-oxoethyl) carbamate		LCMS: Anal. Calcd. for C ₄₇ H ₅₅ N ₉ O ₇ 857; found: 585 (M + H) ⁺ .	see text

-continued

Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 115	methyl ((1S)-1-(4-(((ethoxycarbonyl)amino)methyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{58}N_{10}O_7$ 886; found: 887 ($M + H$) ⁺ .	see text
cj- 116	methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2R)-1-((2R)-2-diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_4$ 782; found: 783 ($M + H$) ⁺ .	121/ 2
cj- 117	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1S,2S)-2-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{48}N_8O_6$ 784; found: 785 ($M + H$) ⁺ .	121/ 4

-continued

Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 118	methyl ((1S,2S)-2-(((2S)-2-(5-(4'-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl) cyclopentyl) carbamate		LCMS: Anal. Calcd. for C ₃₉ H ₄₆ N ₈ O ₆ 722; found: 723 (M + H) ⁺ .	121/ 52
cj- 119	methyl ((1S)-1-(((2S)-2-(5-(4'-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl) carbamate		LCMS: Anal. Calcd. for C ₄₀ H ₅₀ N ₈ O ₇ 754; found: 755 (M + H) ⁺ .	51/ 87
cj- 120	methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(4'-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl) propyl) carbamate		LCMS: Anal. Calcd. for C ₃₈ H ₄₆ N ₈ O ₇ 726; found: 727 (M + H) ⁺ .	52/ 87

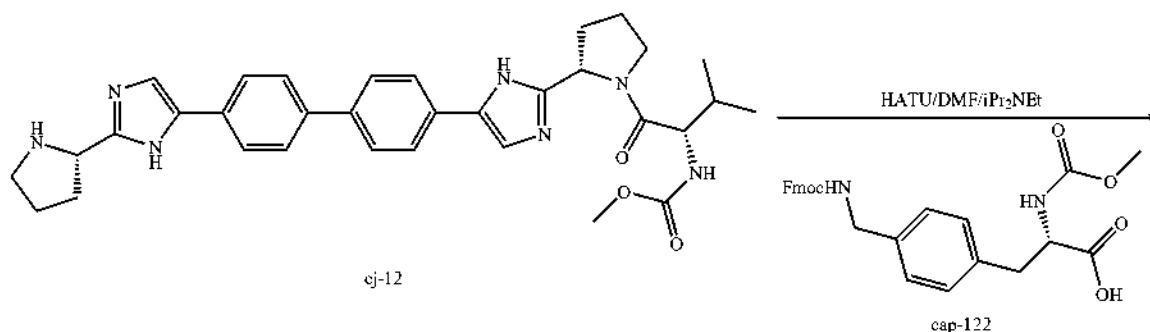
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Ex- am- ple	Compound Name	Structure	LCMS	Cap
cj- 121	methyl ((1S,2R)- 2-methoxy-1- (((2S)-2-(5- (4'-(2-((2S)- 1-(N-((methoxy- carbonyl)- O-methyl-L- homoseryl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl) propyl) carbamate		LCMS: Anal. Calcd. for C ₄₀ H ₅₀ N ₈ O ₈ 770; found: 771 (M + H) ⁺ .	86/ 87
cj- 122	methyl ((1S,2S)- 2-(((2S)-2-(5- (4'-(2-((2S)- 1-(N-((methoxy- carbonyl)- O-methyl-L- homoseryl)-2- pyrrolidinyl)- 1H-imidazol-5- yl)-4- biphenyl)- 1H-imidazol-2- yl)-1- pyrrolidinyl) carbonyl) cyclopentyl) carbamate		LCMS: Anal. Calcd. for C ₄₁ H ₅₀ N ₈ O ₇ 766; found: 767 (M + H) ⁺ .	121/ 87

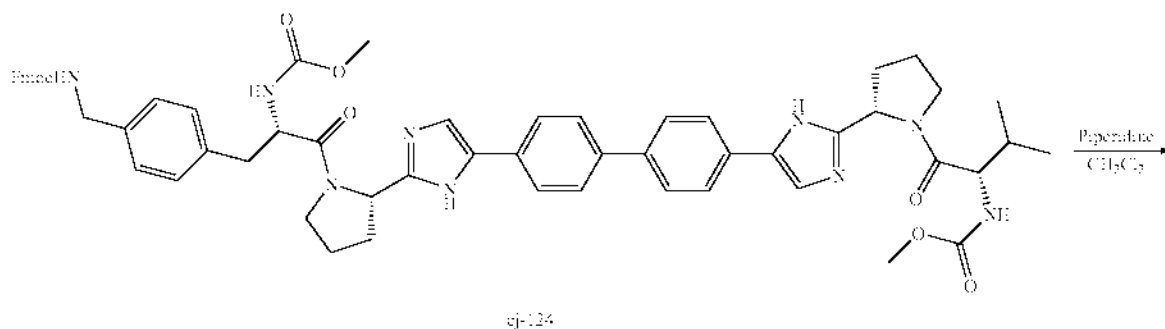
Examples cj-111 to cj-113

[1122] For Examples cj-111 to cj-113 the compounds of Examples cj-105 to cj-107 were hydrogenated under conditions analogous to those used in Example 28, step d (with the exception that K₂CO₃ was not employed).

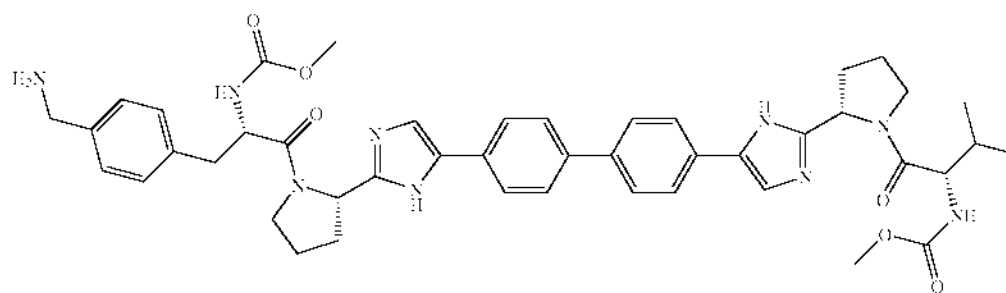
Preparation of examples cj-103, cj-114 and cj-115

[1123]

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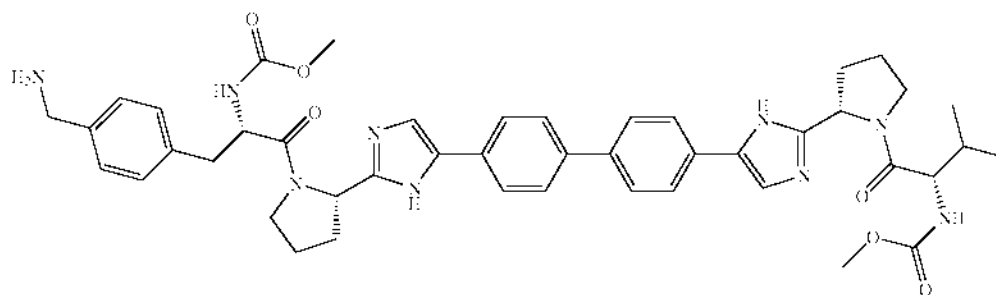
ej-124

ej-103
3- $\text{C}_{12}\text{H}_4\text{CO}_2\text{Et}$

[1124] Intermediate **ej-124** was prepared by coupling of intermediate **ej-12** and **Cap-122**, as described in Example 28, step c. LCMS: Anal. Calcd. for $\text{C}_{60}\text{H}_{61}\text{N}_9\text{O}_8$ 1037; found: 520 ($\frac{1}{2}\text{M}+\text{H}$)⁺. This corresponds to the doubly charged molecular ion.

Example **ej-103**

[1125]



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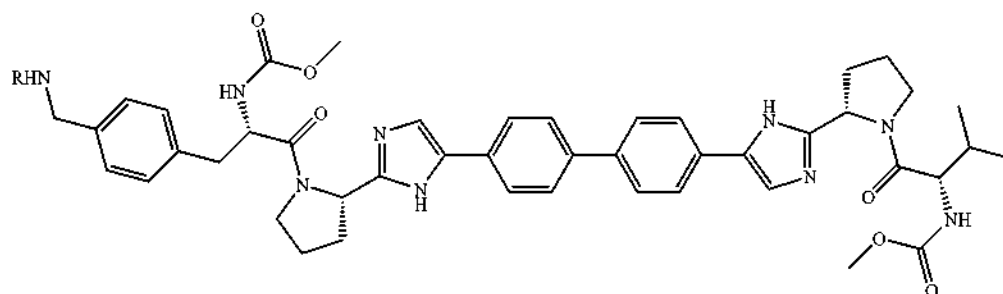
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[1126] Intermediate cj-124 (83.0 mg, 0.08 mmol) was dissolved in DMF (5 mL) and piperidine (1 mL) was added at room temperature. After 2 h the volatiles were removed in vacuo and the residue was purified by preparative HPLC (YMC-Pack C-18, 30×100 mm, CH₃CN—H₂O-TFA) to give

the TFA salt of the amine (87.0 mg, 94%). LCMS: Anal. Calcd. for C₄₅H₅₃N₉O₆ 815; found: 816 (M+H)⁺.

Examples cj-114 to cj-115

[1127]



2-TFA

Example cj-114, R = Ac
Example cj-115, R = CONHt

[1128] The product from Example cj-103 was acylated with either acetic anhydride or ethyl isocyanate as shown in scheme under conditions analogous to those in Example 25.

[1129] Example cj-114, LCMS: Anal. Calcd. for C₄₇H₅₅N₉O₇ 857; found: 858 (M+H)⁺.

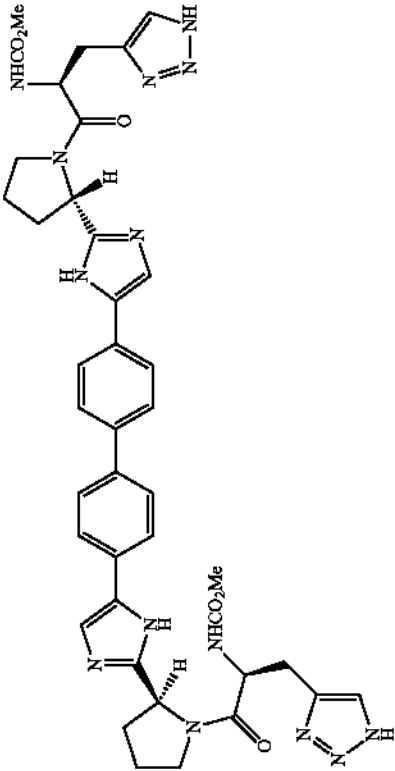
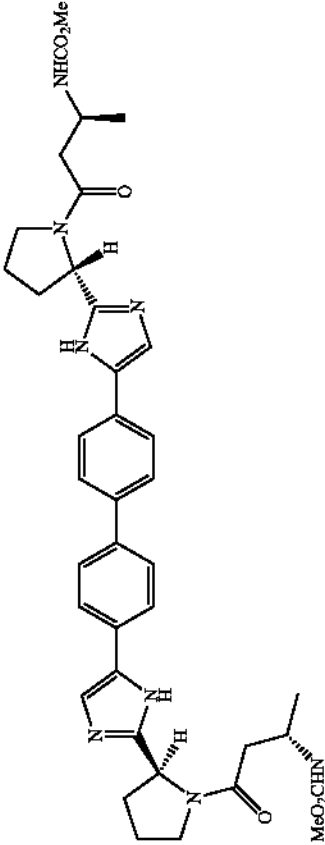
[1130] Example cj-115, LCMS: Anal. Calcd. for C₄₈H₅₈N₁₀O₇ 886; found: 887 (M+H)⁺.

[1131] The following examples were prepared from intermediate 1e using a procedure analogous to Example 1. The appended cap is indicated in the Table and where no cap number is give the carboxylic acid was commercially available.

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Example	Compound Name	Structure	Cap	LCMS
ej-125	methyl ((1S)-2-((2S)-2-(5-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-1,2,3-triazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-yl)methyl)ethyl)-carbamate		128	LCMS: Anal. Calcd. for $C_{40}H_{44}N_{14}O_6$: 816; found: 817 (M + H) ⁺ .
ej-126	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-oxo-4,2-butanediyl)))biscarbamate		115	LCMS: Anal. Calcd. for $C_{38}H_{46}N_{10}O_6$ 710; found: 711 (M + H) ⁺ .

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Example	Compound Name	Structure	Cap	LCMS
cj-127	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((3R)-4-methyl-1-oxo-1,3-pentanediy)))-biscarbamate		116	LCMS: Anal. Calcd. for $C_{42}H_{34}N_8O_6$ 766; found: 777 (M + H) ⁺ .
cj-128	methyl ((1R)-3-((2S)-2-(5-(4'-((1-(3R)-3-((methoxycarbonyl)amino)-3-phenylpropanoyl))-2-pyrrolidinyl))-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-phenylpropyl)-carbamate		92	LCMS: Anal. Calcd. for $C_{48}H_{30}N_{10}O_6$ 834; found: 835 (M + H) ⁺ .

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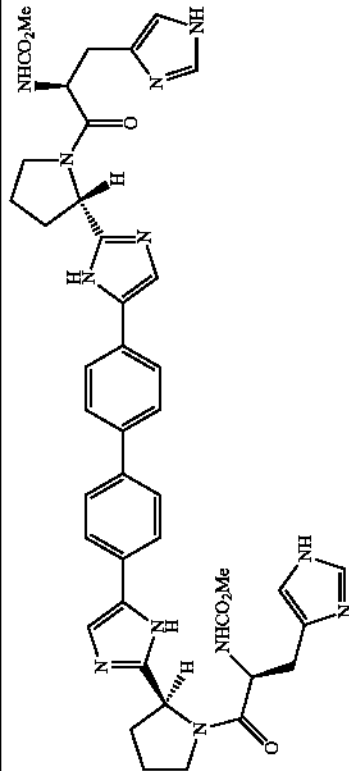
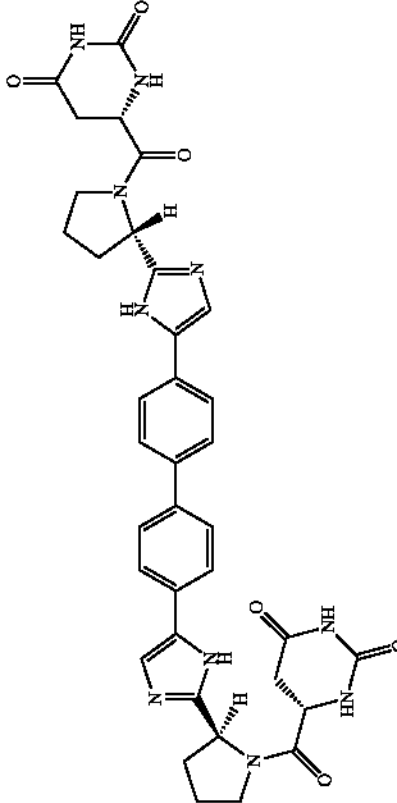
Example	Compound Name	Structure	Cap	LCMS
ej-129	methyl (1S)-2-((2S)-2-(5-(4-(2-(1-(3S)-3-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-phenylpropyl)-carbamate		91	LCMS: Anal. Calcd. for $C_{48}H_{50}N_{10}O_6$ 834; found: 835 (M + H) ⁺ .
ej-130	methyl (1S)-2-((2S)-2-(5-(4-(2-((2S)-1-(2S)-2-((methoxycarbonyl)amino)-3-(2-pyrrolidinyl)propanoyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)-ethyl)carbamate		93	LCMS: Anal. Calcd. for $C_{46}H_{46}N_{10}O_6$ 836; found: 837 (M + H) ⁺ .

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Example	Compound Name	Structure	Cap	LCMS
ej-131	methyl ((1S)-2-((2S)-2-(5-(4-(2-((2S)-1-(2S)-3-(1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl)carbamate		94	LCMS: Anal. Calcd. for C ₄₂ H ₄₆ N ₁₂ O ₆ 814; found: 815 (M + H) ⁺ .
ej-132	(6S,6S)-6,6'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl-carbonyl)dihydro-2,4(1H,3H)-pyrimidin-6-one		—	LCMS: Anal. Calcd. for C ₃₆ H ₃₆ N ₁₀ O ₆ 704; found: 705 (M + H) ⁺ .

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Example	Compound Name	Structure	Cap	LCMS
ej-133	(4 <i>S</i> ,5 <i>R</i> ,4' <i>S</i> ,5' <i>R</i>)- 4,4'-(4,4'- biphenyldiylbis(1 <i>H</i> - imidazole-5,2- diyl(2 <i>S</i>)-2,1- pyrrolidinediyl)- carbonyl))bis(5-methyl- 1,3-oxazolidin-2- one)		124	LCMS: Anal. Calcd. for C ₃₇ H ₄₀ N ₈ O ₅ 676; found: 677 (M + H) ⁺ .
ej-134	N-(3-(2 <i>S</i>)-2-(5-(4'- 2-((2 <i>S</i>)-1-(3- acetamidopropionoyl)- 2-pyrrolidiny)) 1 <i>H</i> -imidazol-5-yl)- 4-biphenyl)-1 <i>H</i> - imidazol-2-yl)-1- pyrrolidiny))3- oxopropyl)acetamide		—	LCMS: Anal. Calcd. for C ₃₆ H ₄₂ N ₈ O ₄ 650; found: 651 (M + H) ⁺ .

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Example	Compound Name	Structure	Cap	LCMS
ej-135	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S))-2,1-pyrrolidinediyl((3R)-1-oxo-5-phenyl-1,3-pentanediy)))-biscarbamate		95	LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_6$ 890; found: 890 (M + H) ⁺ .
ej-136	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S))-2,1-pyrrolidinediyl((2R)-4-oxo-1-(2-thienyl)-4,2-butanediyl))-biscarbamate		119	LCMS: Anal. Calcd. for $C_{46}H_{50}N_8O_6S_2$ 874; found: 875 (M + H) ⁺ .

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Example	Compound Name	Structure	Cap	LCMS
ej-137	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-(3-thienyl)-4,2-butanediyl)))biscarbamate		120	LCMS: Anal. Calcd. for $C_{46}H_{50}N_{10}O_6S_2$ 874; found: 875 (M + H) ⁺ .
ej-138	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-oxo-1-(2-thienyl)-4,2-butanediyl)))biscarbamate		118	LCMS: Anal. Calcd. for $C_{46}H_{50}N_{10}O_6S_2$ 874; found: 875 (M + H) ⁺ .

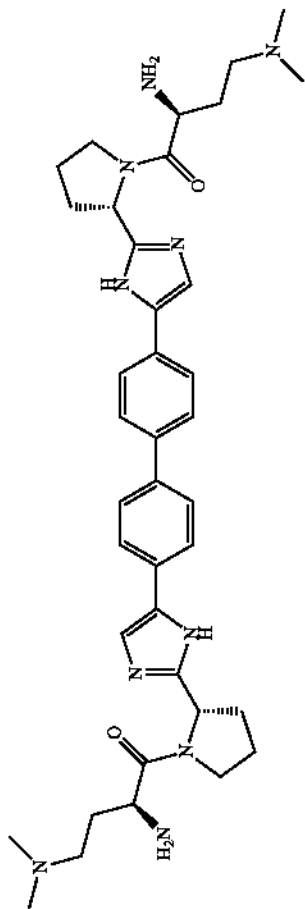
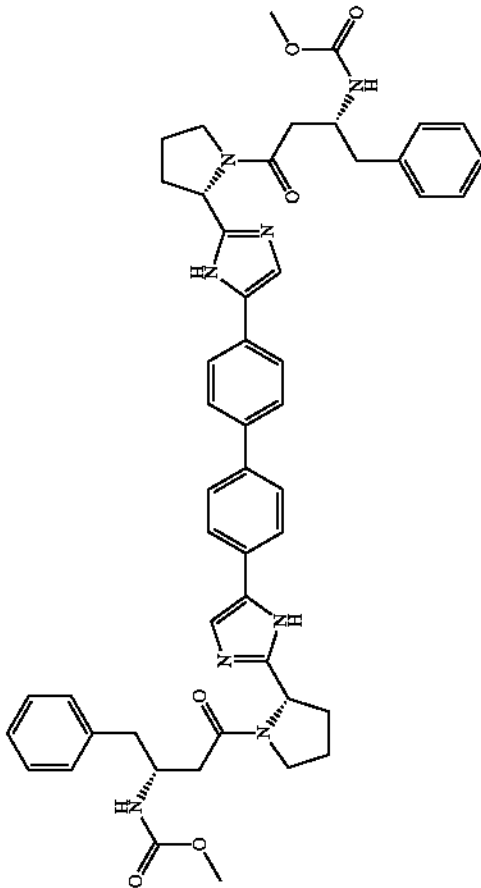
Example	Compound Name	Structure	Cap	LCMS
ej-139	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diy))((2S)-2,1-pyrrolidinediyl)-carbonyl(1R,2R)-2,1-cyclohexanediyl)bis-carbamate		97	LCMS: Anal. Calcd. for C ₄₄ H ₅₄ N ₉ O ₆ 790; found: 791 (M + H) ⁺ .
ej-140	di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diy))((2S)-2,1-pyrrolidinediyl)((2S)-4-(dimethylamino)-1-oxo-1,2-butenediyl)))-biscarbamate		125	LCMS: Anal. Calcd. for C ₄₈ H ₆₈ N ₁₀ O ₆ 880; found: 881 (M + H) ⁺ .
ej-141	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diy))((2S)-2,1-pyrrolidinediyl)-carbonyl(1R,2S)-2,1-cyclohexanediyl)bis-carbamate		98	LCMS: Anal. Calcd. for C ₄₄ H ₅₄ N ₉ O ₆ 790; found: 791 (M + H) ⁺ .

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Example	Compound Name	Structure	Cap size text	LCMS
ej-142	(3 <i>S</i> ,3' <i>S</i>)-4,4'-(4,4'-biphenyldiylbis(1 <i>H</i> -imidazole-5,2-diyl(2 <i>S</i>))-2,1-pyrrolidinediyl))bis((<i>N</i> -1- <i>n</i> -1--dimethyl-4-oxo-1,3-butanediylamine		see text	LCMS: Anal. Calcd. for C ₃₈ H ₅₂ N ₁₀ O ₂ 680; found: 681 (M + H) ⁺ .
ej-143	dimethyl (4,4'-biphenyldiylbis(1 <i>H</i> -imidazole-5,2-diyl(2 <i>S</i>))-2,1-pyrrolidinediyl)((2 <i>R</i>)-4-oxo-1-phenylbutanediyl))-biscarbamate		117	LCMS: Anal. Calcd. for C ₅₀ H ₅₄ N ₈ O ₆ 862; found: 863 (M + H) ⁺ .

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Example	Compound Name	Structure	Cap	LCMS
ej-144	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl-carbonyl(1R,3S)-3,1-cyclopentanediyl))bis-carbamate		99	LCMS: Anal. Calcd. for C ₄₂ H ₅₀ N ₈ O ₆ 762; found: 763 (M + H) ⁺ .
ej-145	methyl ((1R)-1-benzyl-2-((2S)-2-(5-(4-(2-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		101	LCMS: Anal. Calcd. for C ₄₈ H ₅₀ N ₈ O ₆ 834; found: 835 (M + H) ⁺ .

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Example	Compound Name	Structure	Cap	LCMS
ej-146	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-(dimethylamino)-1-oxo-1,2-butanediyl)))biscarbamate		see text	LCMS: Anal. Calcd. for C ₄₂ H ₅₀ N ₁₀ O ₆ 796; found: 797 (M + H) ⁺ .
ej-147	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)))bis(N,N-dimethyl-1-oxo-3-phenyl-2-propanamine)		90	LCMS: Anal. Calcd. for C ₄₈ H ₅₄ N ₈ O ₂ 774; found: 775 (M + H) ⁺ .
ej-148	methyl ((1S)-1-benzyl-2-((2S)-2-(5-(4-(2-((2S)-1-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidiny)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidiny)-2-oxoethyl)carbamate		102	LCMS: Anal. Calcd. for C ₄₈ H ₅₀ N ₈ O ₆ 834; found: 835 (M + H) ⁺ .

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Example	Compound Name	Structure	Cap	LCMS
ej-149	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)-carbonyl(1R,3S)-3,1-cyclopentanediy))bis-carbamate		99a	LCMS: Anal. Calcd. for C ₄₂ H ₅₀ N ₈ O ₆ 806; found: 807 (M + H) ⁺ .
ej-150	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)-carbonyl(1S,4,1-cyclohexanediy))bis-carbamate		104	LCMS: Anal. Calcd. for C ₄₄ H ₅₄ N ₈ O ₆ 790; found: 791 (M + H) ⁺ .
ej-151	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)-carbonyl(1R,3S)-3,1-cyclopentanediy))bis-carbamate		105	LCMS: Anal. Calcd. for C ₄₄ H ₅₄ N ₈ O ₆ 790; found: 791 (M + H) ⁺ .

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Example	Compound Name	Structure	Cap	LCMS
ej-152	(({4 <i>s</i> }-4,4'-(4,4'-biphenyldiylbis(1 <i>H</i> -imidazole-5,2-diyl(2 <i>S</i>))-2,1-pyrrolidinediyl)-carbonyl))bis(<i>N</i> , <i>N</i> -diethylethylhexanamine)		106	LCMS: Anal. Calcd. for C ₄₈ H ₅₆ N ₈ O ₂ 766; found: 777 (M + H) ⁺ .
ej-153	methyl ((1 <i>S</i>)-2-((2 <i>S</i>)-2-(5-(4'-((2 <i>S</i>)-1-((2 <i>S</i>)-2-(methoxycarbonyl)amino)-3-(1,3-thiazol-4-yl)propanoyl)-2-pyrrolidiny)-1 <i>H</i> -imidazol-5-yl)-4-biphenylyl)-1 <i>H</i> -imidazol-2-yl)-1-pyrrolidiny)-2-oxo-1-(1,3-thiazol-4-yl)methyl)ethyl)carbamate		107	LCMS: Anal. Calcd. for C ₄₂ H ₄₄ N ₁₀ O ₆ S ₂ 848; found: 849 (M + H) ⁺ .
ej-154	methyl ((1 <i>S</i>)-2-((2 <i>S</i>)-2-(5-(4'-((2 <i>S</i>)-1-((2 <i>S</i>)-3-(1-benzyl-1 <i>H</i> -imidazol-4-yl)-2-(methoxycarbonyl)amino)propanoyl)-2-pyrrolidiny)-1 <i>H</i> -imidazol-5-yl)-4-biphenylyl)-1 <i>H</i> -imidazol-2-yl)-1-pyrrolidiny)-1-((1-benzyl-1 <i>H</i> -imidazol-4-yl)methyl)carbamate		108	LCMS: Anal. Calcd. for C ₅₆ H ₅₈ N ₁₂ O ₆ 994; found: 995 (M + H) ⁺ .

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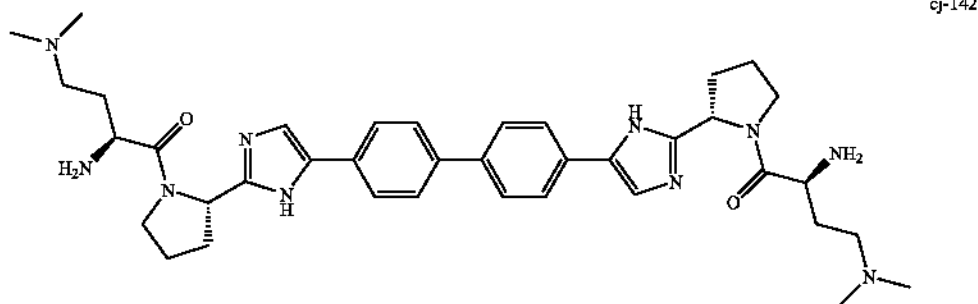
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Example	Compound Name	Structure	Cap	LCMS
ej-155	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)-carbonyl(1S,2S)-2,1-cyclopentanediyl))bis-carbamate		121	LCMS: Anal. Calcd. for $C_{42}H_{50}N_8O_6$ 762; found: 763 (M + H) ⁺ .
ej-156	methyl (1S)-3-methoxy-1-((2S)-2-(5-(4-(2-(2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoserinyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		87	LCMS: Anal. Calcd. for $C_{40}H_{50}N_8O_8$ 770; found: 771 (M + H) ⁺ .

Example cj-142

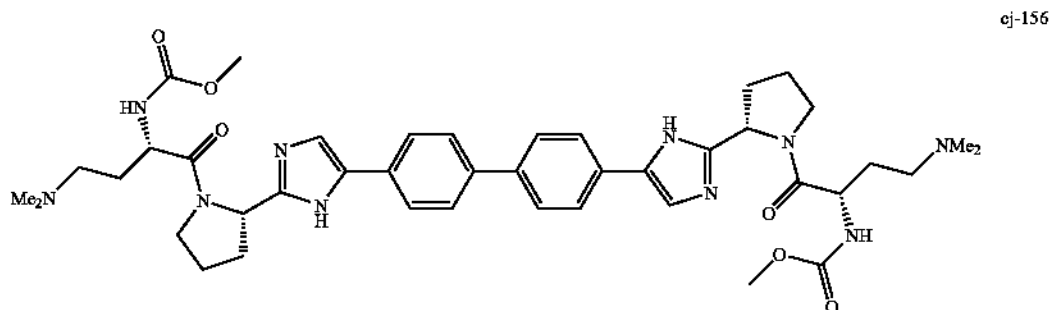
[1132]



[1133] Example cj-142 was prepared from the product obtained in Example cj-140 by treatment with 40% TFA in CH_2Cl_2 . The mixture was allowed to stir for 3 h at room temperature and then concentrated in vacuo. The residue was purified by prep HPLC (YMC-Pack, C18 30x100 mm, $\text{CH}_3\text{CN}-\text{H}_2\text{O}-\text{TFA}$).

Example cj-156

[1134]



[1135] The compound of Example-cj-156 was prepared by carbamoylation of the compound prepared in Example-cj-142 according to the method shown for Cap-51.

Section JG

[1136] Method A: LCMS—Xterra MS C-18 3.0x50 mm, 0 to 100% B over 30.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate.

[1137] Method B: HPLC—X-Terra C-18 4.6x50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA

[1138] Method C: HPLC—YMC C-18 4.6x50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.2% H_3PO_4 , B=90% methanol 10% water 0.2% H_3PO_4 .

[1139] Method D: HPLC—Phenomenex C-18 4.6x150 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold

time, A=10% methanol 90% water 0.2% H_3PO_4 , B=90% methanol 10% water 0.2% H_3PO_4

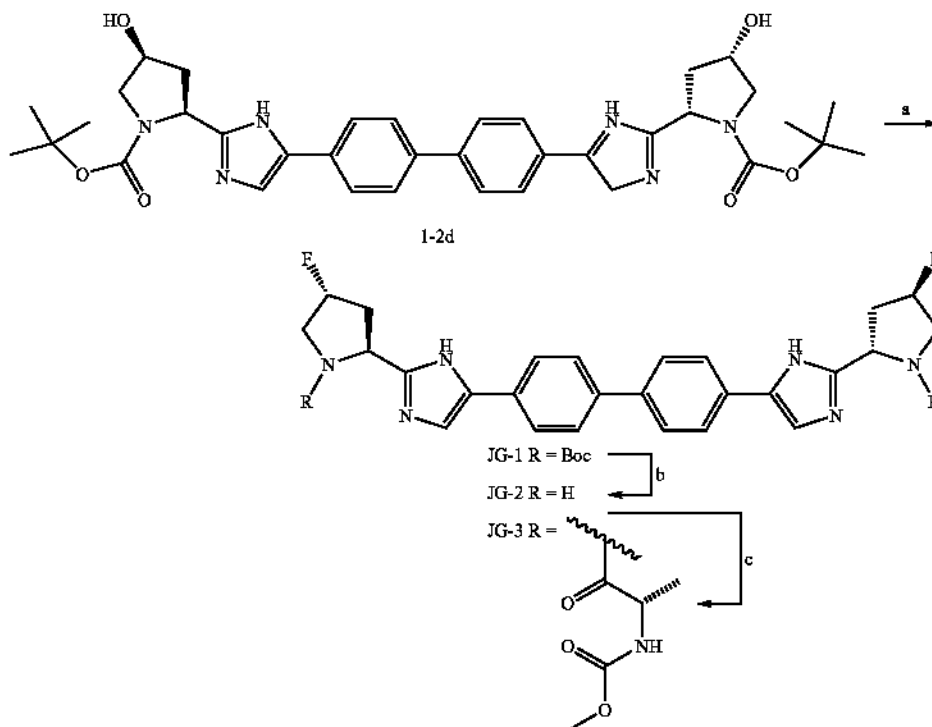
[1140] Method E: LCMS—Gemini C-18 4.6x50 mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate.

[1141] Method F: LCMS—Luna C-18 3.0x50 mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate.

[1142] Method G: HPLC—Phenomenex Gemini C-18 4.6x150 mm, 10 to 80% B over 35 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate

[1143] Method H: HPLC—Phenomenex Gemini C-18 4.6x150 mm, 10 to 80% B over 25 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate

[1144] Method J: HPLC—Waters-X-Bridge C-18 4.6×150 mm, 10 to 70% B over 30 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate



Step a:

[1145] (3S,3'S,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) (1.40 g, 2.13 mmol) was added as a solid to a solution of bis(2-methoxyethyl)aminosulfur trifluoride (0.87 mL, 4.69 mmol) in 14.0 mL CH₂Cl₂ cooled to -78° C. Reaction was stirred at -78° C. for two hours and then warmed to room temperature and stirred for 2 hours. Reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. Layers were separated and aqueous layer washed one time with CH₂Cl₂. Combined organics were washed with brine, dried (MgSO₄), filtered, and concentrated to give a yellow oil. The oil was triturated with CH₂Cl₂ and pentane to yield (3R,3'R,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-fluoropyrrolidine-1-carboxylate) JG-1 as a tan solid (0.98 g, 71%).

[1146] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 12.10 (2H, m) 7.60-7.82 (8H, m) 7.35 (2H, m) 5.45 (1H, s) 5.35 (1H, s) 4.85-4.90 (2H, m) 3.69-3.79 (4H, m) 2.53-2.61 (2H, m) 2.28-2.37 (2H, m) 1.40 (8H, s) 1.12 (10H, s)

[1147] LCMS—Phenomenex C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, (t_R=3.04 min) Anal Calcd. for C₃₆H₄₂F₂N₆O₄ 660.70; found 661.68 (M+H)⁺

Step b:

[1148] To a solution of (3R,3'R,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) (0.098 g, 1.48 mmol) in 4 mL dioxane was added 2.0 mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 4,4'-bis(2-((2S,4S)-4-fluoropyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride JG-2 (0.89 g, 100% yield). No further purification.

[1149] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 9.05 (2H, s), 8.18 (2H, s), 8.00-8.09 (4H, m) 7.89 (4H, d, J=7.63 Hz) 5.71 (1H, s) 5.61 (1H, s) 5.24-5.33 (2H, m) 3.92 (2H, d, J=10.68 Hz) 3.63-3.71 (2H, m) 2.79-2.89 (2H, m)

[1150] LCMS—Phenomenex C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA, (t_R=2.12 min) Anal Calcd. for C₂₆H₂₆F₂N₆ 460.53; found 461.37 (M+H)⁺

Step c:

[1151] To a stirred solution of 4,4'-bis(2-((2S,4R)-4-fluoropyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride (0.060 g, 0.10 mmol), (S)-2-(methoxycarbonylamino)propanoic acid (0.031 g, 0.21 mmol), and HATU

(0.081 g, 0.21 mmol) in 3 mL DMF was added diisopropylethylamine (0.11 mL, 0.61 mmol). The reaction was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The crude product was purified by reverse-phase preparative HPLC and secondly by passing it through a Waters MCX extraction cartridge to provide Dimethyl ((2S,2'S)-1,1'-((3R,3'R,5S,5'S)-5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-fluoropyrrolidine-5,1-diyl))bis(1-oxopropane-2,1-diyl)dicarbamate JG-3, free base (0.0097 g, 7.5%).

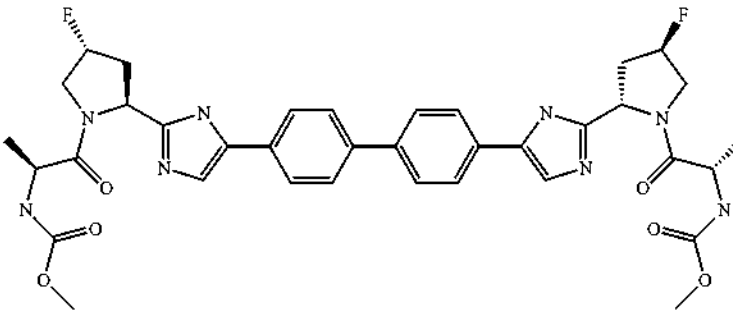
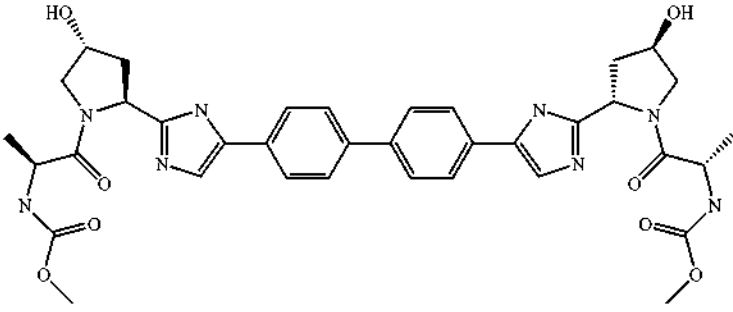
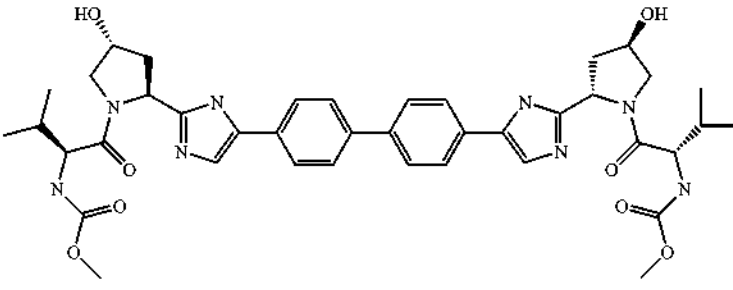
[1152] ^1H NMR (500 MHz, DMSO- d_6) δ ppm 11.91 (2H, m), 7.76-7.84 (3H, m), 7.64-7.84 (5H, m), 7.48-7.58 (2H, m),

5.55 (1H, s), 5.11 (1H, s), 4.29-4.38 (2H, m), 4.13 (2H, d, $J=12.51$ Hz), 3.89-3.98 (2H, m), 3.53 (6H, s), 2.54-2.64 4H, m), 1.21 (6H, s)

[1153] LCMS—Luna C-18 3.0×50 mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate, ($t_R=20.40$ min)

[1154] Nominal/LRMS—Calcd. for $\text{C}_{36}\text{H}_{40}\text{F}_2\text{N}_8\text{O}_6$ 718.30; found 719.24 (M+H) $^+$

[1155] Accurate/HRMS—Calcd. for $\text{C}_{36}\text{H}_{41}\text{F}_2\text{N}_8\text{O}_6$ 719.3117; found 719.3114 (M+H) $^+$

Structure	Compound Name	Data
<p>JG-3</p> 	<p>methyl ((1S)-2-((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate</p>	<p>RT = 13.60 min, method I LRMS: Anal. Calcd. for $\text{C}_{36}\text{H}_{40}\text{F}_2\text{N}_8\text{O}_6$ 718.30 found: 719.24 (M + H)$^+$ HRMS: Anal. Calcd. for $\text{C}_{36}\text{H}_{41}\text{F}_2\text{N}_8\text{O}_6$ 719.3117 found 719.3114 (M + H)$^+$</p>
<p>JG-4</p> 	<p>methyl ((1S)-2-((2S,4R)-4-hydroxy-2-(5-(4'-(2-((2S,4R)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate</p>	<p>RT = 9.27 min, method H LRMS: Anal. Calcd. for $\text{C}_{36}\text{H}_{42}\text{N}_8\text{O}_8$ 714.77 found: 715.33 (M + H)$^+$ HRMS: Anal. Calcd. for $\text{C}_{36}\text{H}_{43}\text{N}_8\text{O}_8$ 715.3204 found: 715.3186 (M + H)$^+$</p>
<p>JG-5</p> 	<p>methyl ((1S)-1-(((2S,4R)-4-hydroxy-2-(5-(4'-(2-((2S,4R)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate</p>	<p>RT = 15.08 min, method G LRMS: Anal. Calcd. for $\text{C}_{40}\text{H}_{50}\text{N}_8\text{O}_8$ 770.88 found: 771.76 (M + H)$^+$ HRMS: Anal. Calcd. for $\text{C}_{40}\text{H}_{51}\text{N}_8\text{O}_8$ 771.3830 found: 771.3798 (M + H)$^+$</p>

From 1-1e and Cap-12

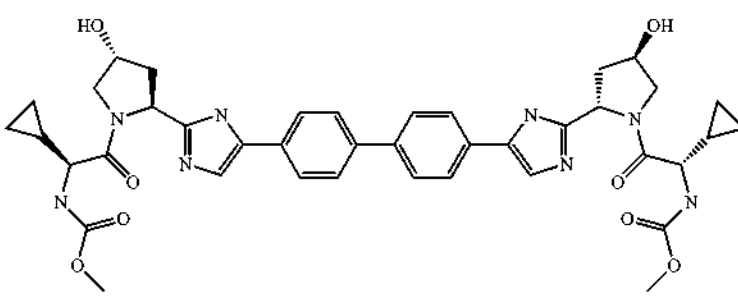
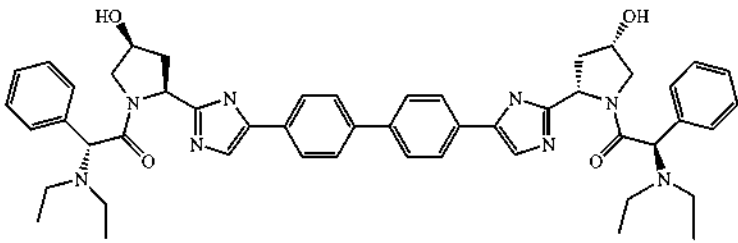
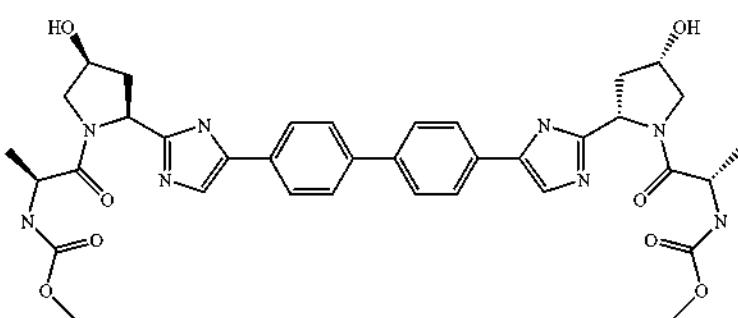
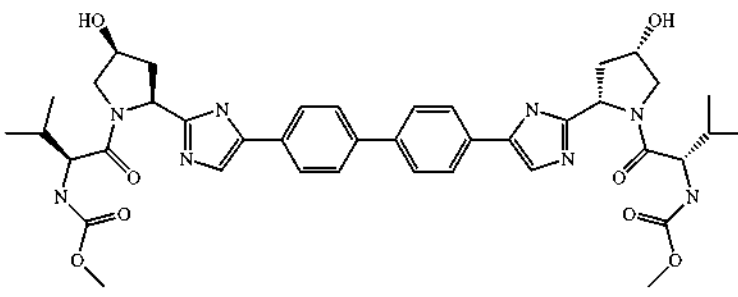
From 1-1e and Cap-51

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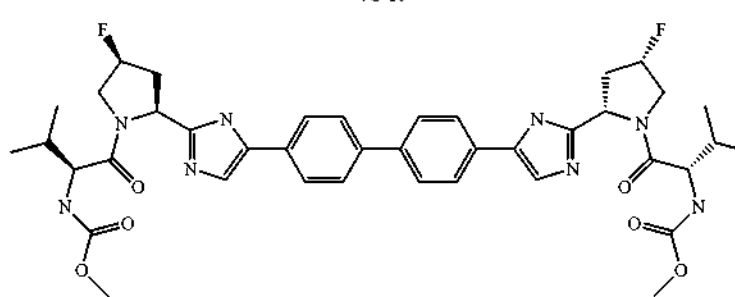
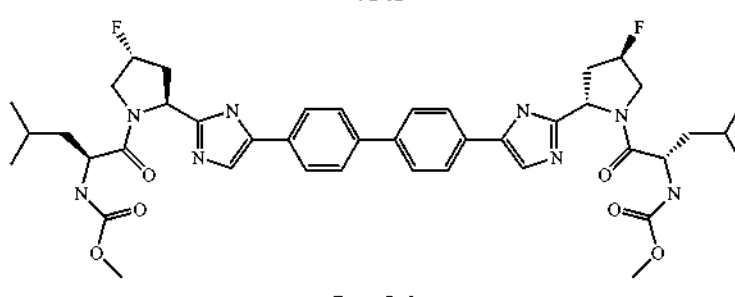
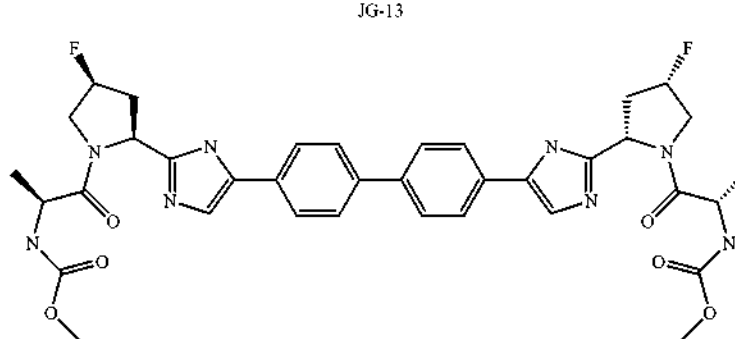
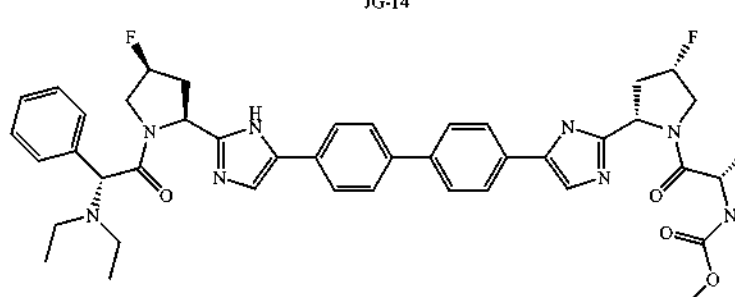
Structure	Compound Name	Data
<p>JG-6</p>  <p>From 1-1e and Cap-54b</p>	<p>dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl)-((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)-((1S)-1-cyclopropyl-2-oxo-2,1-ethane-diyl))biscarbamate</p>	<p>RT = 13.67 min, method G LRMS: Anal. Calcd. for C₄₀H₄₆N₈O₈ 766.85 found: 767.65 (M + H)⁺ HRMS: Anal. Calcd. for C₄₀H₄₇N₈O₈ 767.3517 found: 767.3483 (M + H)⁺</p>
<p>JG-7</p>  <p>From 1-2e and Cap-2</p>	<p>(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))-bis(1-((2R)-2-(diethylamino)-2-phenylacetyl)-3-pyrrolidinol)</p>	<p>RT = 15.88 min, method H LRMS: Anal. Calcd. for C₅₀H₅₈N₈O₄ 834.45 found: 835.38 (M + H)⁺ HRMS: Anal. Calcd. for C₅₀H₅₉N₈O₄ 835.4659 found: 835.4627 (M + H)⁺</p>
<p>JG-8</p>  <p>From 1-2e and Cap-52</p>	<p>methyl ((1S)-2-((2S,4S)-4-hydroxy-2-(5-(4'-(2-((2S,4S)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate</p>	<p>RT = 9.99 min, method H LRMS: Anal. Calcd. for C₃₆H₄₂N₈O₈ 714.77 found: 715.71 (M + H)⁺ HRMS: Anal. Calcd. for C₃₆H₄₃N₈O₈ 715.3204 found: 715.3188 (M + H)⁺</p>
<p>JG-9</p>  <p>From 1-2e and Cap-51</p>	<p>methyl ((1S)-1-(((2S,4S)-4-hydroxy-2-(5-(4'-(2-((2S,4S)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)-amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate</p>	<p>RT = 14.12 min, method H LRMS: Anal. Calcd. for C₄₀H₅₀N₈O₈ 770.88 found: 771.74 (M + H)⁺ HRMS: Anal. Calcd. for C₄₀H₅₁N₈O₈ 771.3830 found: 771.3799 (M + H)⁺</p>

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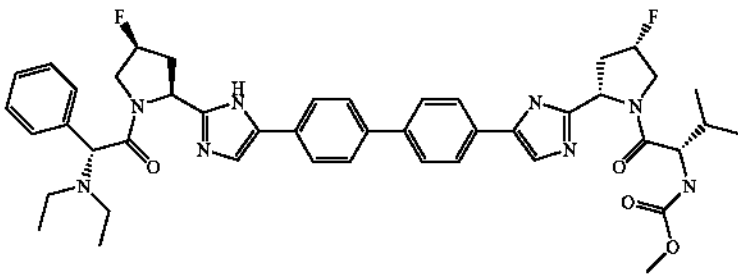
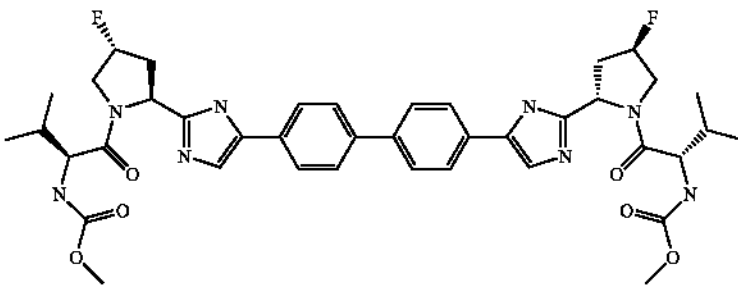
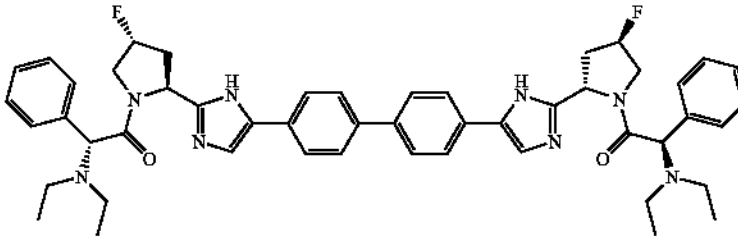
Structure	Compound Name	Data
<p>JG-10</p>  <p>From 1-2e2 and Cap-51</p>	<p>methyl ((1S)-1-(((2S,4S)-4-fluoro-2-(5-(4'-((2S,4S)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate</p>	<p>RT = 17.66 min, method I LRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_6$ 774.86 found: 775.49 (M + H)⁺ HRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_6$ 775.3743 found: 775.3717 (M + H)⁺</p>
<p>JG-12</p>  <p>From (S)-2-(methoxycarbonylamino)-4-methylpentanoic acid and JG-2</p>	<p>methyl ((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-((2S,4R)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)carbamate</p>	<p>RT = 9.69 min, method I LRMS: Anal. Calcd. for $C_{42}H_{52}F_2N_8O_6$ 802.92 found: 803.42 (M + H)⁺ HRMS: Anal. Calcd. for $C_{42}H_{52}F_2N_8O_6$ 803.4056 found: 803.4018 (M + H)⁺</p>
<p>JG-13</p>  <p>From 1-2e2 and Cap-52</p>	<p>methyl ((1S)-2-(((2S,4S)-4-fluoro-2-(5-(4'-((2S,4S)-4-fluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate</p>	<p>RT = 13.60 min, method I LRMS: Anal. Calcd. for $C_{36}H_{40}F_2N_8O_6$ 718.30 found: 719.45 (M + H)⁺ HRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.3117 found: 719.3090 (M + H)⁺</p>
<p>JG-14</p>  <p>From JG-25 and Cap-52</p>	<p>methyl ((1S)-2-(((2S,4S)-2-(5-(4'-((2S,4S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4-fluoro-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-4-fluoro-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate</p>	<p>RT = 15.13 min, method I LCMS: Anal. Calcd. for $C_{43}H_{48}F_2N_8O_4$ 778.91 found: 779.79 (M + H)⁺</p>

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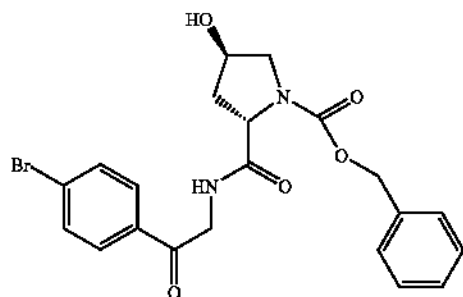
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Structure	Compound Name	Data
<p>JG-15</p>  <p>From JG-25 and Cap-51</p>	<p>methyl ((1S)-1-(((2S,4S)-2-(5-(4'-((2S,4S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4-fluoro-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-4-fluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate</p>	<p>RT = 17.51 min, method I LCMS: Anal. Calcd. for $C_{45}H_{52}F_2N_8O_4$ 806.96 found: 807.50 (M + H)⁺</p>
<p>JG-16</p>  <p>From JG-2 and Cap-51</p>	<p>methyl ((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-((2S,4R)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate</p>	<p>RT = 16.51 min, method I LRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_6$ 774.86 found: 775.39 (M + H)⁺ HRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_6$ 775.3743 found: 775.3740 (M + H)⁺</p>
<p>JG-17</p>  <p>From JG-2 and Cap-2</p>	<p>((1R,1'R)-2,2'-(4,4'-biphenyl)diylbis(1H-imidazole-5,2-diyl((2S,4R)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethylamine)</p>	<p>RT = 8.13 min, method I LCMS: Anal. Calcd. for $C_{50}H_{56}F_2N_8O_2$ 839.04 found: 839.46 (M + H)⁺ HRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.4572 found: 839.4543 (M + H)⁺</p>

Synthesis of JG-18 as in Example 28 Step a Using Hydroxyproline in Place of Proline

[1156]



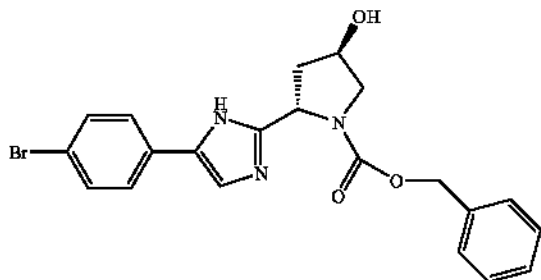
JG-18

[1157] ^1H NMR (500 MHz, DMSO- d_6) δ ppm 7.89 (2H, t, $J=8.39$ Hz) 7.74 (2H, t, $J=8.24$ Hz) 7.28-7.37 (5H, m) 5.01-5.08 (3H, m) 4.27-4.57 (4H, m) 3.44-3.53 (1H, m) 3.37 (1H, d, $J=10.99$ Hz) 2.12 (1H, d, $J=11.60$ Hz) 1.93 (1H, dd, $J=12.05$ Hz, 6.56 Hz)

[1158] LCMS—Phenomenex C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate, $t_R=3.62$ min, Anal. Calcd. for $\text{C}_{21}\text{H}_{21}\text{BrN}_2\text{O}_5$ 461.32; found 462.64 (M+H) $^+$.

Synthesis of JG-19 from JG-18 as in Example 28 Step b

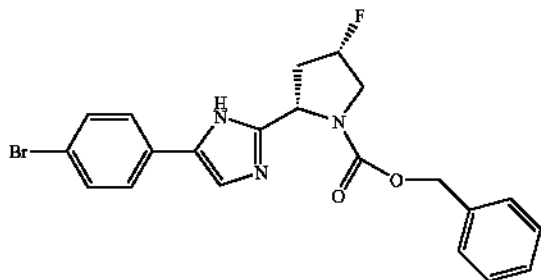
[1159]



JG-19

[1160] LCMS—Luna C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate, $t_R=1.88$ min, Anal. Calcd. for $\text{C}_{21}\text{H}_{20}\text{BN}_2\text{O}_3$ 441.07; found 442.22 (M+H) $^+$.

JG-20

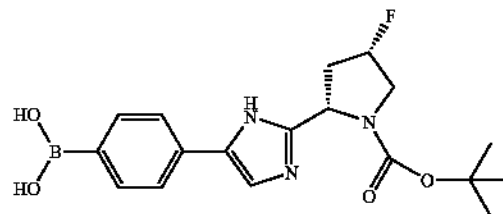


[1161] (2S,4R)-benzyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (1.5 g, 3.4 mmol) was added as a solid to a solution of bis(2-methoxyethyl)aminosulfur trifluoride (0.98 mL, 5.1 mmol) in 15 mL CH_2Cl_2 cooled to -78°C . Reaction was stirred at -78°C for two hours and then warmed to room temperature and stirred for 2 hours. Reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. Layers were separated and aqueous layer washed one time with CH_2Cl_2 . Combined organics were washed with brine, dried (MgSO_4), filtered, and concentrated to give a yellow oil. The oil was triturated with CH_2Cl_2 and pentane to yield (2S,4S)-benzyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-4-fluoropyrrolidine-1-carboxylate JG-20 as a yellow solid (0.96 g, 62%).

[1162] ^1H NMR (500 MHz, DMSO- d_6) δ ppm 7.70 (2H, d, $J=7.02$ Hz) 7.48-7.55 (3H, m) 7.41-7.35 (3H, m) 7.19-7.11 (2H, m) 5.15-5.02 (3H, m) 3.84-3.78 (2H, m) 3.33 (2H, s) 2.53-2.61 (1H, m) 2.33-2.42 (1H, m)

[1163] LCMS—Luna C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate, $t_R=2.10$ min, Anal. Calcd. for $\text{C}_{21}\text{H}_{19}\text{BrF}_1\text{N}_3\text{O}_2$ 443.06; found 444.05 (M+H) $^+$.

JG-21



[1164] (2S,4R)-tert-butyl 4-hydroxy-2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate, 1-2c (1.5 g, 3.3 mmol) was added as a solid to a solution of bis(2-methoxyethyl)aminosulfur trifluoride (0.91 mL, 5.0 mmol) in 15 mL CH_2Cl_2 cooled to -78°C . Reaction was stirred at -78°C for two hours and then warmed to room temperature and stirred for 2 hours. Reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. Layers were separated and aqueous layer washed one time with CH_2Cl_2 . Combined organics were washed with brine, dried (MgSO_4), filtered, and concentrated to give a brown oil. The oil was chromatographed on silica gel with 5% MeOH/ CH_2Cl_2 to yield 4-(2-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidin-2-yl)-1H-imidazol-5-yl)phenylboronic acid as a tan solid (0.46 g, 37%).

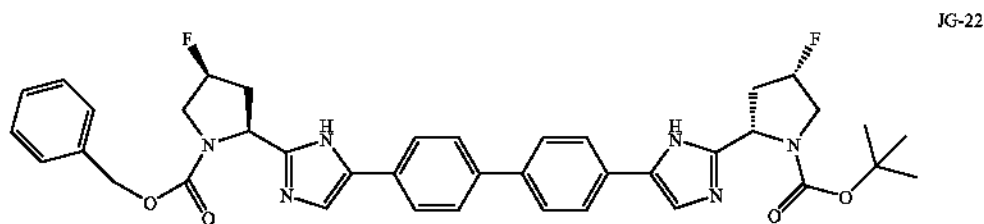
[1165] LCMS—Luna C-18 3.0x50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate, $t_R=1.46$ min, Anal. Calcd. for $\text{C}_{18}\text{H}_{23}\text{B}_1\text{F}_1\text{N}_3\text{O}_4$ 375.18; found 376.12 (M+H) $^+$.

[1166] JG-22 is synthesized from JG-20 and JG-21 as described in Example 28 step c.

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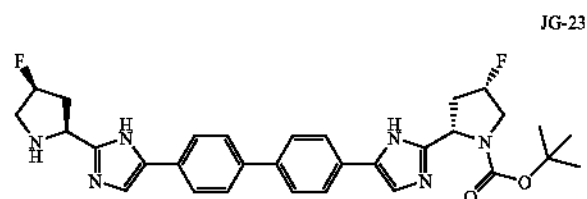
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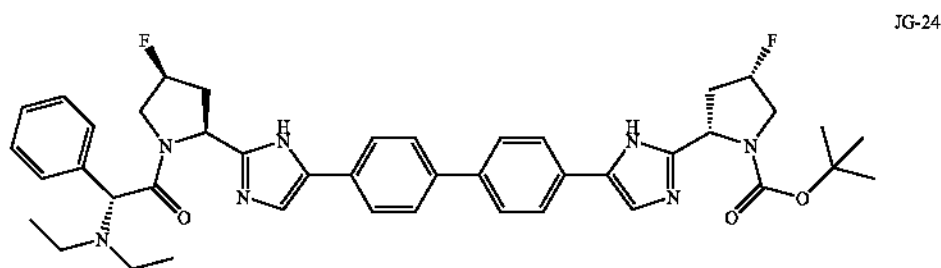
[1167] LCMS—Luna C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mM ammonium acetate, B=95% acetonitrile, 5% water, 10 mM ammonium acetate, t_R =2.27 min, Anal. Calcd. for $C_{39}H_{40}F_2N_6O_4$ 694.31; found 695.35 (M+H)⁺

[1168] JG-23 is synthesized from JG-22 as described in Example 28 step d.



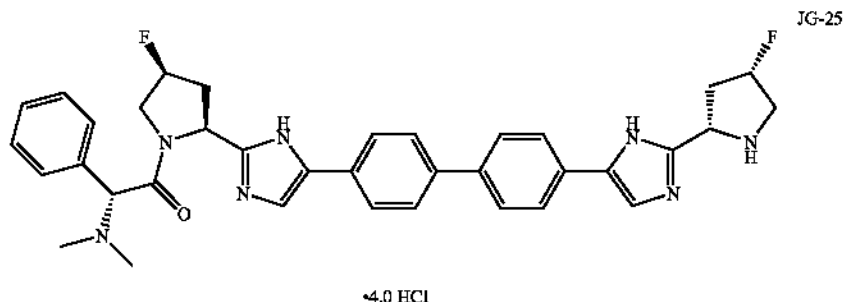
[1169] LCMS—Phenomenex C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=10% methanol 90% water 0.1% TFA, B=90% methanol 10% water 0.1% TFA mobile phase, t_R =2.62 min, Anal. Calcd. for $C_{31}H_{34}F_2N_6O_2$ 560.27; found 561.52 (M+H)⁺

[1170] JG-24 is synthesized from JG-22 and Cap-2 as in Example 28 step e.



[1171] LCMS—Luna C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mM ammonium acetate, B=95% acetonitrile, 5% water, 10 mM ammonium acetate, t_R =2.30 min, Anal. Calcd. for $C_{41}H_{45}F_2N_7O_3$ 721.36; found 722.42 (M+H)⁺

[1172] JG-25 is synthesized from JG-24 via reaction with methanolic HCl as described in Example LS14 step b.



[1173] LCMS—Luna C-18 3.0×50 mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A=5% acetonitrile, 95% water, 10 mm ammonium acetate, B=95% acetonitrile, 5% water, 10 mm ammonium acetate, t_R =1.98 min, Anal. Calcd. for $C_{36}H_{37}F_2N_7O_1$ 621.30; found 622.48 (M+H)⁺

Section OL LC Conditions:

[1174] Condition 1: Solvent A: 5% acetonitrile/95% water/10 mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10 mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6×5.0 mm; Wavelength: 220 nm; Flow rate: 4 ml/min; 0% B to 100% B over 3 min with a 1 min hold time.

[1175] Condition 2: Solvent A: 5% acetonitrile/95% water/10 mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10 mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6×5.0 mm; Wavelength: 220 nm; Flow rate: 4 ml/min; 0% B to 100% B over 2 min with a 1 min hold time.

[1176] Condition 3: Solvent A: 5% acetonitrile/95% water/10 mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10 mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6×5.0 mm; Wavelength: 220 nm; Flow rate: 4 ml/min; 0% B to 100% B over 4 min with a 1 min hold time.

[1177] Condition 4: Solvent A: 10% MeOH/90% water/0.1% TFA; Solvent B: 90% MeOH/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0×5.0 mm; Wavelength: 220 nm; Flow rate: 4 ml/min; 0% B to 100% B over 4 min with a 1 min hold time.

[1178] Condition 5: Solvent A: 5% acetonitrile/95% water/10 mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10 mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6×5.0 mm; Wavelength: 220 nm; Flow rate: 4 ml/min; 0% B to 100% B over 9 min with a 1 min hold time.

[1179] Condition 6: Solvent A: 10% MeOH/90% water/0.2% H_3PO_4 ; Solvent B: 90% MeOH/10% water/0.2% H_3PO_4 ; Column: Phenomenex 5u C-18 4.6×50 mm; Wavelength: 220 nm; Flow rate: 1.5 ml/min; 0% B to 100% B over 14 min with a 3 min hold time.

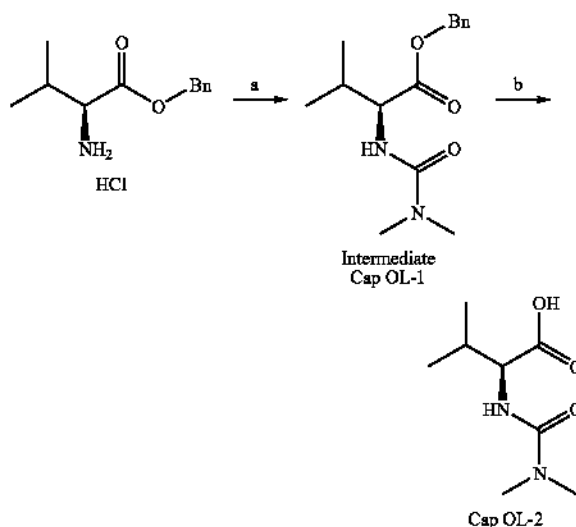
[1180] Condition 7: Solvent A: 10% MeOH/90% water/0.1% TFA; Solvent B: 90% MeOH/10% water/0.1% TFA; Col-

umn: Phenomenex 10u C18 3.0×5.0 mm; Wavelength: 220 nm; Flow rate: 4 ml/min; 0% B to 100% B over 3 min with a 1 min hold time.

[1181] Condition 8: Solvent A: 10% MeOH/90% water/0.1% TFA; Solvent B: 90% MeOH/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0×5.0 mm; Wavelength: 220 nm; Flow rate: 4 ml/min; 0% B to 100% B over 2 min with a 1 min hold time.

Experimentals Caps:

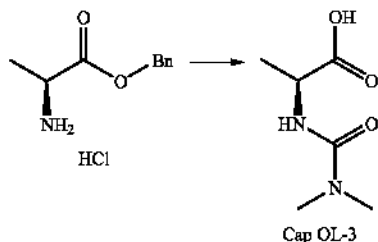
[1182]



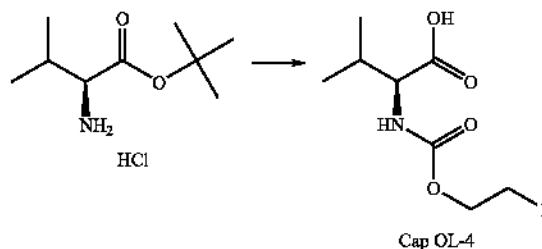
[1183] Step a: Dimethylcarbamoyl chloride (0.92 mL, 10 mmol) was added slowly to a solution of (S)-benzyl 2-amino-3-methylbutanoate hydrochloride (2.44 g; 10 mmol) and Hunig's base (3.67 mL, 21 mmol) in THF (50 mL). The resulting white suspension was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure.

The resulting yellow oil was purified by flash chromatography, eluting with ethyl acetate:hexanes (1:1). Collected fractions were concentrated under vacuum providing 2.35 g (85%) of Intermediate Cap OL-1 as a clear oil. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 0.84 (d, $J=6.95$ Hz, 3H) 0.89 (d, $J=6.59$ Hz, 3H) 1.98-2.15 (m, 1H) 2.80 (s, 6H) 5.01-5.09 (m, $J=12.44$ Hz, 1H) 5.13 (d, $J=12.44$ Hz, 1H) 6.22 (d, $J=8.05$ Hz, 1H) 7.26-7.42 (m, 5H). LC (Cond. 1): RT=1.76 min; MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3$: 279.17; found 279.03.

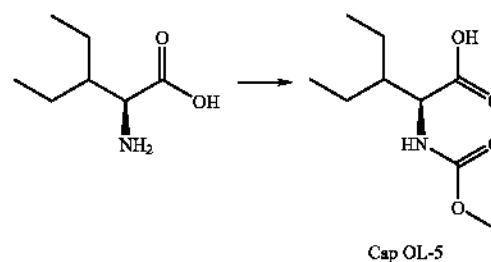
[1184] Step b: To Intermediate Cap OL-1 (2.35 g; 8.45 mmol) in 50 ml MeOH was added Pd/C (10%; 200 mg) and the resulting black suspension was flushed with N_2 (3 \times) and placed under 1 atm of H_2 . The mixture was stirred at room temperature overnight and filtered through a microfiber filter to remove the catalyst. The resulting clear solution was then concentrated under reduced pressure to obtain 1.43 g (89%) of Cap OL-2 as a white foam, which was used without further purification. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 0.87 (d, $J=4.27$ Hz, 3H) 0.88 (d, $J=3.97$ Hz, 3H) 1.93-2.11 (m, 1H) 2.80 (s, 6H) 3.90 (dd, $J=8.39, 6.87$ Hz, 1H) 5.93 (d, $J=8.54$ Hz, 1H) 12.36 (s, 1H). LC (Cond. 1): RT=0.33 min; MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_8\text{H}_{17}\text{N}_2\text{O}_3$: 189.12; found 189.04.



[1185] Cap OL-3 was prepared from (S)-benzyl 2-amino-3-methylbutanoate hydrochloride according to the method described for Cap OL-2. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 1.27 (d, $J=7.32$ Hz, 3H) 2.80 (s, 6H) 4.06 (qt, 1H) 6.36 (d, $J=7.32$ Hz, 1H) 12.27 (s, 1H). LC (Cond. 1): RT=0.15 min; MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_6\text{H}_{13}\text{N}_2\text{O}_3$: 161.09; found 161.00.



[1186] Cap OL-4 was prepared from (S)-tert-butyl 2-amino-3-methylbutanoate hydrochloride and 2-fluoroethyl chloroformate according to the method described for Cap-47. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 0.87 (t, $J=6.71$ Hz, 6H) 1.97-2.10 (m, 1H) 3.83 (dd, $J=8.39, 5.95$ Hz, 1H) 4.14-4.18 (m, 1H) 4.20-4.25 (m, 1H) 4.50-4.54 (m, 1H) 4.59-4.65 (m, 1H) 7.51 (d, $J=8.54$ Hz, 1H) 12.54 (s, 1H)



[1187] Cap OL-5 was prepared from (S)-diethyl alanine and methyl chloroformate according to the method described for Cap-51. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 0.72-0.89 (m, 6H) 1.15-1.38 (m, 4H) 1.54-1.66 (m, 1H) 3.46-3.63 (m, 3H) 4.09 (dd, $J=8.85, 5.19$ Hz, 1H) 7.24 (d, $J=8.85$ Hz, 1H) 12.55 (s, 1H). LC (Cond. 2): RT=0.66 min; MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_9\text{H}_{18}\text{NO}_4$: 204.12; found 204.02.

New Examples

[1188] The following analogs were prepared from 1e in similar fashion to the preparation of Example 1 and employing the appropriate Cap.

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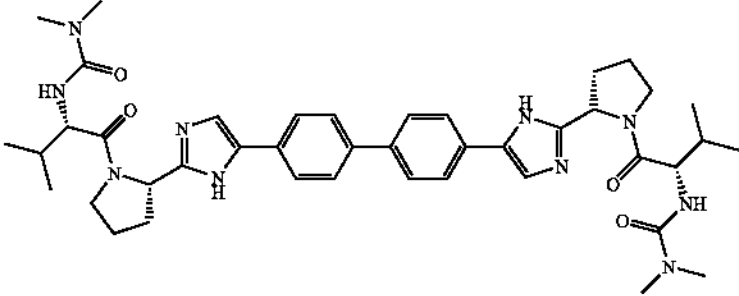
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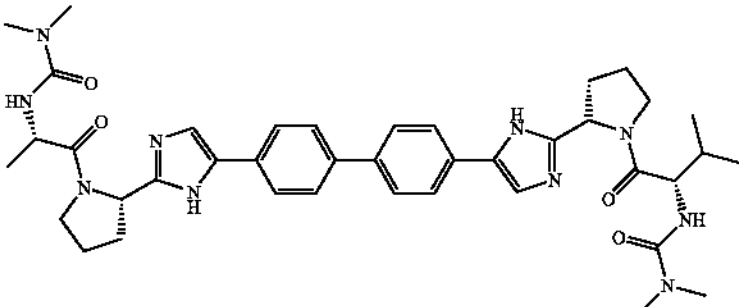
OL-1 3-(((1S)-1-(((2S)-2-(4-(4'-
(2-(((2S)-1-((2S)-2-
((dimethylcarbamoyl)-
amino)-3-methyl-
butanoyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-1H-imidazol-
2-yl)-1-
pyrrolidinyl)carbonyl)-2-
methylpropyl)-1,1-
dimethylurea



LC/MS: 2.16 min
(Cond'n 3);
Anal. Calcd. for
[M + H]⁺
C₄₂H₅₇N₁₀O₄:
765.45; found
765.47.

From 1e and Cap OL-2

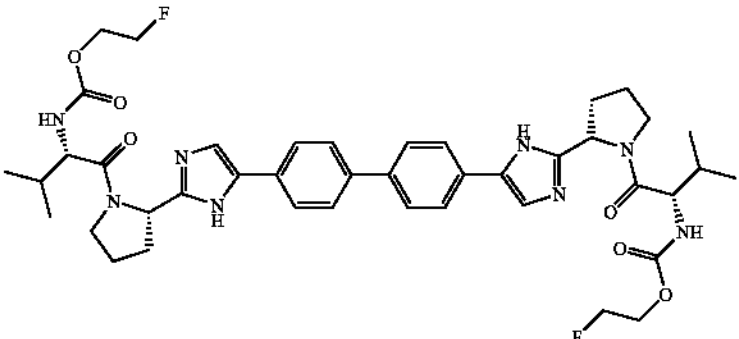
OL-2 3-(((1S)-2-(((2S)-2-(4-(4'-
(2-(((2S)-1-(N-
(dimethylcarbamoyl)-L-
alanyl)-2-pyrrolidinyl)-
1H-imidazol-4-yl)-4-
biphenyl)-1H-imidazol-
2-yl)-1-pyrrolidinyl)-1-
methyl-2-oxoethyl)-1,1-
dimethylurea



LC/MS: 1.86 min
(Cond'n 3);
Anal. Calcd. for
[M + H]⁺
C₃₈H₄₉N₁₀O₄:
709.39; found
709.43.

From 1e and Cap OL-3

OL-3 2-fluoroethyl (((1S)-1-
(((2S)-2-(4-(4'-
(2-(((2S)-1-
(2S)-2-(((2-
fluoroethoxy)carbonyl)-
amino)-3-
methylbutanoyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-1H-imidazol-
2-yl)-1-
pyrrolidinyl)carbonyl)-2-
methylpropyl)carbamate

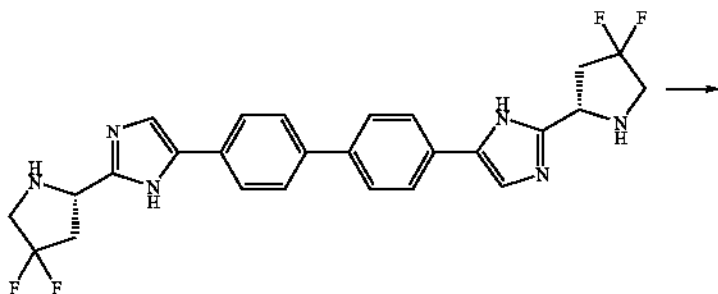


LC/MS: 2.83 min
(Cond'n 4);
Anal. Calcd. for
[M + H]⁺
C₄₂H₅₃F₂N₈O₆:
803.40; found
803.47.

From 1e and Cap OL-4

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
OL-4	methyl (((1S)-2-ethyl-1-((2S)-2-(4-(4'-((2S)-1-((2S)-3-ethyl-2-((methoxycarbonyl)-amino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-butyl)carbamate		LC/MS: 2.64 min (Cond'n 3); Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₉ N ₉ O ₆ : 795.45; found 795.48.
		From 1e and Cap OL-5	
OL-5	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-butane-diyl)))dihydro-2(1H)-pyrimidinone		LC/MS: 2.95 min (Cond'n 4); Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₇ N ₁₀ O ₆ : 789.46; found 789.52.
		From 1e and (S)-3-methyl-2-(2-oxotetrahydropyrimidin-1(2H)-yl)butanoic acid	
OL-6	methyl (((1S)-1-(((2S)-2-(4-(4'-((2S)-1-((2S)-2-((methoxycarbonyl)-amino)-4-methyl-pentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)carbamate		LC/MS: 2.95 min (Cond'n 3); Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₃ N ₈ O ₆ : 767.42; found 767.43.
		From 1e and (S)-2-(methoxycarbonylamino)-4-methylpentanoic acid which was prepared from L-Isoleucine and methylchloroformate in similar fashion to the preparation of Cap-51	

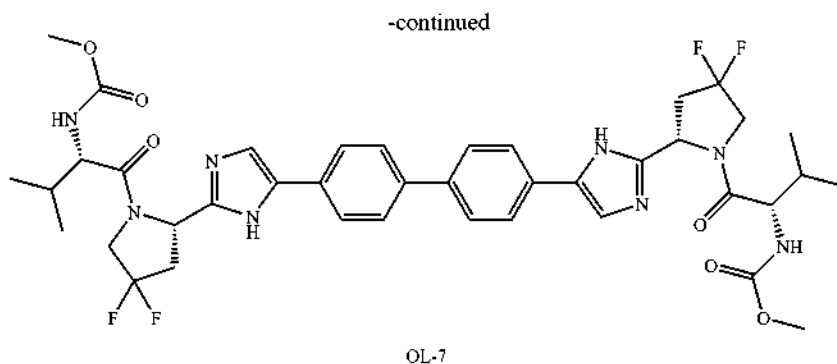


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Example OL-7

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1189] Example OL-7 was prepared from 1-2e-3 in similar fashion to the preparation of Example 1, using Cap-51 as the coupling partner. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.80

(dd, J=6.41, 2.44 Hz, 12H) 1.87-1.98 (m, 2H) 2.79-2.91 (m, 2H) 3.01-3.13 (m, 2H) 3.54 (s, 6H) 3.98 (t, J=7.93 Hz, 2H) 4.22-4.37 (m, 2H) 4.52 (t, J=14.19 Hz, 2H) 5.31 (t, J=8.39 Hz, 2H) 7.50 (d, J=7.93 Hz, 2H) 7.82-7.87 (m, 4H) 7.88-7.97 (m, 6H) 8.08 (s, 2H). LC (Cond'n 6): 7.64 min; MS: Anal. Calcd. for [M+H]⁺ C₄₀H₄₇F₄N₈O₆: 811.35; found 811.46. HRMS: Anal. Calcd. for (M+H)⁺ C₄₀H₄₇F₄N₈O₆ 811.3549 found 811.3553.

[1190] The following analogs were prepared from 1-2e-3 in similar fashion to the preparation of Example 1 and employing the appropriate Cap.

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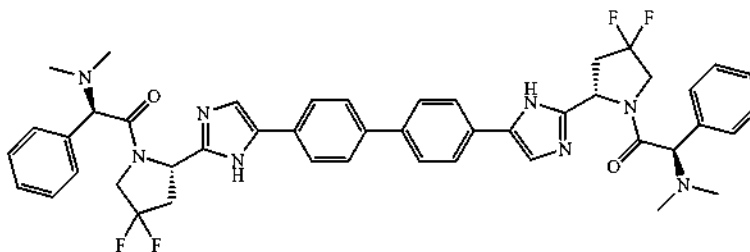
Compound Name

Structure

Analytical Data

OL-8

((1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

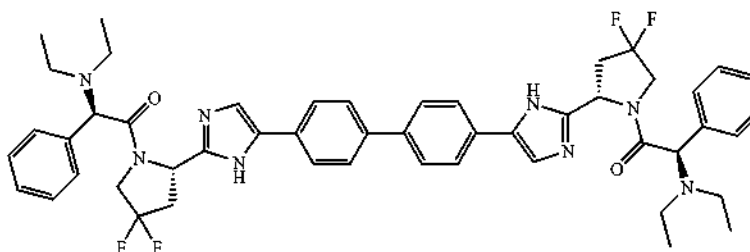


From 1-2e-3 and Cap-1

LC/MS: 3.98 min (Cond'n 5); Anal. Calcd. for [M+H]⁺ C₄₆H₄₇F₄N₈O₂: 819.37; found 819.78.

OL-9

((1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine)



From 1-2e-3 and Cap-2

LC/MS: 4.58 min (Cond'n 5); Anal. Calcd. for [M+H]⁺ C₅₀H₅₅F₄N₈O₂: 875.449; found 875.90.

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
OL-10	methyl ((1S,2R)-1-(((2S)-2-(4-(4'-(2-(2S)-4,4-difluoro-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methoxy propyl)-carbamate		LC/MS: 2.18 min (Cond'n 7); Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₇ F ₄ N ₈ O ₈ : 843.84; found 844.04.
		From 1-2e-3 and Cap-86	
OL-11	methyl ((1S)-2-((2S)-2-(4-(4'-(2-(2S)-4,4-difluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LC/MS: 2.04 min (Cond'n 7); Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₃₉ F ₄ N ₈ O ₆ : 755.29; found 755.78.
		From 1-2e-3 and Cap-52	

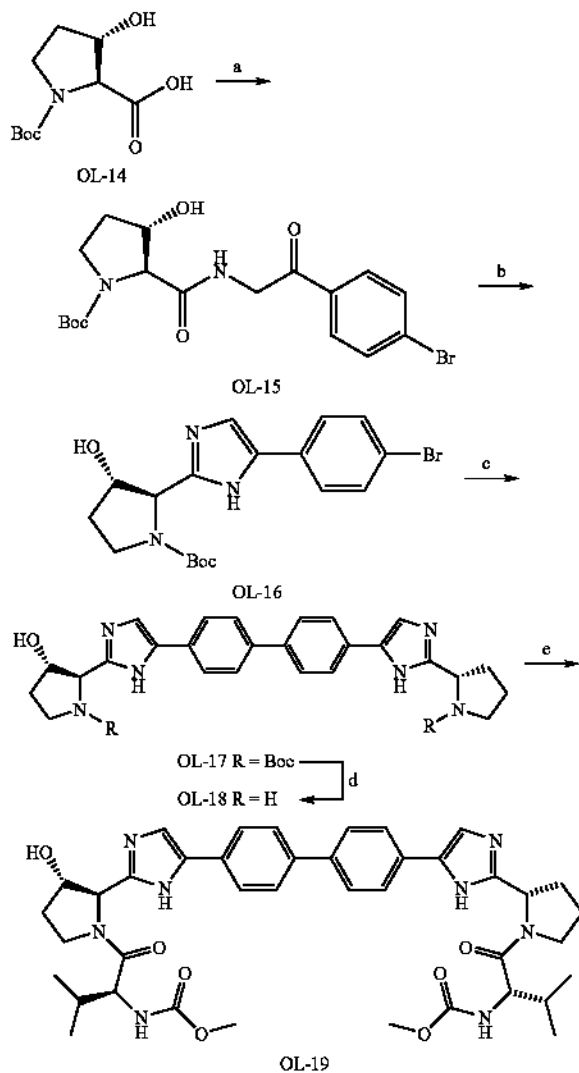
[1191] The following analogs were prepared from 1-3e in similar fashion to the preparation of Example 1 and employing the appropriate Cap.

Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
OL-12	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-(2S)-4,4-difluoro-1-(2S)-2-((methoxycarbonyl)-amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-carbonyl)-2-methylpropyl)-carbamate		LC/MS: 2.33 min (Cond'n 3); Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₉ F ₂ N ₈ O ₂ : 775.37; found 775.37.
		From 1-3e and Cap-51	

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
OL-13	rac-(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4,4-difluoro-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine		LC/MS: 3.93 min (Cond'n 5); Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₇ F ₂ N ₈ O ₂ : 839.40; found 839.93.
		From 1-3e and Cap-2	

Example OL-19



methyl ((1S)-1-(((2R,3S)-3-hydroxy-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl)carbamate

[1192] Step a: Intermediate OL-15 was prepared in similar fashion as intermediate 1a, where N-Boc-L-proline was substituted for N-Boc-trans-3-hydroxy-L-proline. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.34/1.4 (2 br. s., 9H) 1.65-1.77 (m, 1H) 1.83-1.95 (m, 1H) 3.33-3.42 (m, 1H) 3.43-3.51 (m, 1H) 3.96-4.07 (m, 1H) 4.16 (s, 1H) 4.44-4.65 (m, 2H) 5.22-5.28 (m, 1H) 7.74 (d, J=8.54 Hz, 2H) 7.86-7.94 (m, 2H) 8.15-8.32 (m, 1H). LC (Cond. 4): RT=3.33 min; MS: Anal. Calcd. for [2M+Na]⁺ C₃₆H₄₆Br₂N₄NaO₁₀: 877.57; found 877.11.

[1193] Step b: Intermediate OL-16 was prepared from intermediate OL-15 in similar fashion as intermediate 1b. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.16/1.39 (2 br. s., 9H) 1.71-1.81 (m, J=6.10 Hz, 1H) 2.01-2.17 (m, 1H) 3.37-3.50 (m, 1H) 3.50-3.62 (m, 1H) 4.15 (s, 1H) 4.49-4.70 (m, 1H) 5.36 (dd, J=6.71, 3.66 Hz, 1H) 7.44-7.62 (m, 3H) 7.68 (d, J=7.02 Hz, 2H) 11.96/11.99/12.26/12.30 (m, 1H). LC (Cond. 8): RT=1.87 min; MS: Anal. Calcd. for [M+H]⁺ C₁₈H₂₃BrN₃O₃: 408.08; found 408.09.

[1194] Step c: Intermediate OL-17 was prepared by coupling intermediate OL-16 with 1c in similar fashion to the preparation of 1d. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.09-1.49 (m, 18H) 1.71-2.04 (m, 4H) 2.06-2.28 (m, 2H) 3.33-3.40 (m, 1H) 3.41-3.65 (m, 3H) 4.18 (s, 1H) 4.52-4.69 (m, 1H) 4.70-4.88 (m, 1H) 5.38 (s, 1H) 6.64-7.35 (m, 1H) 7.39-7.96 (m, 9H) 11.71-12.0/12.10-12.36 (m, 2H). LC (Cond. 2): RT=1.36 min; MS: Anal. Calcd. for [M+H]⁺ C₃₆H₄₅N₆O₅: 641.77; found 641.39.

[1195] Step d: Intermediate OL-18 was prepared by deprotection of intermediate OL-17 with HCl in similar fashion to the preparation of 1-1e. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.92-2.07 (m, 2H) 2.14-2.25 (m, 1H) 2.35-2.44 (m, 1H) 3.15 (s, 4H) 3.32-3.41 (m, J=7.02, 7.02, 7.02 Hz, 1H) 3.41-3.51 (m, J=7.32 Hz, 2H) 3.54-3.66 (m, 1H) 4.68 (d, J=4.27 Hz, 1H) 4.78-4.89 (m, J=4.88 Hz, 1H) 5.04 (s, 1H) 6.89/7.73 (2d, J=8.70 Hz, 1H) 7.89 (dd, J=8.24, 4.58 Hz, 4H) 7.96-8.07 (m, 4H) 8.15 (d, J=23.19 Hz, 2H) 9.62-10.12 (m, 2H) 10.21-

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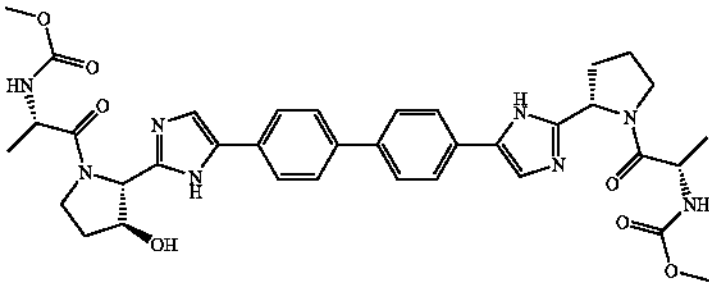
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10.74 (m, 2H). LC (Cond. 8): RT=1.30 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6O$: 441.24; found 441.18.

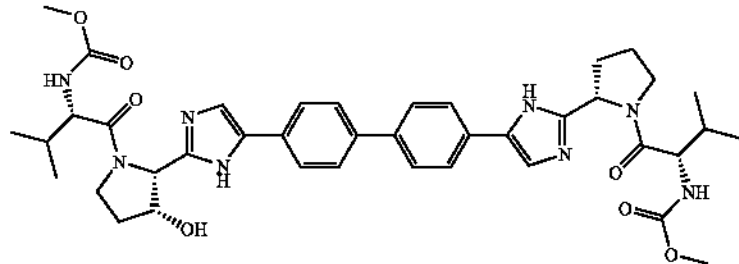
[1196] Step e: Example OL-19 was prepared by coupling of intermediate OL-18 with Cap-51 in similar fashion to the preparation of Example 1. 1H NMR (500 MHz, DMSO- d_6) δ ppm 0.78 (d, J=6.41 Hz, 6H) 0.83 (d, J=6.71 Hz, 6H) 1.92-2.12 (m, 5H) 2.12-2.21 (m, 1H) 2.31 (dd, J=12.21, 5.80 Hz, 1H) 2.35-2.43 (m, 1H) 3.54 (d, J=4.27 Hz, 6H) 3.78-3.89 (m, 3H) 3.91-4.02 (m, 1H) 4.07-4.19 (m, 2H) 4.36-4.50 (m, 1H) 4.81 (d, J=3.66 Hz, 1H) 5.13 (t, J=7.17 Hz, 1H) 5.79 (s, 1H)

7.34 (dd, J=11.29, 8.85 Hz, 2H) 7.83-7.90 (m, 4H) 7.90-8.01 (m, 4H) 8.12 (s, 2H) [Note: the signal for the imidazole NH was too broad to assign a chemical shift]. LC (Cond. 4): RT=2.76 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$: 755.39; found 755.38. HRMS: Anal. Calcd. for $(M+H)^+$ $C_{40}H_{51}N_8O_7$ 755.3881 found 755.3873.

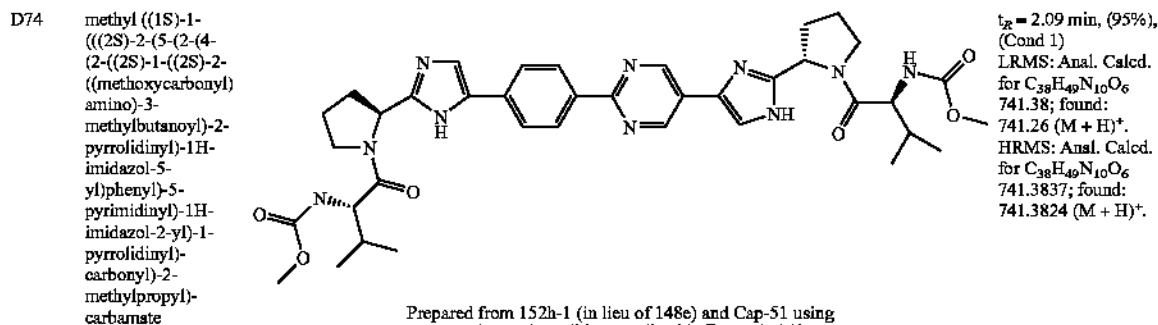
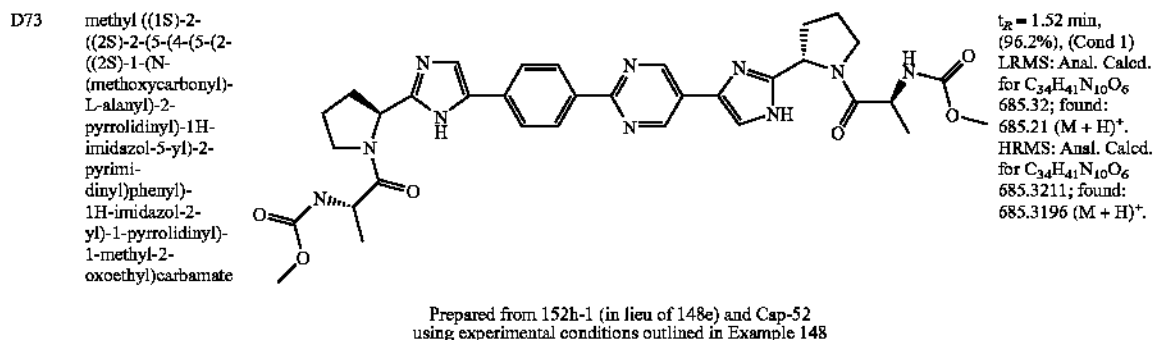
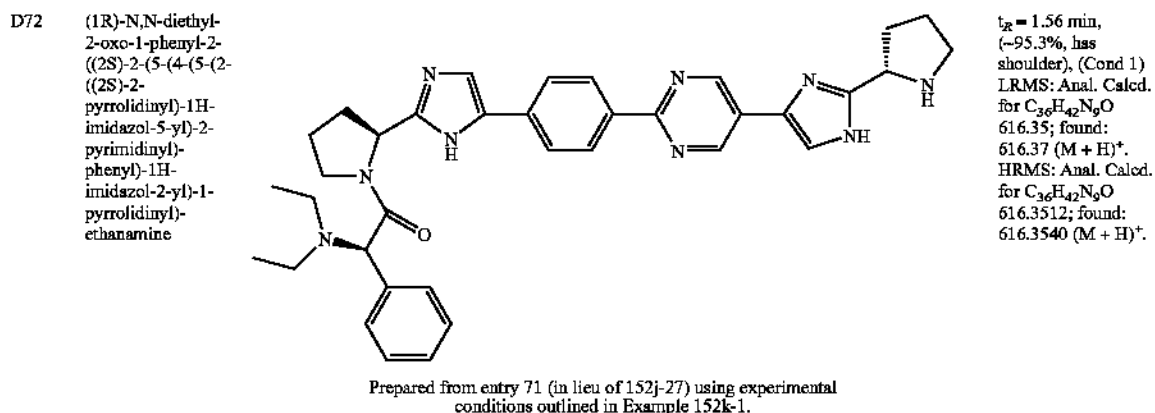
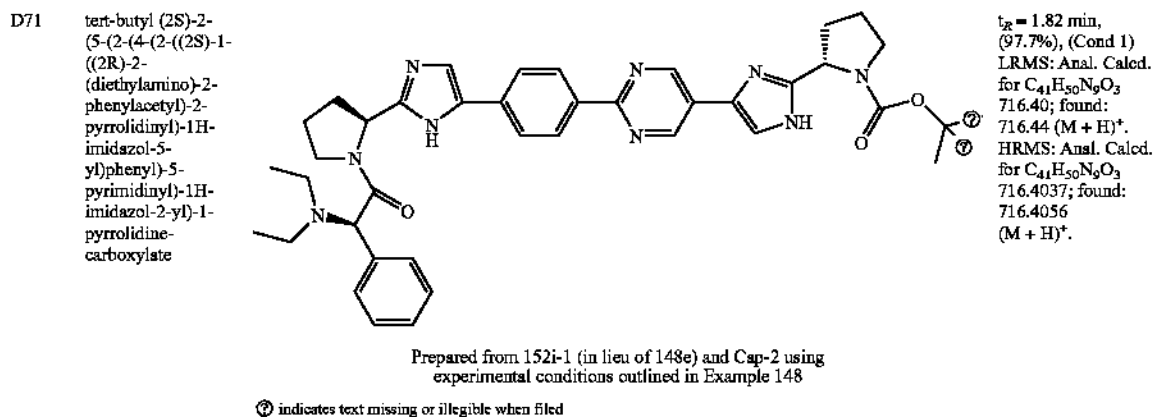
[1197] The following analog was prepared from intermediate OL-18 in similar fashion to the preparation of Example 1 and employing Cap-52.

Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
OL-20	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2R,3S)-3-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LC/MS: 2.32 min (Cond'n 4); Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_7$: 699.78; found 699.32.
From OL-18 and Cap-52			

[1198] The following analog was prepared in similar fashion to the preparation of OL-19 but using N-Boc-cis-3-hydroxy-L-proline as starting material.

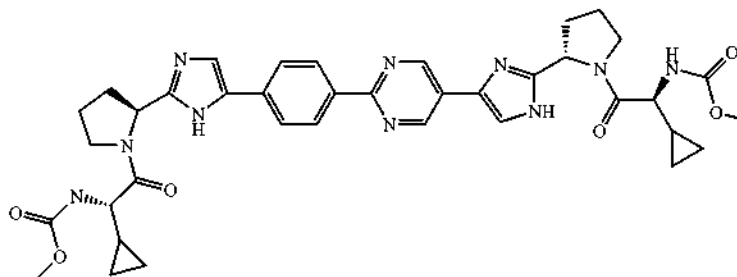
Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
OL-21	methyl ((1S)-1-(((2R)-3-hydroxy-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)-amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.74 min (Cond'n 4); Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$: 755.39; found 755.34.
From N-Boc-cis-3-hydroxy-L-proline and Cap-51			
Ex- am- ple Num- ber	Compound Name	Heterocycles with New Caps	Analytical Data
			(Cond 1: 3 min gradient, 4 min run; Cond 2: 2 min gradient, 3 min run)

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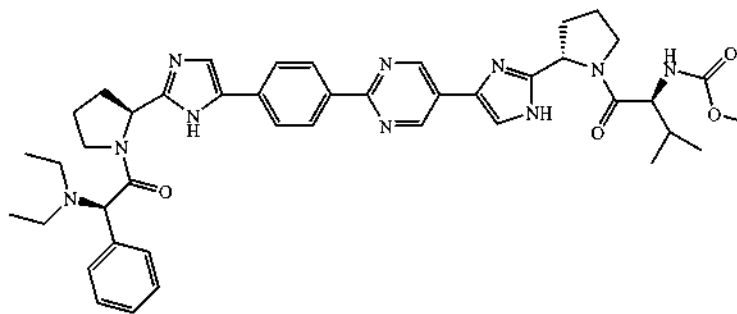
D75 methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-cyclopropyl-2-(methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate



$t_R = 1.98$ min, (95%), (Cond 1)
LRMS: Anal. Calcd. for $C_{38}H_{45}N_{10}O_6$ 737.35; found: 737.22 (M + H)⁺.
HRMS: Anal. Calcd. for $C_{38}H_{45}N_{10}O_6$ 737.3524; found: 737.3555 (M + H)⁺.

Prepared from 152h-1 (in lieu of 148e) and Cap-54b using experimental conditions outlined in Example 148

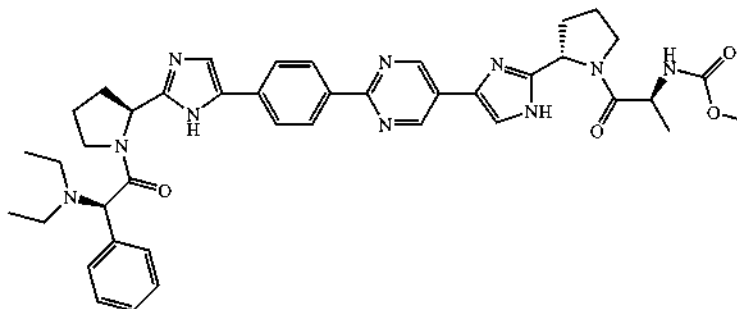
D76 methyl ((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-carbonyl)-2-methylpropyl)carbamate



$t_R = 1.69$ min, (95%), (Cond 1)
LRMS: Anal. Calcd. for $C_{43}H_{53}N_{10}O_4$ 773.43; found: 773.30 (M + H)⁺.
HRMS: Anal. Calcd. for $C_{43}H_{53}N_{10}O_4$ 773.4251; found: 773.4280 (M + H)⁺.

Prepared from entry D72 (in lieu of 148e) and Cap-51 using experimental conditions outlined in Example 148

D77 methyl ((1S)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate



$t_R = 1.81$ min, (97.5%), (Cond 1)
LRMS: Anal. Calcd. for $C_{41}H_{49}N_{10}O_4$ 745.39; found: 745.27 (M + H)⁺.
HRMS: Anal. Calcd. for $C_{41}H_{49}N_{10}O_4$ 745.3938; found: 745.3939 (M + H)⁺.

Prepared from entry D72 (in lieu of 148e) and Cap-52 using experimental conditions outlined in Example 148

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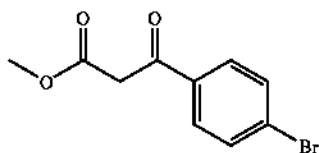
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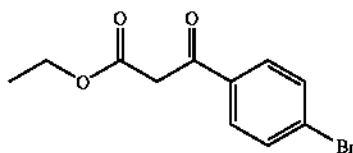
J.1a



Prepared from 4-bromoacetophenone and dimethylcarbonate from Bioorg. Med. Chem. Lett (2001)11, 641

$t_R = 1.7$ min, (Cond 2);
LCMS: $C_{10}H_9BrO_3$
found: 257 (M + H)⁺.

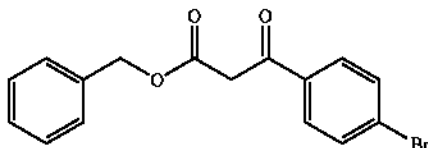
J.1b



Prepared from 4-bromoacetophenone and diethylcarbonate from Bioorg. Med. Chem. Lett (2001)11, 641.

$t_R = 1.9$ min, (Cond 2);
LCMS: $C_{11}H_{11}BrO_3$
found: 271 (M + H)⁺.

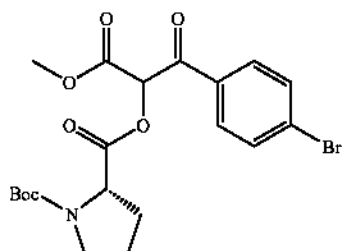
J.1c



Prepared from 4-bromoacetophenone and dibenzylcarbonate from Bioorg. Med. Chem. Lett (2001)11, 641.

$t_R = 2.1$ min, (Cond 2);
LCMS: $C_{16}H_{13}BrO_3$
found: 332 (M + H)⁺.

J.1



Prepared from entry J.1a (in lieu of J.1b) and proline using experimental conditions in Example J2.

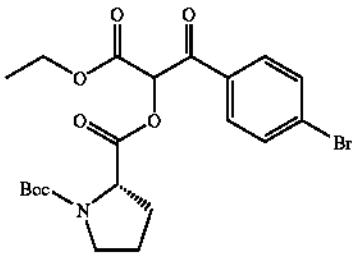
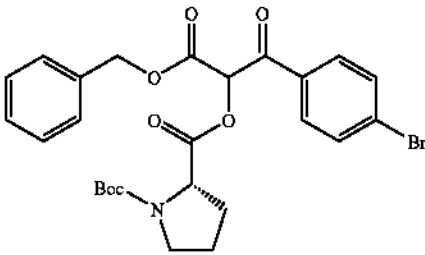
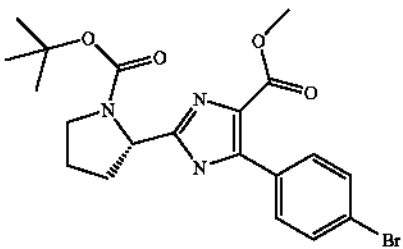
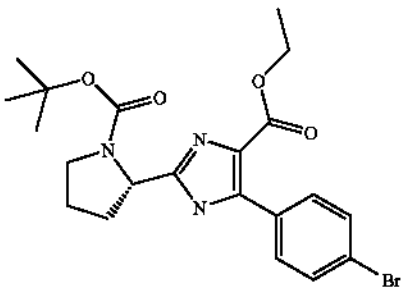
$t_R = 2.2$ min, (Cond 2);
LCMS: $C_{20}H_{24}BrNO_7$
found: 470 (M + H)⁺.

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J2		 <p>Prepared from entry J.1b and proline using experimental conditions in Example J2.</p>	$t_R = 2.2$ min, (Cond 2); LCMS: $C_{21}H_{26}BrNO_7$ found: 484 (M + H) ⁺ .
J3		 <p>Prepared from entry J.1c (in lieu of J.1b) and proline using experimental conditions in Example J2.</p>	$t_R = 2.3$ min, (Cond 2); LCMS: $C_{26}H_{28}BrNO_7$ found: 546 (M + H) ⁺ .
J4		 <p>Prepared from entry J.1 and (in lieu of J.2) using experimental conditions in Example J2.</p>	$t_R = 1.84$ min, (100%) (Cond 2); LRMS: Anal. Calcd. for $C_{20}H_{24}BrN_3O_4$; 450.10; found: 450.13 and 452.13 (M + H) ⁺ .
J5		 <p>Prepared from entry J2 using experimental conditions in J5.</p>	$t_R = 1.93$ min, (99%) (Cond 2); Reported in J5.

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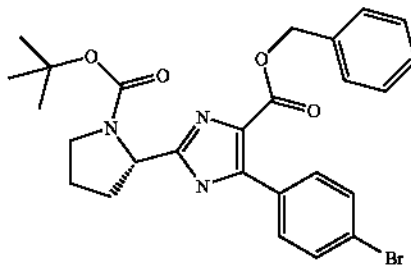
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Compound Name

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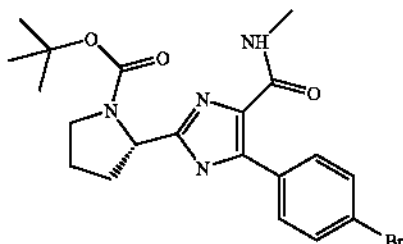
J6



Prepared from entry J3 (in lieu of entry J1) using experimental conditions in J5.

$t_R = 2.1$ min, (93%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{26}H_{29}BrN_3O_4$
526.13; found:
526.16 and 528.16
(M + H)⁺.

J7

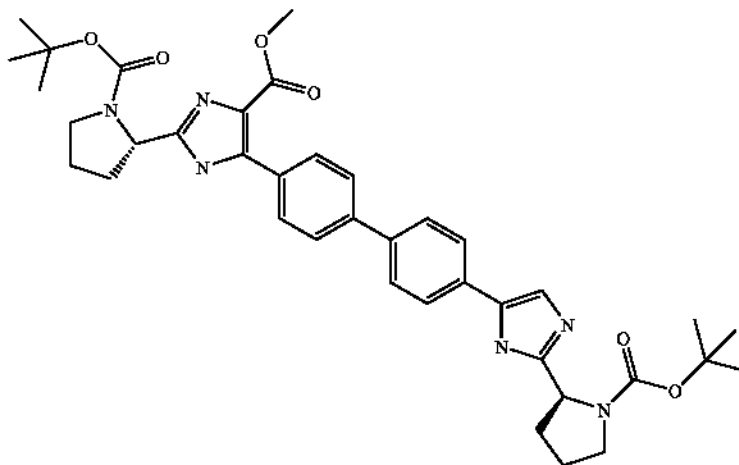


Prepared from entry J5 using experimental in J7.

$t_R = 1.7$ min, (100%)
(Cond 2);
Reported in J7.

J8

methyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate



Prepared from entry J4 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.

$t_R = 1.70$ min, (95%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{38}H_{47}N_8O_6$
683.36; found:
683.42 (M + H)⁺.

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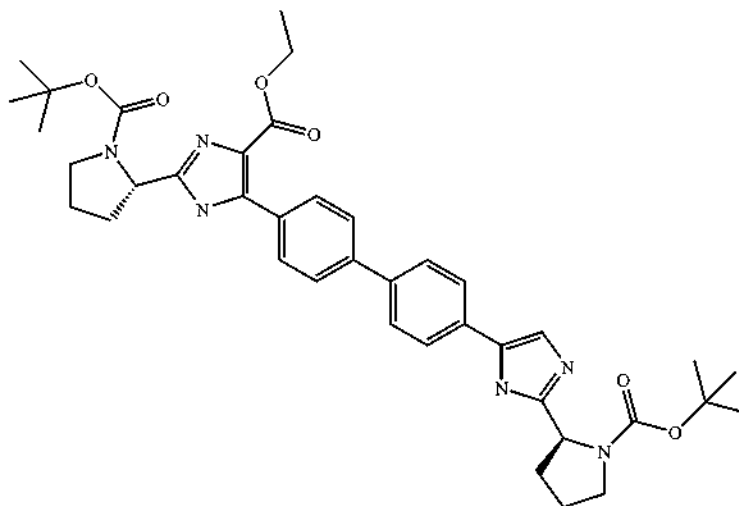
Compound Name

Structure

Analytical Data

J9

ethyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate

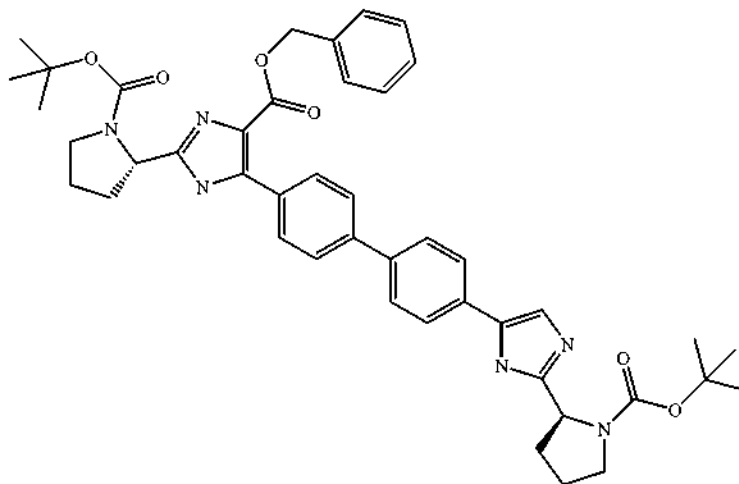


$t_R = 1.78$ min,
(97.5%) (Cond 2);
LRMS: Anal. Calcd.
for $C_{39}H_{49}N_6O_6$
697.37; found:
697.38 (M + H)⁺.

Prepared from entry J5 (in lieu of 152e-1) and 1c using
experimental conditions outlined in Example 152g-1.

J10

benzyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate



$t_R = 1.88$ min, (85%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{44}H_{51}N_6O_6$
759.39; found:
759.48 (M + H)⁺.

Prepared from entry J6 (in lieu of
152e-1) and 1c using
experimental conditions outlined
in Example 152g-1.

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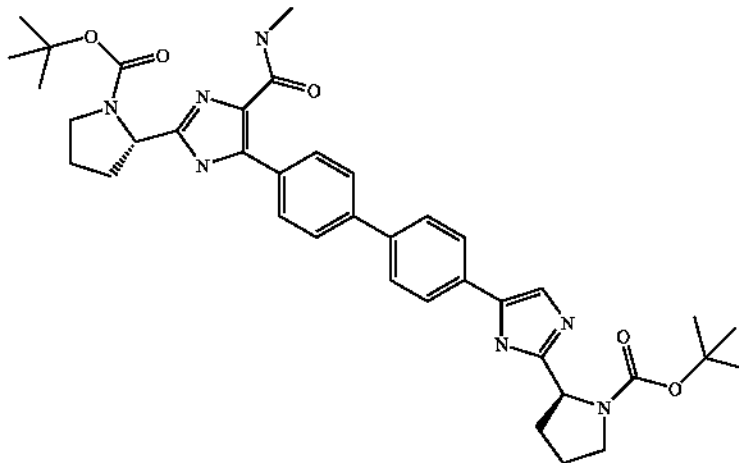
Compound Name

Structure

Analytical Data

J11

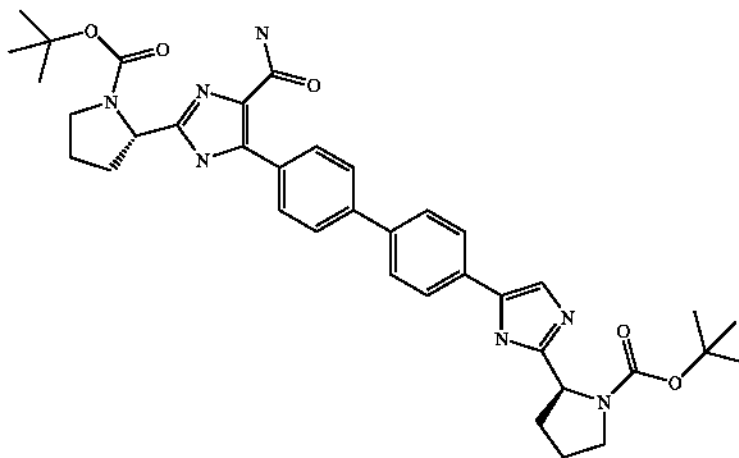
tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate



$t_R = 1.65$ min, (90%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{39}H_{48}N_7O_5$
682.37; found:
682.42 ($M + H$)⁺.

Prepared from entry J7 (in lieu of
152e-1) and 1c using
experimental conditions outlined
in Example 152g-1.

J11.a



$t_R = 1.60$ min, (Cond
2);
LCMS: $C_{37}H_{46}N_7O_5$
found: 668 ($M + H$)⁺.

Prepared from entry J9 as
described in J11.a.

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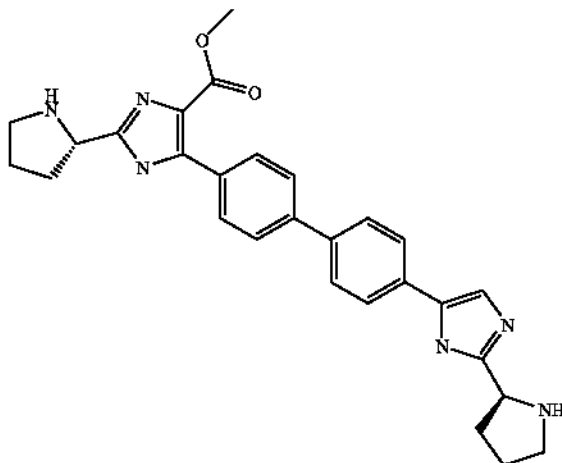
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Compound Name

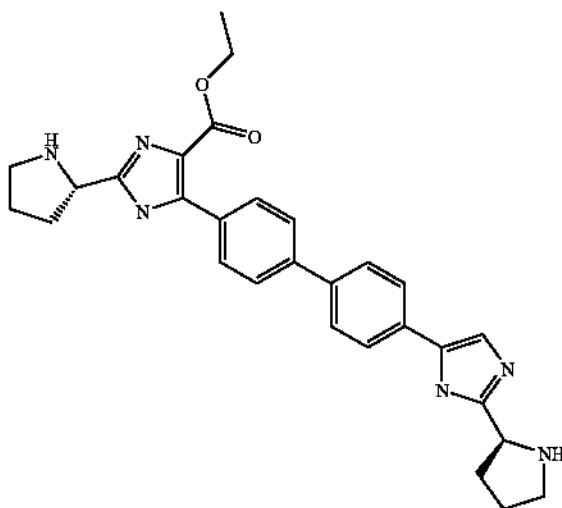
Structure

Analytical Data

J12

 $t_R = 1.25$ min, (97%)
(Cond 2);
LCMS: $C_{28}H_{31}N_5O_2$
found: 483 (M + H)⁺.Prepared from entry J8 (in lieu of
152j-27) using experimental
conditions outlined in Example
152k-1.

J13

 $t_R = 1.34$ min, (Cond
2);
LCMS: $C_{29}H_{33}N_5O_2$
found: 497 (M + H)⁺.Prepared from entry J9 (in lieu of
152j-27) using experimental
conditions outlined in Example
152k-1.

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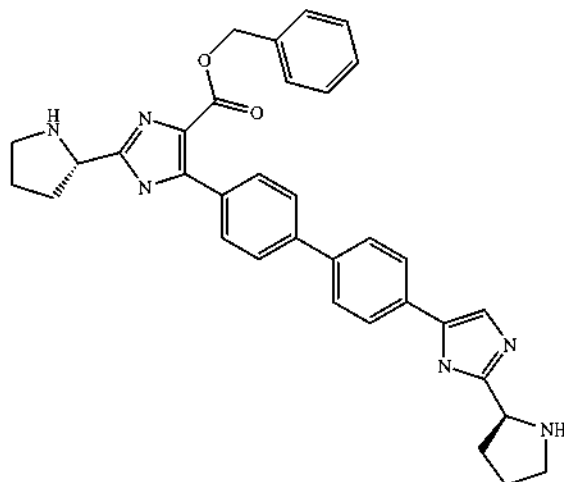
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Compound Name

Structure

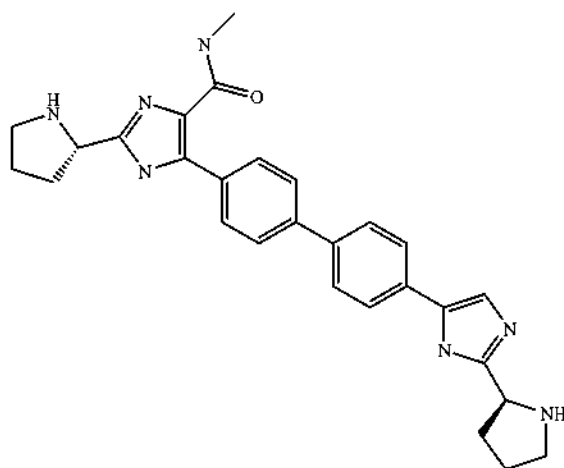
Analytical Data

J14

 $t_R = 1.51$ min, (90%)
(Cond 2);
LCMS: $C_{34}H_{35}N_6O_2$
found: 559 (M + H)⁺.

Prepared from entry J10 (in lieu
of 152j-27) using experimental
conditions outlined in Example
152k-1.

J15

 $t_R = 1.32$ min, (99%)
(Cond 2);
LCMS: $C_{28}H_{32}N_7O$
found: 482 (M + H)⁺.

Prepared from entry J11 (in lieu
of 152j-27) using experimental
conditions outlined in Example
152k-1.

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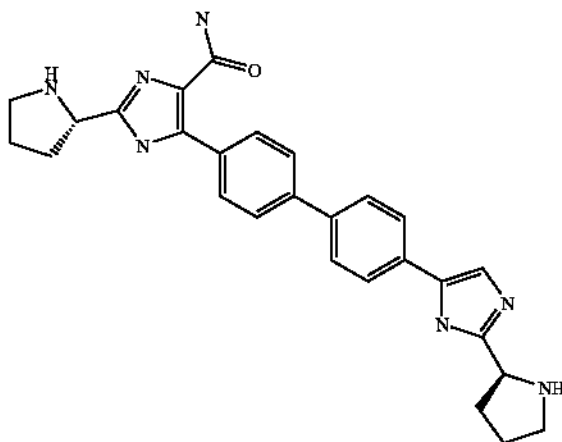
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Compound Name

Structure

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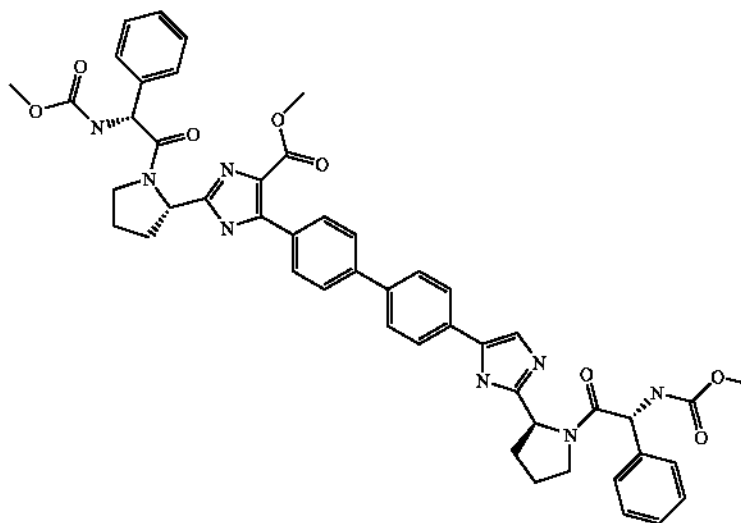
J15.a



$t_R = 1.07$ min, (98%)
(Cond 2);
LCMS: $C_{27}H_{30}N_7O$
found: 468 (M + H)⁺.

Prepared from entry J11.a (in lieu
of 152j-27) using experimental
conditions outlined in Example
152k-1.

J16 methyl 2-((2S)-1-
((2R)-2-
(methoxycarbonyl)
amino)-2-
phenylacetyl)-2-
pyrrolidinyl)-5-(4'-
(2-((2S)-1-((2R)-2-
(methoxycarbonyl)
amino)-2-
phenylacetyl)-2-
pyrrolidinyl)-1H-
imidazol-5-yl)-4-
biphenyl)-1H-
imidazole-4-
carboxylate



$t_R = 1.62$ min,
(99.5%) (Cond 2);
LRMS: Anal. Calcd.
for $C_{48}H_{49}N_8O_8$
865.37; found:
865.34 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{48}H_{49}N_8O_8$
865.3673; found:
865.3715 (M + H)⁺.

Prepared from entry J12 (in lieu
of 148e) and Cap-4 using
experimental conditions outlined
in Example 148.

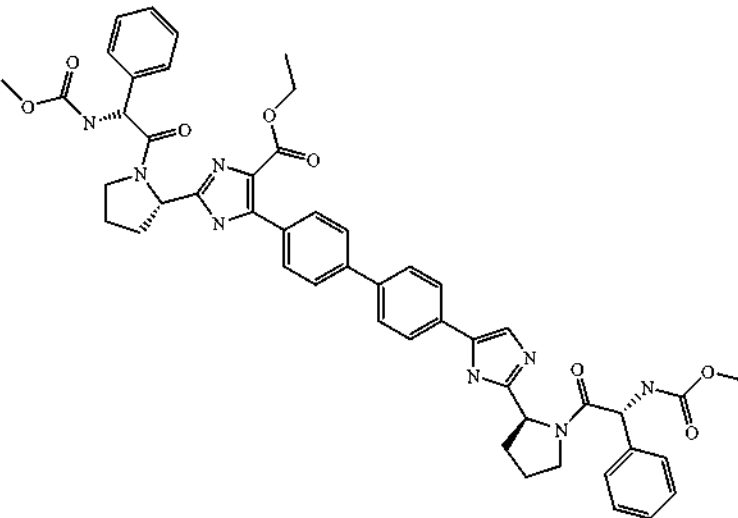
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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J17	methyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate		$t_R = 1.37$ min, (92%) (Cond 2); LRMS: Anal. Calcd. for $C_{48}H_{53}N_8O_4$ 804.42; found: 805.51 ($M + H$) ⁺ . HRMS: Anal. Calcd. for $C_{48}H_{53}N_8O_4$ 805.4190; found: 805.4211 ($M + H$) ⁺ .
J18	methyl 2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate		$t_R = 1.46$ min, (94%) (Cond 2); LRMS: Anal. Calcd. for $C_{54}H_{61}N_8O_6$ 885.48; found: 885.48 ($M + H$) ⁺ . HRMS: Anal. Calcd. for $C_{54}H_{61}N_8O_6$ 885.4816; found: 885.4852 ($M + H$) ⁺ .

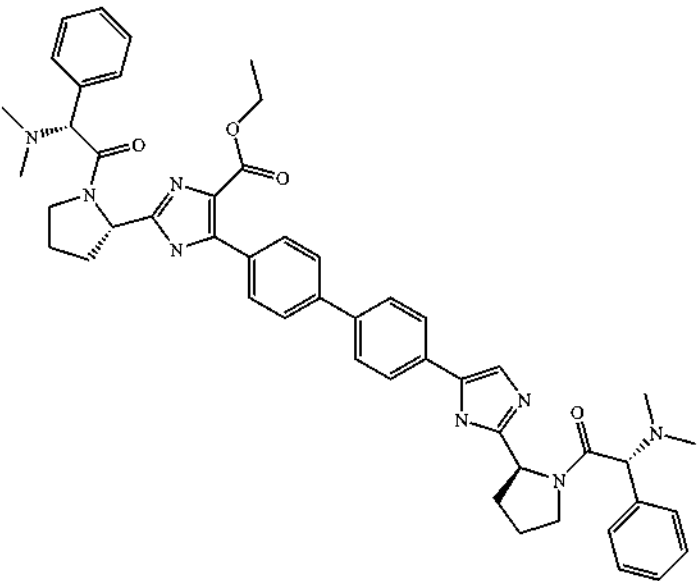
Prepared from entry J12 (in lieu
of 148e) and Cap-1 using
experimental conditions outlined
in Example 148.

Prepared from entry J12 (in lieu
of 148e) and Cap-14 using
experimental conditions outlined
in Example 148.

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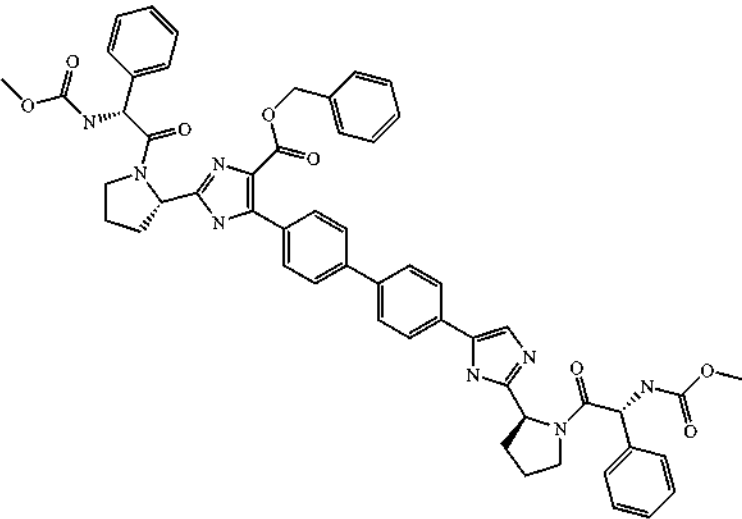
Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J19	ethyl 2-((2S)-1-((2R)-2-(methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate		$t_R = 1.68$ min, (99%) (Cond 2); LRMS: Anal. Calcd. for C ₄₉ H ₅₁ N ₈ O ₈ 879.38; found: 879.37 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₄₉ H ₅₁ N ₈ O ₈ 879.3830; found: 879.3814 (M + H) ⁺ .

Prepared from entry J13 (in lieu
of 148e) and Cap-4 using
experimental conditions outlined
in Example 148.

J20	ethyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate		$t_R = 1.45$ min, (89%) (Cond 2); LRMS: Anal. Calcd. for C ₄₉ H ₅₅ N ₈ O ₄ 818.44; found: 818.40 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₄₉ H ₅₅ N ₈ O ₄ 819.4346; found: 819.4340 (M + H) ⁺ .
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Prepared from entry J13 (in lieu of 148e) and Cap-1 using
experimental conditions outlined in Example 148.

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J21	benzyl 2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate		$t_R = 1.80$ min, (92%) (Cond 2); LRMS: Anal. Calcd. for C ₅₄ H ₅₃ N ₈ O ₈ 941.40; found: 941.39 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₅₄ H ₅₃ N ₈ O ₈ 941.3986; found: 941.4033 (M + H) ⁺ .

Prepared from entry J14 (in lieu of 148e) and Cap-4 using experimental conditions outlined in Example 148.

J22

benzyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate

$t_R = 1.56$ min, (96%)
(Cond 2);
LRMS: Anal. Calcd. for $C_{54}H_{57}N_8O_4$ 881.45; found: 881.46 ($M + H$)⁺.
HRMS: Anal. Calcd. for $C_{54}H_{57}N_8O_4$ 881.4503; found: 881.4536 ($M + H$)⁺.

Prepared from entry J14 (in lieu of 148e) and Cap-1 using experimental conditions outlined in Example 148.

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J23	benzyl 2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate		$t_R = 1.63$ min, (96%) (Cond 2); LRMS: Anal. Calcd. for C ₆₀ H ₆₅ N ₈ O ₄ 961.51; found: 961.54 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₆₀ H ₆₅ N ₈ O ₄ 961.5129; found: 961.5164 (M + H) ⁺ .
Prepared from entry J14 (in lieu of 148e) and Cap-14 using experimental conditions outlined in Example 148.			
J24	benzyl 2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate		$t_R = 1.64$ min, (94%) (Cond 2); LRMS: Anal. Calcd. for C ₄₄ H ₄₉ N ₈ O ₈ 817.37; found: 817.38 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₄₄ H ₄₉ N ₈ O ₈ 817.3673; found: 817.3675 (M + H) ⁺ .
Prepared from entry J14 (in lieu of 148e) and Cap-52 using experimental conditions outlined in Example 148.			

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J25	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-4-(methoxycarbonyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.58$ min, (99.6%) (Cond 2); LRMS: Anal. Calcd. for C ₄₈ H ₅₀ N ₉ O ₇ 864.38; found: 864.47 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₄₈ H ₅₀ N ₉ O ₇ 864.3833; found: 864.3849 (M + H) ⁺ .

Prepared from entry J15 (in lieu
of 148e) and Cap-4 using
experimental conditions outlined
in Example 148.

J26	2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-N-methyl-1H-imidazole-4-carboxamide		$t_R = 1.31$ min, (93.2%) (Cond 2); LRMS: Anal. Calcd. for C ₄₈ H ₅₄ N ₉ O ₃ 804.44; found: 804.51 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₄₈ H ₅₄ N ₉ O ₃ 804.4350; found: 804.4369 (M + H) ⁺ .
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Prepared from entry J15 (in lieu of 148e) and Cap-1 using
experimental conditions outlined in Example 148.

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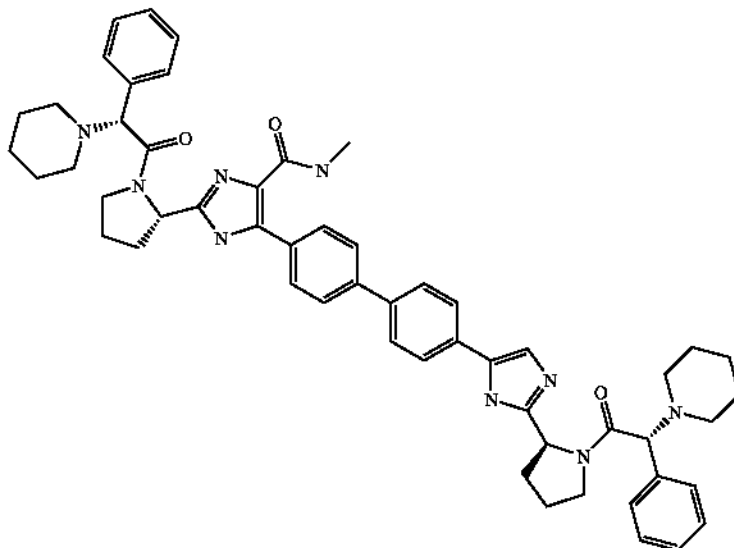
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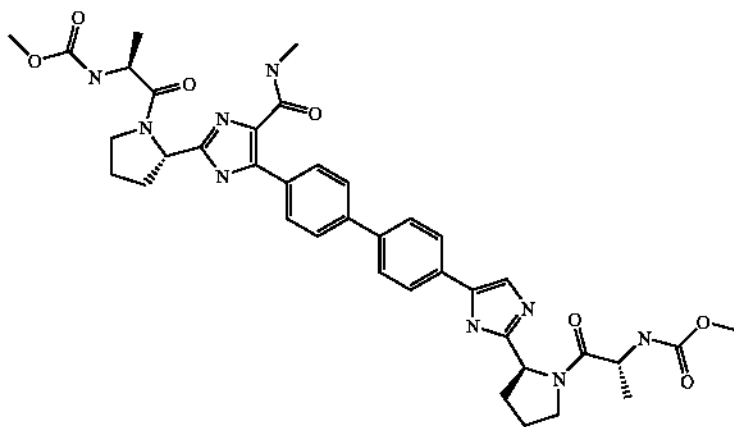
J27 N-methyl-2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxamide



$t_R = 1.39$ min,
(95.4%) (Cond 2);
LRMS: Anal. Calcd.
for C₅₄H₆₂N₉O₃
884.50; found:
884.52 (M + H)⁺.
HRMS: Anal. Calcd.
for C₅₄H₆₂N₉O₃
884.4976; found:
884.4973 (M + H)⁺.

Prepared from entry J15 (in lieu
of 148e) and Cap-14 using
experimental conditions outlined
in Example 148.

J28 methyl ((1S)-2-((2S)-2-(5-(4'-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(methylcarbamoyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate



$t_R = 1.34$ min,
(89.3%) (Cond 2);
LRMS: Anal. Calcd.
for C₃₈H₄₆N₉O₇
740.35; found:
740.31 (M + H)⁺.
HRMS: Anal. Calcd.
for C₃₈H₄₆N₉O₇
740.3520; found:
740.3597 (M + H)⁺.

Prepared from entry J15 (in lieu
of 148e) and Cap-52 using
experimental conditions outlined
in Example 148.

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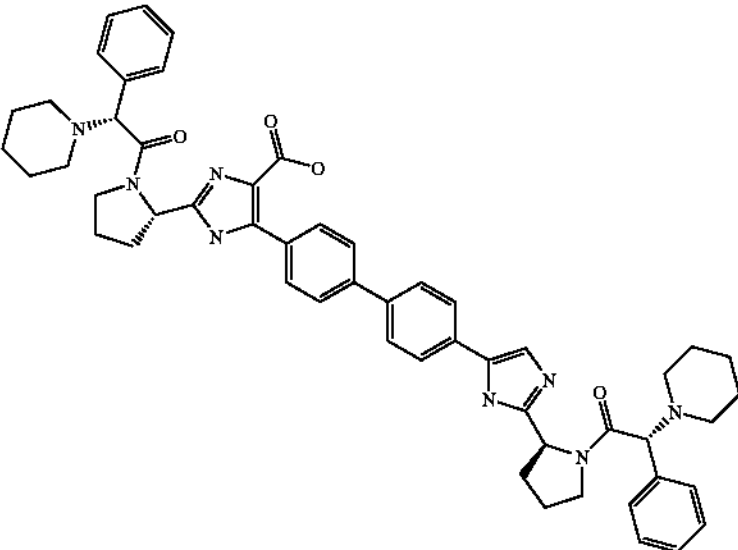
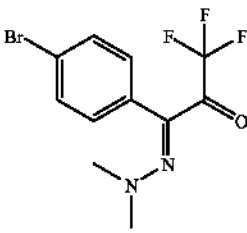
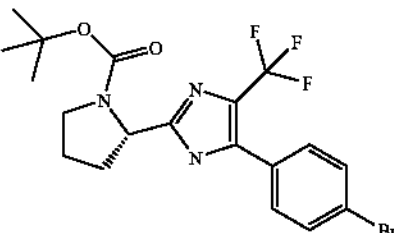
Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J29	methyl ((1R)-2-((2S)-2-(4-carbamoyl-5-(4'-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.55$ min, (96.4%) (Cond 2); LRMS: Anal. Calcd. for C ₄₇ H ₄₈ N ₉ O ₇ 740.35; found: 740.31 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₄₇ H ₄₈ N ₉ O ₇ 740.3520; found: 740.3497 (M + H) ⁺ .
		Prepared from entry J15.a (in lieu of 148e) and Cap-4 using experimental conditions outlined in Example 148.	
J30	2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylic acid		$t_R = 1.52$ min, (92.8%) (Cond 2); LRMS: Anal. Calcd. for C ₄₇ H ₄₇ N ₈ O ₈ 851.35; found: 851.37 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₄₇ H ₄₇ N ₈ O ₈ 851.3517; found: 851.3553 (M + H) ⁺ .

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J31	2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylic acid		$t_R = 1.36$ min, (96.5%) (Cond 2); LRMS: Anal. Calcd. for $C_{53}H_{59}N_8O_4$ 871.147; found: 871.47 ($M + H$) ⁺ . HRMS: Anal. Calcd. for $C_{53}H_{59}N_8O_4$ 871.4659; found: 871.4692 ($M + H$) ⁺ .
		Prepared from entry 23 (in lieu of 28c) using experimental conditions outlined in Example 28 step d.	
J32			$t_R = 1.96$ min, (96%) (Cond 2); LRMS: Anal. Calcd. for $C_{11}H_{11}BrF_3N_2O$ 323.00; found: 323.05 and 325.05 ($M + H$) ⁺ . ¹ H NMR (300 MHz, DMSO- d_6) δ 7.58 (d, $J = 8.4$ Hz, 2 H), 7.21 (d, $J = 8.4$ Hz, 2 H), 3.06 (s, 6 H).
		Prepared from 4-bromobenzaldehyde according to procedure described in J. Org. Chem. (1988), 53, 129.	
J32.a			$t_R = 2.19$ min, (96%) (Cond 2); Reported in J32.a
		Prepared from entry J32 using experimental conditions in J32.a	

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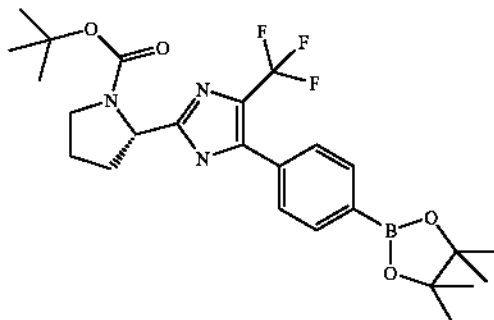
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J32.b

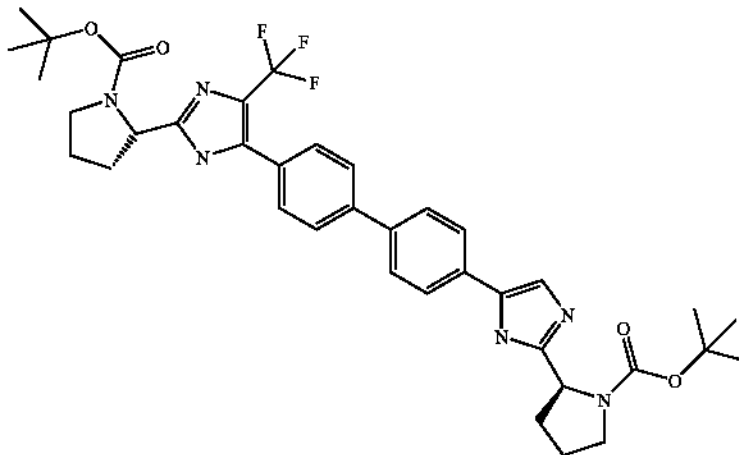


Prepared from entry J32.a (in lieu of 1b) using experimental conditions outlined in Example 1 step c.

$t_R = 2.3$ min, (73%)
(Cond 2);
LCMS:
 $C_{25}H_{34}BF_3N_3O_4$
found: 508 (M + H)⁺.

J33

tert-butyl (2S)-2-
(5-(4'-((2S)-1-
(tert-
butoxycarbonyl)-2-
pyrrolidinyl)-1H-
imidazol-5-yl)-4-
biphenyl)-4-
(trifluoromethyl)-
1H-imidazol-2-yl)-
1-pyrrolidine-
carboxylate



Prepared from entry J32.a (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.

$t_R = 2.7$ min, (95%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{37}H_{44}F_3N_6O_4$
693.34; found:
693.33 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{37}H_{44}F_3N_6O_4$
693.3376; found:
693.3370 (M + H)⁺.

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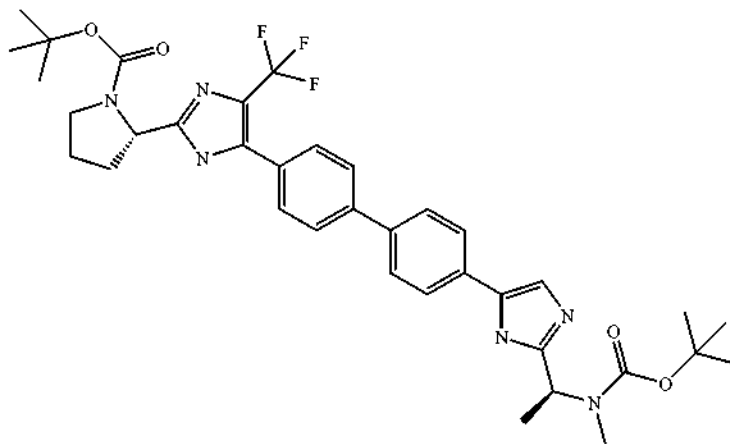
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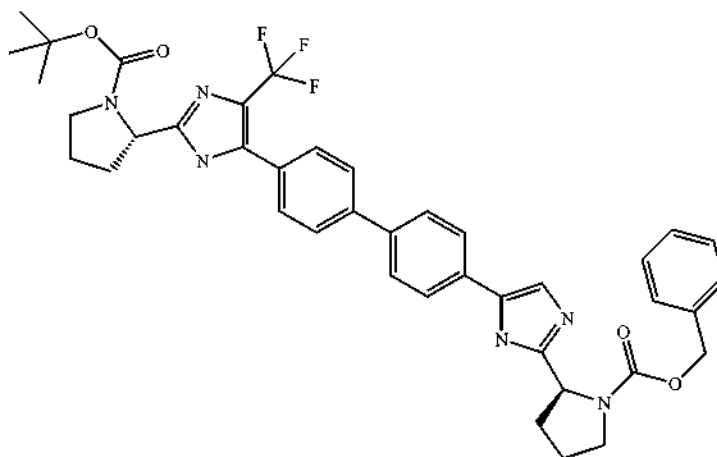
J33.a tert-butyl (2S)-2-(5-(4'-(2-((1S)-1-(tert-butoxycarbonyl)(methylamino)ethyl)-1H-imidazol-5-yl)-4-biphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate



$t_R = 1.97$ min, (97%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{36}H_{44}F_3N_6O_4$
681.34; found:
681.31 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{36}H_{44}F_3N_6O_4$
681.3376; found:
681.3383 (M + H)⁺.

Prepared from entry J32.a (in
lieu of 152e-1) and 1-8c using
experimental conditions outlined
in Example 152g-1.

J34 tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-(benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate



$t_R = 2.0$ min, (95%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{40}H_{42}F_3N_6O_4$
727.32; found:
727.19 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{40}H_{42}F_3N_6O_4$
727.3220; found:
727.3251 (M + H)⁺.

Prepared from entry J32.a (in
lieu of 152e-1) and 1-5c using
experimental conditions outlined
in Example 152g-1.

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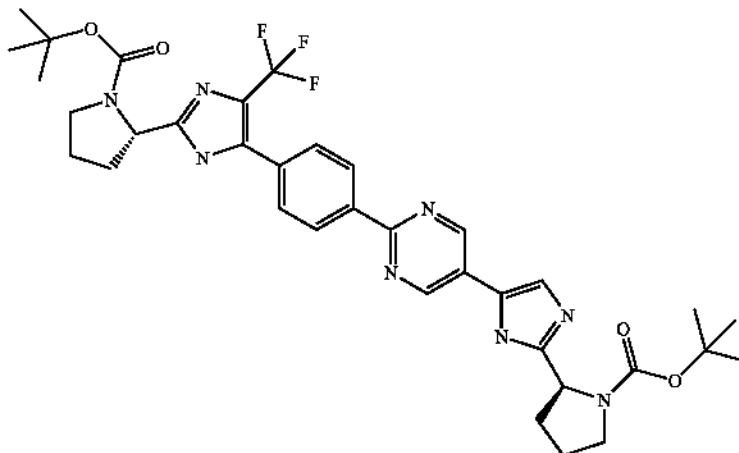
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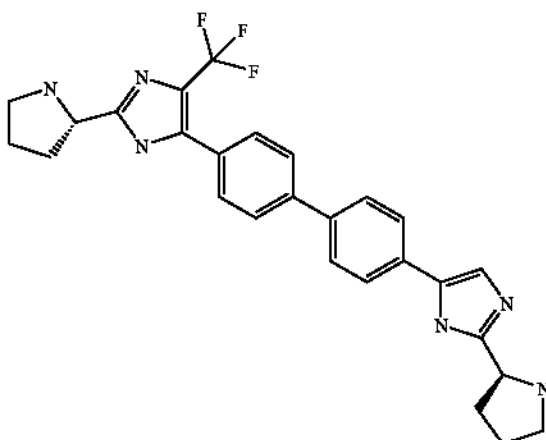
J34.a tert-butyl (2S)-2-
(5-(4-(5-(2-((2S)-1-
(tert-
butoxycarbonyl)-2-
pyrrolidinyl)-1H-
imidazol-5-yl)-2-
pyrimidinyl)phenyl)-
4-
(trifluoromethyl)-
1H-imidazol-2-yl)-
1-
pyrrolidinecarboxyl-
ate



$t_R = 1.97$ min, (93%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{35}H_{42}F_3N_8O_4$
695.33; found:
695.28 ($M + H$)⁺.

Prepared from entry J32.b (in
lieu of 152e-1) and 152d-1 using
experimental conditions outlined
in Example 152g-1.

J35



$t_R = 1.46$ min, (92%)
(Cond 2);
LCMS: $C_{27}H_{28}F_3N_6O$
found: 493 ($M + H$)⁺.

Prepared from entry J33 (in lieu
of 152j-27) using experimental
conditions outlined in Example
152k-1.

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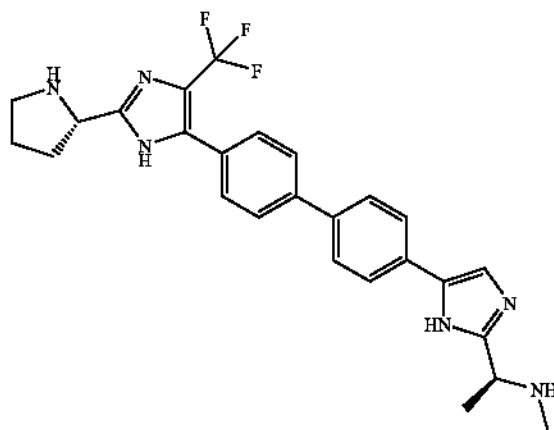
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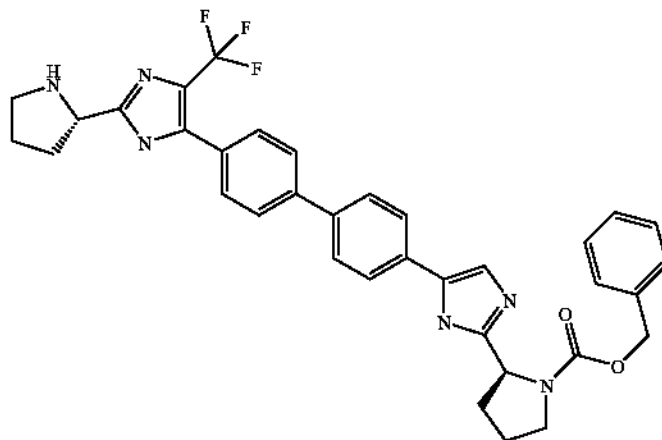
Structure

Analytical Data

J35.a

LCMS: $C_{26}H_{28}F_3N_6$
found: 481 (M + H)⁺.Prepared from entry J33.a (in
lieu of 152j-27) using
experimental conditions outlined
in Example 152k-1.

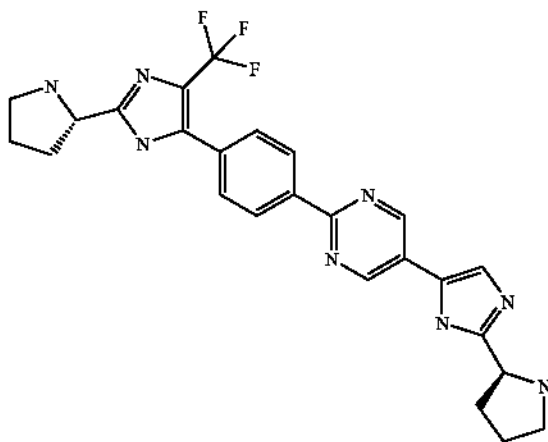
J36

LCMS:
 $C_{35}H_{34}F_3N_6O_2$
found: 626 (M + H)⁺.Prepared from entry J34 (in lieu
of 152j-27) using experimental
conditions outlined in Example
152k-1.

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
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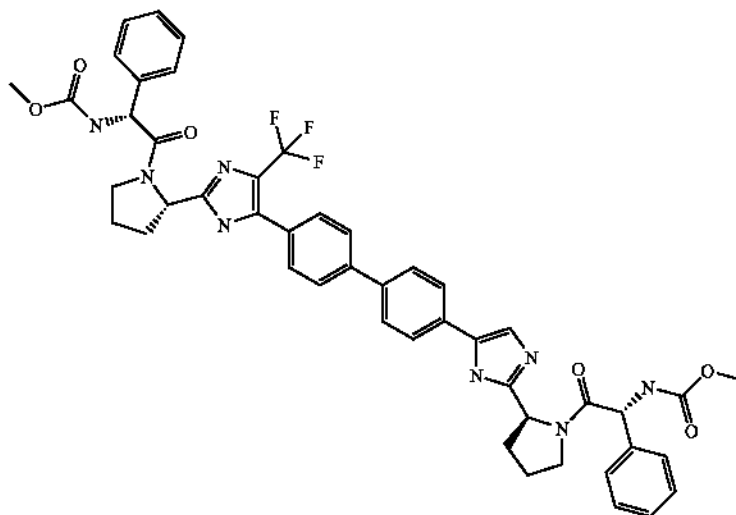
136.9



$t_R = 1.45$ min. (Cond 2);
LCMS: $C_{25}H_{26}F_3N_8$
found: 495 ($M + H$) $^+$.

Prepared from entry J34.a (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.

J37 methyl-((1R)-2-
((2S)-2-(5-(4'-(2-
((2S)-1-((2R)-2-
((methoxycarbonyl)-
amino)-2-
phenylacetyl)-2-
pyrrolidinyl)-1H-
imidazol-5-yl)-4-
biphenyl)-4-
(trifluoromethyl)-
1H-imidazol-2-yl)-
1-pyrrolidinyl)-2-
oxo-1-
phenylethyl)-
carbamate



$t_R = 1.9$ min, (95%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{47}H_{46}F_3N_8O_4$
875.35; found:
875.35 ($M + H$)⁺.
HRMS: Anal. Calcd.
for $C_{47}H_{46}F_3N_8O_4$
875.3492; found:
875.3504 ($M + H$)⁺.

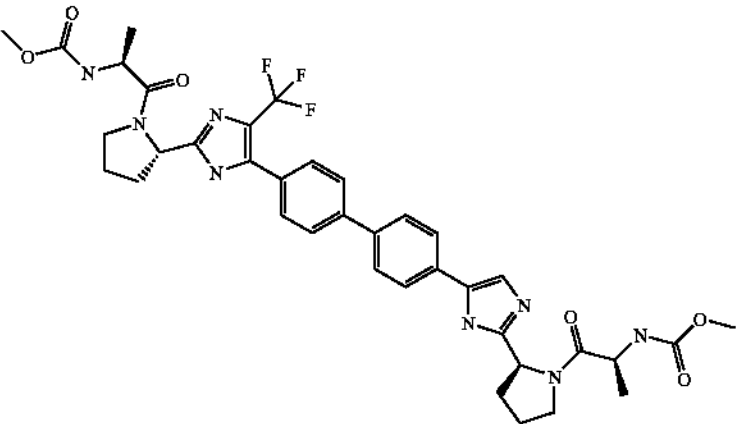
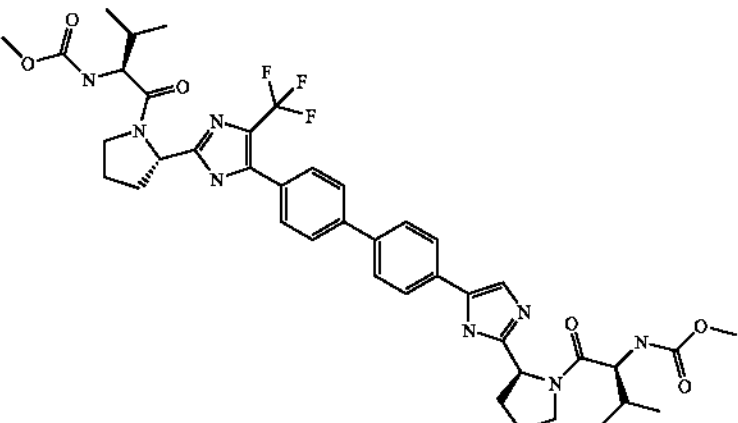
Prepared from entry J35 (in lieu of 148e) and Cap-4 using experimental conditions outlined in Example 148.

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J38	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		$t_R = 1.7$ min, (95.5%) (Cond 2); LRMS: Anal. Calcd. for $C_{37}H_{42}F_3N_8O_6$ 751.32; found: 751.32 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{37}H_{42}F_3N_8O_6$ 751.3179; found: 751.3163 (M + H) ⁺ .
		Prepared from entry J35 (in lieu of 148e) and Cap-52 using experimental conditions outlined in Example 148.	
J39	methyl (((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbon yl)-2-methylpropyl)carbamate		$t_R = 1.9$ min, (96%) (Cond 2); LRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_8O_6$ 807.38; found: 807.33 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_8O_6$ 807.3805; found: 807.3773 (M + H) ⁺ .
		Prepared from entry J35 (in lieu of 148e) and Cap-51 using experimental conditions outlined in Example 148.	

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Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J40	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine		$t_R = 1.6$ min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{51}H_{58}F_3N_8O_2$ 871.46; found: 871.48 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{51}H_{58}F_3N_8O_2$ 871.4635; found: 871.4647 (M + H) ⁺ .
		Prepared from entry J35 (in lieu of 148e) and Cap-2 using experimental conditions outlined in Example 148.	
J41	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		$t_R = 1.8$ min, (96.9%) (Cond 2); LRMS: Anal. Calcd. for $C_{41}H_{46}F_3N_8O_6$ 803.35; found: 803.35 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{41}H_{46}F_3N_8O_6$ 803.3492; found: 803.3507 (M + H) ⁺ .
		Prepared from entry J35 (in lieu of 148e) and Cap-54b using experimental conditions outlined in Example 148.	

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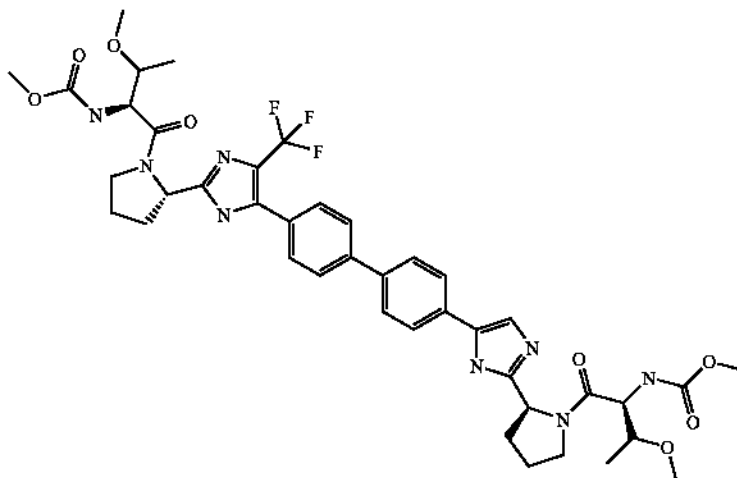
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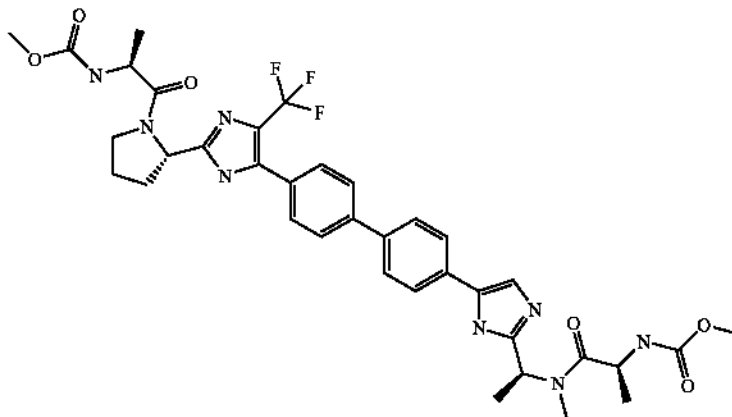
J42 methyl ((1*S*,2*R*)-2-methoxy-1-((2*S*)-2-(5-(4'-(2-((2*S*)-1-(*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1*H*-imidazol-5-yl)-4-biphenyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate



$t_R = 1.8$ min, (92%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{41}H_{50}F_3N_8O_8$
839.37; found:
839.30 ($M + H$)⁺.
HRMS: Anal. Calcd.
for $C_{41}H_{50}F_3N_8O_8$
839.3704; found:
839.3677 ($M + H$)⁺.

Prepared from entry J35 (in lieu
of 148e) and Cap-86 using
experimental conditions outlined
in Example 148.

J42.a methyl ((1*S*)-2-((2*S*)-2-(5-(4'-(2-((1*S*)-1-(*N*-(methoxycarbonyl)-L-alanyl(methyl)amino)ethyl)-1*H*-imidazol-5-yl)-4-biphenyl)-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate



$t_R = 1.69$ min,
(100%) (Cond 2);
LRMS: Anal. Calcd.
for $C_{36}H_{42}F_3N_8O_6$
739.32; found:
739.31 ($M + H$)⁺.
HRMS: Anal. Calcd.
for $C_{36}H_{42}F_3N_8O_6$
739.3179; found:
739.3195 ($M + H$)⁺.

Prepared from entry J35.a (in
lieu of 148e) and Cap-52 using
experimental conditions outlined
in Example 148.

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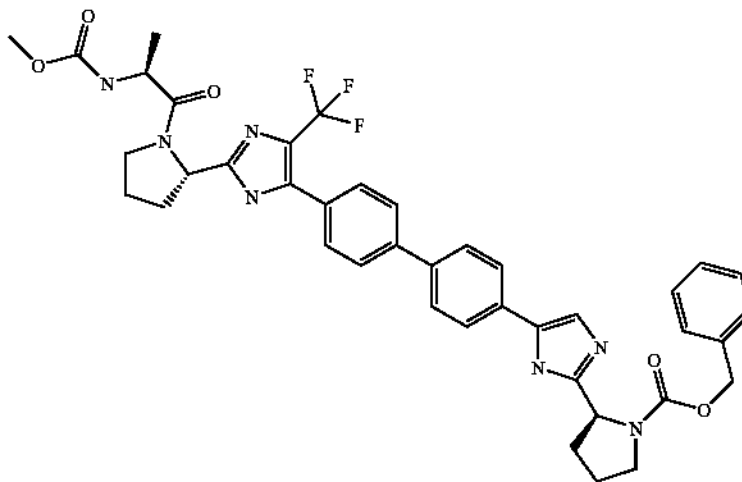
363

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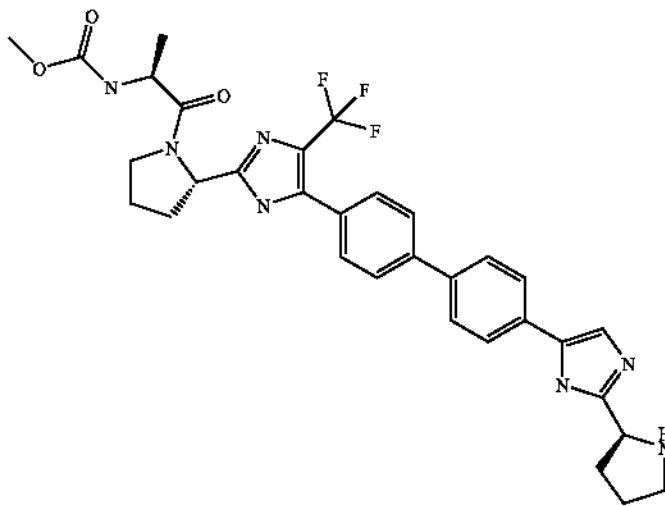
J43 benzyl (2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate



$t_R = 1.9$ min, (95%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{40}H_{41}F_3N_7O_5$
756.31; found:
756.19 ($M + H$)⁺.
HRMS: Anal. Calcd.
for $C_{40}H_{41}F_3N_7O_5$
756.3121; found:
756.3127 ($M + H$)⁺.

Prepared from entry J36 (in lieu
of 148e) and Cap-52 using
experimental conditions outlined
in Example 148.

J44



LCMS:
 $C_{32}H_{35}F_3N_7O_3$ found:
622 ($M + H$)⁺.

Prepared from entry J43 (in lieu
of 152g-8) using experimental
conditions outlined in Example
152i-1.

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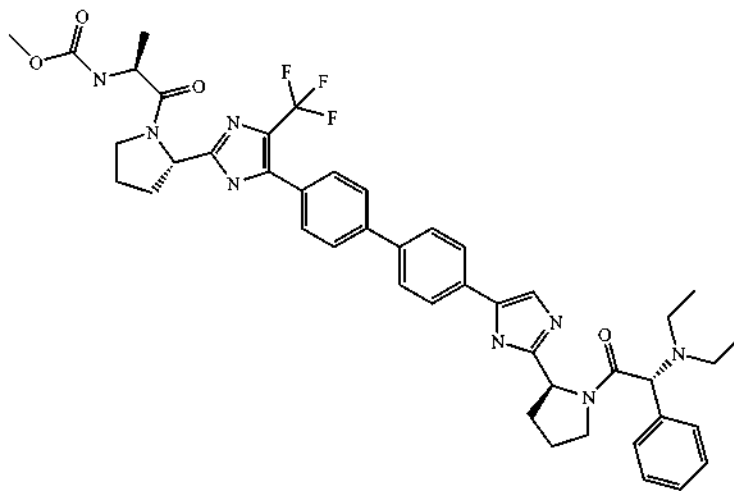
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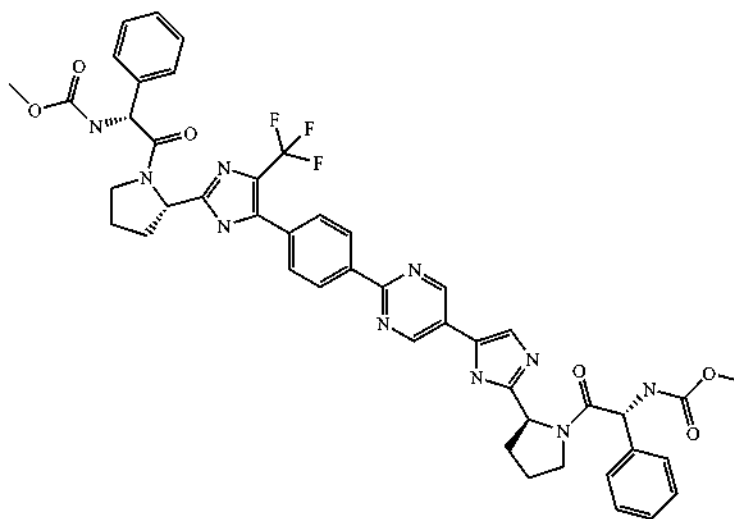
J45 methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate



$t_R = 1.7$ min, (93%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{44}H_{50}F_3N_8O_4$
811.39; found:
811.34 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{44}H_{50}F_3N_8O_4$
811.3907; found:
811.3913 (M + H)⁺.

Prepared from entry J44 (in lieu
of 148e) and Cap-2 using
experimental conditions outlined
in Example 148.

J46 methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(2R)-2-(methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



$t_R = 1.82$ min, (98%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{45}H_{44}F_3N_{10}O_6$
877.34; found:
877.29 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{45}H_{44}F_3N_{10}O_6$
877.3397; found:
877.3403 (M + H)⁺.

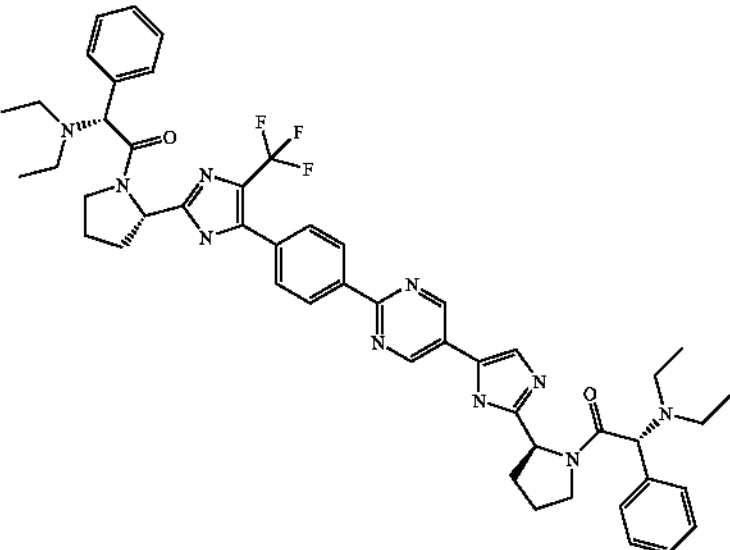
Prepared from entry J34.a (in
lieu of 148e) and Cap-4 using
experimental conditions outlined
in Example 148

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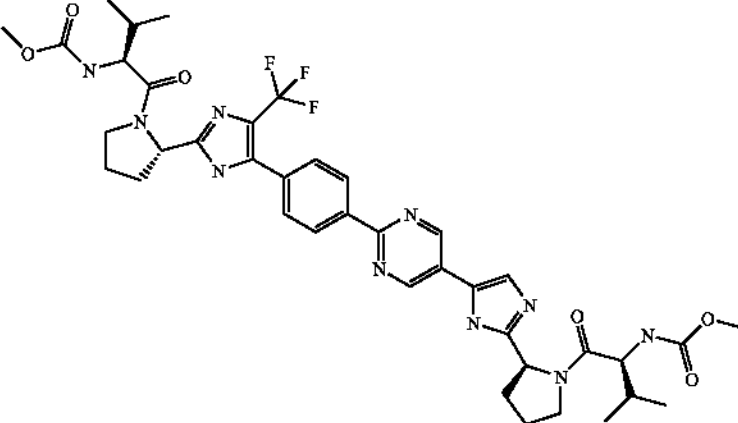
365

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-continued

Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J47	(1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine		$t_R = 1.58$ min, (97%) (Cond 2); LRMS: Anal. Calcd. for $C_{49}H_{56}F_3N_{10}O_2$ 873.44; found: 873.40 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{49}H_{56}F_3N_{10}O_2$ 873.4540; found: 873.4536 (M + H) ⁺ .

Prepared from entry J34.a (in
lieu of 148e) and Cap-2 using
experimental conditions outlined
in Example 148

J48	methyl ((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-carbamate		$t_R = 1.85$ min, (99%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{48}F_3N_{10}O_6$ 809.37; found: 809.37 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{39}H_{48}F_3N_{10}O_6$ 809.3710; found: 809.3683 (M + H) ⁺ .
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Prepared from entry J34.a (in
lieu of 148e) and Cap-51 using
experimental conditions outlined
in Example 148

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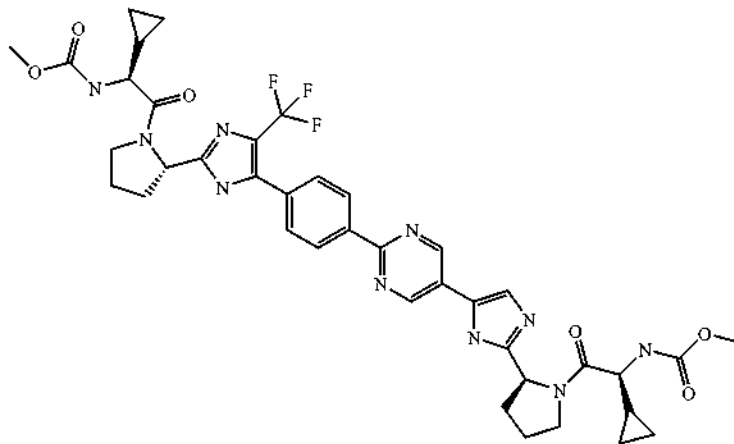
366

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Ex-
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ber Compound Name Structure Analytical Data

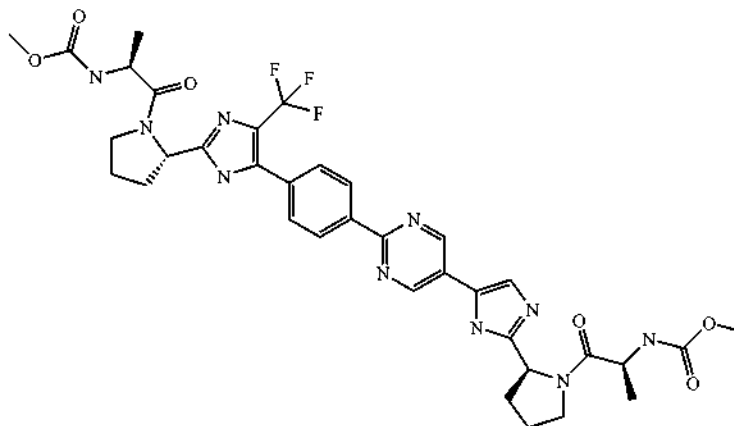
J49 methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2S)-2-cyclopropyl-2-(methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate



t_R = 1.75 min,
(100%) (Cond 2);
LRMS: Anal. Calcd.
for $C_{39}H_{44}F_3N_{10}O_6$
805.34; found:
805.34 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{39}H_{44}F_3N_{10}O_6$
805.3397; found:
805.3384 (M + H)⁺.

Prepared from entry J34.a (in
lieu of 148e) and Cap-54b using
experimental conditions outlined
in Example 148

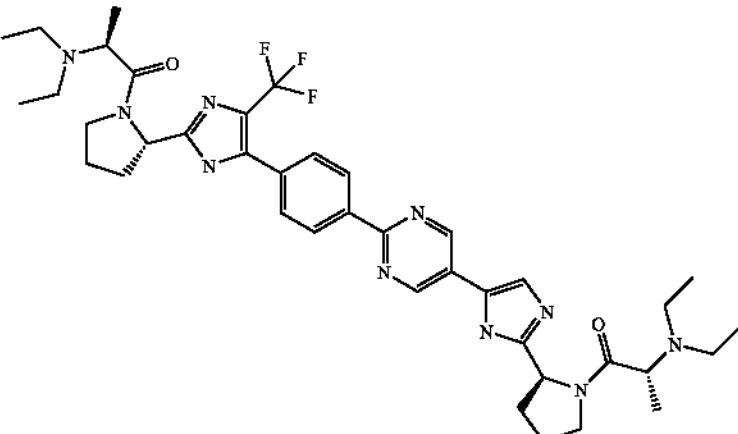
J50 methyl ((1S)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate



t_R = 1.61 min, (94%)
(Cond 2);
LRMS: Anal. Calcd.
for $C_{35}H_{40}F_3N_{10}O_6$
753.31; found:
753.31 (M + H)⁺.
HRMS: Anal. Calcd.
for $C_{35}H_{40}F_3N_{10}O_6$
753.3084; found:
753.3099 (M + H)⁺.

Prepared from entry J34.a (in
lieu of 148e) and Cap-52 using
experimental conditions outlined
in Example 148

-continued

Ex- am- ple Num- ber	Compound Name	Structure	Analytical Data
J51	(2R)-1-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(diethylamino)prop-1-en-1-yl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine		$t_R = 1.41$ min, (92%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{52}F_3N_{10}O_2$ 749.42; found: 749.37 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{39}H_{52}F_3N_{10}O_2$ 749.4227; found: 749.4223 (M + H) ⁺ .
Prepared from entry J34.a (in lieu of 148e) and Cap-70b using experimental conditions outlined in Example 148			

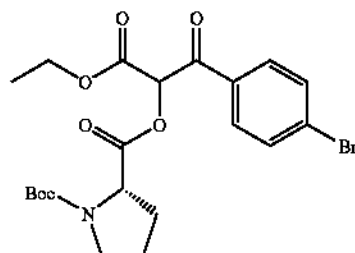
[1200] Cond 1: LCMS conditions: Phenomenex-Luna 4.6×50 mm S10 to 100% B over 3 min, 4 min stop time, 4 mL/min, 220 nm, A: 10% MeOH—90% H₂O—0.1% TFA; B: 90% MeOH—10% H₂O—0.1% TFA

[1201] Cond 2: LCMS conditions: Phenomenex-Luna 4.6×50 mm S10, 0 to 100% B over 2 min, 3 min stop time, 4 mL/min, 220 nm, A: 10% MeOH—90% H₂O—0.1% TFA; B: 90% MeOH—10% H₂O—0.1% TFA

Example J2

(2S)-2-(1-(4-bromophenyl)-3-ethoxy-1,3-dioxopropan-2-yl) 1-tert-butyl pyrrolidine-1,2-dicarboxylate

[1202]



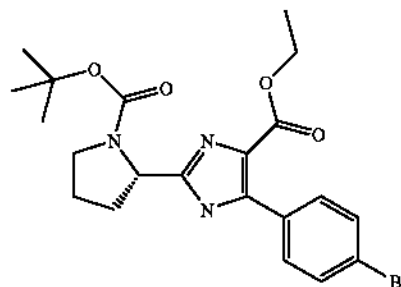
[1203] The ethyl 3-(4-bromophenyl)-3-oxopropanoate (15 g, 55 mmol) was dissolved in CH₂Cl₂ (600 mL) and freshly recrystallized NBS (9.8 g, 55 mmol) was added and the solution stirred 18 hr. The reaction mixture was washed with NaHCO₃ solution, brine, and dried (MgSO₄), filtered, and concentrated to give a residue which was not purified. Ethyl 2-bromo-3-(4-bromophenyl)-3-oxopropanoate (16.5 g, 48

mmol) and N-Boc-L-proline (10 g, 48 mmol) were taken up in acetonitrile (450 mL) and Hunig's base (16 mL, 95 mmol) was added and the solution stirred 18 hr. The solvent was removed by rotary evaporation and the residue taken up in ethyl acetate, washed with 0.1 N HCl, and brine. ¹H NMR (300 MHz, DMSO-d₆) δ 7.95 (d, J=8.4 Hz, 2H), 7.79 (d, J=8.4 Hz, 2H), 6.68-6.65 (m, 1H), 4.39-4.30 (m, 1H), 4.21-4.12 (m, 2H), 2.27-2.21 (m, 1H), 2.0-1.95 (m, 1H), 1.90-1.76 (m, 2H), 1.39 (s, 2H), 1.31 (s, 9H), 1.11 (t, J=7.3 Hz, 3H).
[1204] LRMS: Anal. Calcd. for C₂₁H₂₆BrNO₇ 484.09; found: 410.08 (M+H)⁺.

Example J5

(S)-ethyl 5-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazole-4-carboxylate

[1205]



J5

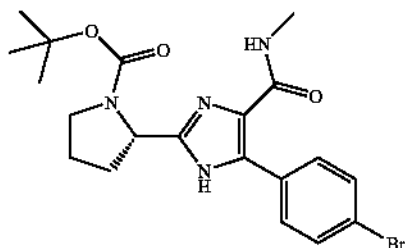
[1206] A 1 L pressure bottle was charged with (2S)-2-(1-(4-bromophenyl)-3-ethoxy-1,3-dioxopropan-2-yl) 1-tert-butyl pyrrolidine-1,2-dicarboxylate J2 (7 g, 35 mmol) and 11 g

of NH_4OAc in 125 mL of Xylene, and the reaction was heated at 140°C . for 3.5 hr. After being cooled, the solution was partition between ethyl acetate and water. The organic layer was concentrated and the resultant residue applied to a Biotage 40 m silica gel cartridge and eluted by 20-100% gradient, ethyl acetate/Hex to give 3 g (45%). ^1H NMR (300 MHz, CDCl_3) δ 12.75 (br. s, 7.82), (br. s, 2H), 7.50 (d, $J=8.4$ Hz, 2H), 4.96-4.92 (m, 1H), 4.23 (q, $J=6.6$ Hz, 2H), 3.68-3.50 (m, 1H), 3.40-3.32 (m, 1H), 2.19-2.15 (m, 1H), 1.99-1.89 (m, 3H), 1.48/1.13 (s, 9H), 1.23 (t, $J=7.3$ Hz, 3H). LRMS: Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{BrN}_3\text{O}_4$ 464.12; found: 464.15 and 466.15 ($\text{M}+\text{H}$) $^+$.

Example J7

(S)-tert-butyl 2-(5-(4-bromophenyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[1207]



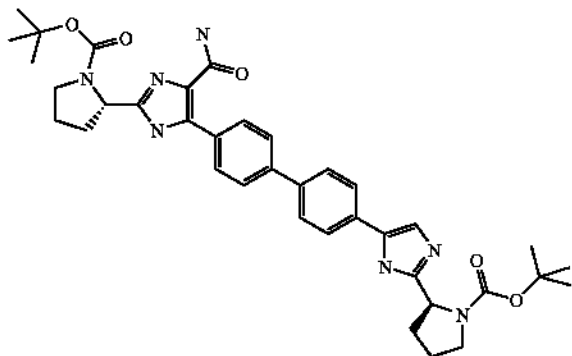
J7

[1208] (S)-ethyl 5-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazole-4-carboxylate (1 g, 2.1 mmol) was dissolved in 2M methylamine in MeOH (35 mL) and heated in a pressure vessel at 70°C . for 48 h. The reaction mixture was concentrated and the residue applied to a Biotage 25 m silica gel cartridge and eluted by 10-100% gradient, ethyl acetate/Hex to give 556 mg (57%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.5 (br.s, 1H), 7.86-7.82 (m, 1H), 7.77 (d, $J=8.4$ Hz, 2H), 7.61 (d, $J=8.7$ Hz, 2H), 4.83-4.70 (m, 1H), 3.69-3.52 (br.s, 1H), 3.42-3.32 (m, 1H), 2.71 (d, 4.8 Hz, 3H), 2.30-1.78 (m, 4H), 1.19-1.14 (m, 9H).

[1209] LRMS: Anal. Calcd. for $\text{C}_{20}\text{H}_{26}\text{BrN}_4\text{O}_3$ 449.12; found: 449.15 and 451.14 ($\text{M}+\text{H}$) $^+$.

Example J11.a

[1210]



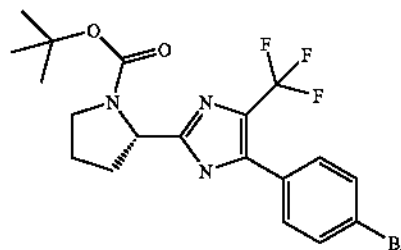
J11.a

[1211] Entry J9 (1.1 g, 1.58 mmol) was taken up in ethanol (60 mL), 28% concentrated ammonium hydroxide soln (10 mL) was added, and the reaction heated in a pressure vessel at 75°C . for 48 h. The solvent was removed by rotary evaporation and the residue taken up in ethyl acetate and washed with water, brine. Concentration and application to a 25 M Biotage cartridge, gradient elution with 10%-100% ethyl acetate/ CH_2Cl_2 , gave J11.a 90 mg (8.5%) and recovered starting material J9 696 mg (63%).

Example J32.a

(S)-tert-butyl 2-(5-(4-bromophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[1212]



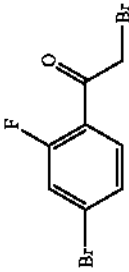
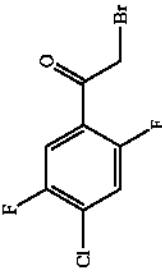
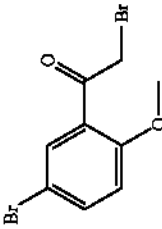
J32.a

[1213] 3-(4-bromophenyl)-3-(2,2-dimethylhydrazono)-1,1-trifluoropropan-2-one (2.0 g, 6.2 mmol) was suspended in 5N sulfuric acid (60 mL) and heated at 45°C . for 6 h. The temperature was raised to 85°C . for 2 h, and upon cooling a precipitate formed. This material which was isolated by filtration to give 1-(4-bromophenyl)-3,3,3-trifluoropropane-1,2-dione 1.6 g (92%) as a yellow solid. The dione (1.6 g, 5.7 mmol) was taken up in methanol (30 mL), N-(tert-butoxycarbonyl)-L-proline (1 g, 5.0 mmol) was added, followed by addition of 28% ammonium hydroxide solution (10 mL). The reaction was stirred at room temperature for 18 h, poured onto dichloromethane (200 mL), washed with water and dried with MgSO_4 . Filtration, concentration and application to a 40 M Biotage cartridge, gradient elution with 5%-30% ethyl acetate/Hexanes, gave J32.a 1.3 g (50%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.88 (br.s, 1H), 7.72 (d, $J=8.4$ Hz, 2H), 7.39 (d, $J=8.0$ Hz, 2H), 4.84-4.70 (m, 1H), 3.57-3.49 (m, 1H), 3.39-3.29 (m, 1H), 2.31-2.20 (m, 1H), 1.98-1.78 (m, 3H), 1.39/1.13 (m, 9H). LRMS: Anal. Calcd. for $\text{C}_{19}\text{H}_{20}\text{BrF}_3\text{N}_3\text{O}_2$ 458.07; found: 458.06 and 460.06 ($\text{M}-\text{H}$) $^-$. HRMS: Anal. Calcd. for $\text{C}_{19}\text{H}_{22}\text{BrF}_3\text{N}_3\text{O}_2$ 460.0847; found: 460.0866 and 462.0840 ($\text{M}+\text{H}$) $^+$.

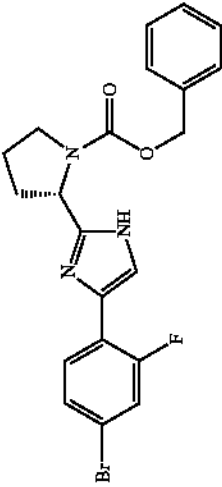
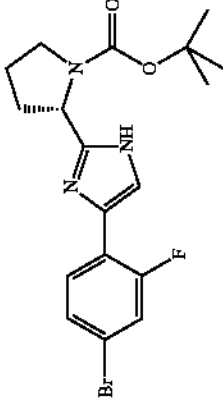
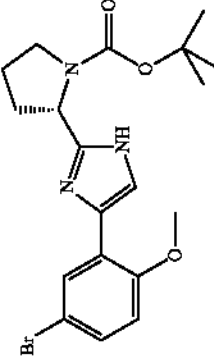
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Section D		
Entry	Compound Name	Structure
D1		 <p>Prepared from 1-(4-bromo-2-fluorophenyl)ethanone (Vendor: Marshallton 50043) using bromination conditions outlined in D5.</p>
D2		 <p>Prepared from 1-(4-chloro-2,5-difluorophenyl)ethanone (Vendor: Oakwood products, 001626) using bromination conditions outlined in D5.</p>
D3		 <p>Prepared from 2-bromo-1-(5-bromo-2-methoxyphenyl)ethanone (Andersh et al., Synth. Commun. 2000, 30 (12), 2091-98) using bromination conditions outlined in D5.</p>
		**Data
		<p>$t_R = 2.65$ min, (86.7%) LCMS: Anal. Calcd. for C_8H_7BrFO 296.88; found: 296.91 (M + H)⁺.</p>
		<p>$t_R = 2.66$ min, (80%) LCMS: Anal. Calcd. for $C_8H_7BrClFO$ 270.92; found: ND (M + H)⁺.</p>
		<p>$t_R = 2.57$ min, (95%) LCMS: Anal. Calcd. for $C_9H_9BrO_2$ 228.99; found: 229.00 (M + H)⁺.</p>

-continued

Entry	Compound Name	Structure	Section D	**Data
D4		 <p data-bbox="612 1278 712 1478">Prepared from entry D1 and CBz-L-proline (in lieu of Boc-L-proline) using experimental conditions outlined in D5.</p>	Section D	$t_R = 2.38$ min, (95.0%) LRMS: Anal. Calcd. for $C_{19}H_{20}^{79}BrFN_3O_2$ 444.07; found: 444.04 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{19}H_{20}^{79}BrFN_3O_2$ 444.0721; found: 444.0736 (M + H) ⁺
D5		 <p data-bbox="981 1310 1014 1520">Experimental conditions in D5</p>		$t_R = 2.27$ min, (95%) LRMS: Anal. Calcd. for $C_{19}H_{22}BrFN_3O_2$ 410.09 and 412.08; found: 410.08 and 412.08 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{19}H_{22}^{79}BrFN_3O_2$ 410.0879; found: 410.0893 (M + H) ⁺
D6		 <p data-bbox="1290 1341 1372 1541">Prepared from entry D3 (in lieu of entry D1) using experimental conditions outlined in D5.</p>		$t_R = 2.26$ min, (95%) LRMS: Anal. Calcd. for $C_{19}H_{22}BrFN_3O_3$ 422.11 and 424.11; found: 422.10 and 424.10 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{19}H_{22}^{79}BrFN_3O_3$ 422.1079; found: 422.1089 (M + H) ⁺

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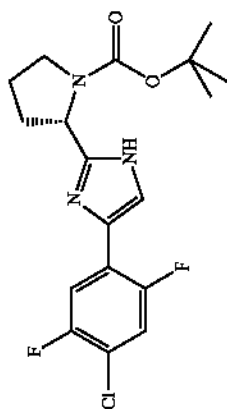
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Section D

Entry **Compound Name** **Structure** ****Data**



Prepared from entry D2
(in lieu of entry D1) using
experimental
conditions outlined in
enclosed experiment.

D8

$t_R = 2.62$ min, (~50%) and
 1.95 min (~50%, boronic
acid)
LRMS: Anal. Calcd. for
 $C_{22}H_{24}BFN_3O_4$ 458.26;
found: 458.23 (M + H)⁺.
HRMS: Anal. Calcd. for
 $C_{22}H_{24}BFN_3O_4$
458.2626; found: 458.2610
(M + H)⁺.

Prepared
from entry D5 (in lieu
of 1b) using experimental
conditions outlined in
Example 1, Step c.

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Section D			
Entry	Compound Name	Structure	**Data
D9	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-methoxy-3-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidine-carboxylate		$t_R = 2.28$ min, (95%) LRMS: Anal. Calcd. for $C_{37}H_{47}N_6O_5$ 655.36; found: 655.37 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{37}H_{47}N_6O_5$ 655.3608; found: 655.3627 (M + H) ⁺ .
		Prepared from entry D6 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	
D10	di-tert-butyl (2S,2'S)-2,2'-(3-fluoro-4,4'-biphenyl-diyl)bis(1H-imidazole-4,2-diyl)di(1-pyrrolidinecarboxylate)		$t_R = 2.21$ min, (99.2%) LCMS: Anal. Calcd. for $C_{36}H_{44}FN_6O_4$ 643.34; found: 643.51 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{36}H_{44}FN_6O_4$ 643.3403; found: 643.3390 (M + H) ⁺ .
		Prepared from entry D5 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	

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Entry	Compound Name	Structure	Section D	**Data
D11	tert-butyl (2S)-2-(4-(4'-(2-(2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,5-difluoro-4-biphenyl)-1-imidazol-2-yl)-1-pyrrolidinecarboxylate		Section D	$t_R = 2.24$ min. (95%) LRMS: Anal. Calcd. for $C_{36}H_{43}F_2N_6O_4$: 661.33; found: 661.35 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{36}H_{43}F_2N_6O_4$: 661.3314; found: 661.3336 (M + H) ⁺ .

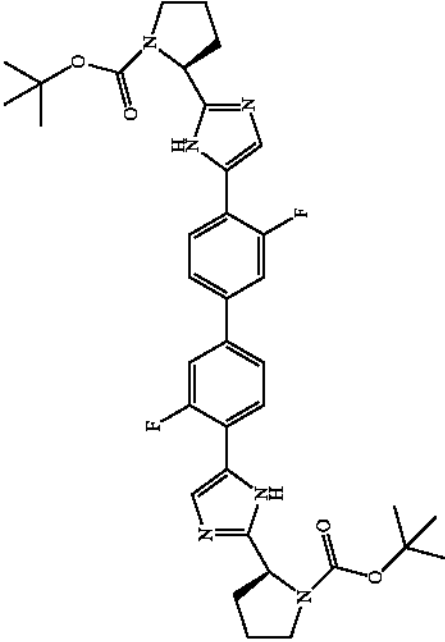
Prepared from entry D7
 (in lieu of 152e-1) and 1c
 using experimental
 conditions outlined in
 Example 152g-1.

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Section D			
Entry	Compound Name	Structure	**Data
D12	di-tert-butyl (2S,2'S)- 2,2'-(3,3'-difluoro- 4,4'- biphenylidyl)bis(1H- imidazole-5,2- diyl)di(1- pyrrolidinecarboxylate)		t _R = 2.20 min, (95%) LRMS: Anal. Calcd. for C ₃₆ H ₄₃ F ₂ N ₆ O ₄ 661.33; found: 661.22 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₃₆ H ₄₃ F ₂ N ₆ O ₄ 661.3314; found: 661.3307 (M + H) ⁺ .

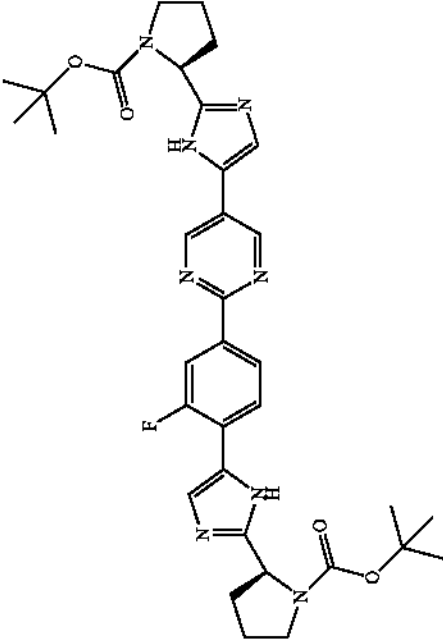
Prepared from entry D5
 (in lieu of 152e-1) using
 experimental
 conditions outlined in
 Example 153a-1.

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Section D	
Entry	Compound Name
D13	tert-butyl (2S)-2-(S-(2-(4-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-3-fluorophenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate
	
	**Data $t_R = 2.27$ min, (95%) LRMS: Anal. Calcd. for $C_{34}H_{42}FN_9O_4$ 645.33; found: 645.34 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{34}H_{42}FN_9O_4$ 645.3313; found: 645.3323 (M + H) ⁺ .

Prepared from entry D8
(in lieu of 1c) and 152b-1
using experimental
conditions outlined in
Example 152g-1.

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-continued

Entry	Compound Name	Structure	Section D	**Data
D14	tert-butyl (2S)-2-(4-(4-(2-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		Section D	$t_R = 2.26$ min, (95%) LRMS: Anal. Calcd. for $C_{39}H_{42}FN_6O_4$ 677.33; found: 677.33 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{39}H_{42}FN_6O_4$ 677.3252; found: 677.3278 (M + H) ⁺ .

Prepared from entry D5
 (in lieu of 152e-1) and 1-
 5c using experimental
 conditions outlined in
 Example 152g-1.

-continued

Entry	Compound Name	Structure	Section D	**Data
D15	tert-butyl (2S)-2-(4-(4'-(2-(2S)-1-(benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		Section D	$t_R = 2.36$ min. (97.3%) LRMS: Anal. Calcd. for $C_{39}H_{41}F_2N_6O_4$: 695.32; found: 695.33 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{39}H_{41}F_2N_6O_4$: 695.3157; found: 695.3151 (M + H) ⁺ .

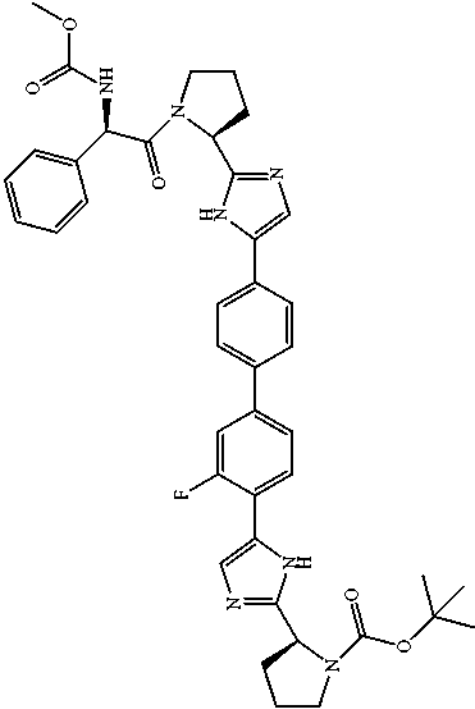
Prepared from entry D8
 (in lieu of 1c) and entry
 D4 using experimental
 conditions outlined in
 Example 152g-1.

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Section D			
Entry	Compound Name	Structure	**Data
D16	tert-butyl (2S)-2-(5-(3-fluoro-4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		$t_R = 2.16$ min. (91.0%) LRMS: Anal. Calcd. for $C_{41}H_{43}FN_7O_5$ 734.35; found: 734.36 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{41}H_{43}FN_7O_5$ 734.3466; found: 734.3474 (M + H) ⁺

Prepared from entry D21
(in lieu of 148e) and Cap-
4 using experimental
conditions outlined in
Example 148.

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Entry	Compound Name	Structure	Section D	**Data
D17	tert-butyl (2S)-2-(5-(4-(2-(2S)-1-(2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		Section D	$t_R = 1.95$ min. (95%) LRMS: Anal. Calcd. for $C_{43}H_{51}FN_7O_3$ 732.40; found: 732.44 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{43}H_{51}FN_7O_3$ 732.4037; found: 732.4065 (M + H) ⁺

Prepared from entry D21
 (in lieu of 148c) and
 Cap-2 using experimental
 conditions outlined in
 Example 148.

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Section D			
Entry	Compound Name	Structure	**Data
D18	tert-butyl (2S)-2-(S-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		$t_R = 2.14$ min, (95%) LRMS: Anal. Calcd. for $C_{39}H_{47}FN_7O_5$: 700.36; found: 700.37 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{39}H_{47}FN_7O_5$: 700.3623; found: 700.3596 (M + H) ⁺ .

Prepared from entry D21
 (in lieu of 148e) and Cap-
 51 using experimental
 conditions outlined in
 Example 148.

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Entry	Compound Name	Structure	Section D	**Data
D19	tert-butyl (2S)-2-(S-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)-amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		Section D	$t_R = 2.23$ min, (95%) LRMS: Anal. Calcd. for $C_{41}H_{44}F_2N_7O_5$: 752.34; found: 752.35 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{41}H_{44}F_2N_7O_5$: 752.3372; found: 752.3385 (M + H) ⁺ .

Prepared from entry D22
 (in lieu of 148e) and Cap-
 4 using experimental
 conditions outlined in
 Example 148.

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-continued

Entry	Compound Name	Structure	Section D	**Data
D20	tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate			t _R = 2.16 min, (90%) LRMS: Anal. Calcd. for C ₃₉ H ₄₆ F ₂ N ₇ O ₅ : 718.35; found: 718.36 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₃₉ H ₄₆ F ₂ N ₇ O ₅ : 718.3528; found: 718.3505 (M + H) ⁺ .
D21	tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate triacetate		Prepared from entry D22 (in lieu of 148e) and Cap-51 using experimental conditions outlined in Example 148.	t _R = 1.94 min, (95%) LRMS: Anal. Calcd. for C ₃₁ N ₅ FN ₆ O ₂ : 543.29; found: 543.30. HRMS: Anal. Calcd. for C ₃₁ N ₅ FN ₆ O ₂ : 543.2884; found: 543.2872 (M + H) ⁺ .
Prepared from entry D14 (in lieu of 152g-8) using experimental conditions outlined in Example 152f-1.				

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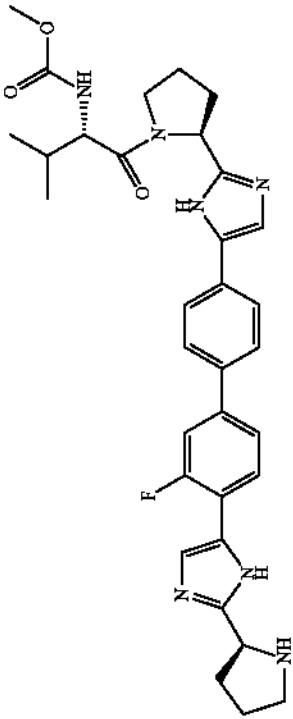
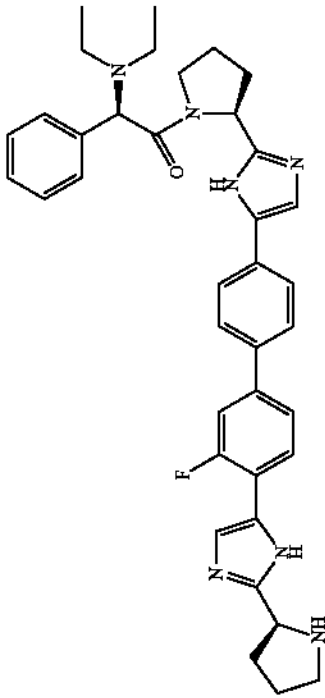
Entry	Compound Name	Structure	Section D	**Data
D22	tert-butyl (2S)-2-(5-(3,3-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate			$t_R = 2.14$ min. (95%) LRM/MS: Anal. Calcd. for $C_{31}H_{33}F_2N_6O_2$ 561.28; found: 561.29 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{31}H_{33}F_2N_6O_2$ 561.2790; found: 561.2766 (M + H) ⁺ .
D23	methyl (1R)-2-((2S)-2-(5-(3-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidine)-2-oxo-1-phenylethyl)carbamate		Prepared from entry D15 (in lieu of 152g-8) using experimental conditions outlined in Example 152h-1.	$t_R = 1.90$ min. (94%) LRM/MS: Anal. Calcd. for $C_{36}H_{37}FN_5O_3$ 634.29; found: 634.29 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{36}H_{37}FN_5O_3$ 634.2942; found: 634.2948 (M + H) ⁺ .

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Section D		Section D	
Entry	Compound Name	Structure	**Data
D24	methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-(2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbamoyl)-2-methylpropyl)carbamate		$t_R = 1.89$ min, (95%) LRMS: Anal. Calcd. for $C_{33}H_{39}FN_7O_3$: 600.31; found: 600.32 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{33}H_{39}FN_7O_3$: 600.3098; found: 600.3121 (M + H) ⁺ .
		Prepared from entry D18 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	
D25	(1R)-N,N-diethyl-2-((2S)-2-(5-(3'-fluoro-4'-(2-(2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-phenylethanamine		$t_R = 1.72$ min, (90%) LRMS: Anal. Calcd. for $C_{38}H_{43}FN_7O_3$: 632.35; found: 632.36 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{38}H_{43}FN_7O_3$: 632.3513; found: 632.3527 (M + H) ⁺ .
		Prepared from entry D17 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	

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Entry	Compound Name	Structure	Section D	**Data
D26	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-(2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)acetyl)-2-methylpropyl)carbamate		Section D	$t_R = 1.56$ min, (95%) LRMS: Anal. Calcd. for $C_{33}H_{38}F_2N_7O_3$ 618.30; found: 618.31 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{33}H_{38}F_2N_7O_3$ 618.3004; found: 618.3024 (M + H) ⁺ .
D27	methyl ((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-(2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)acetyl)-2-oxo-1-phenylethyl)carbamate		Prepared from entry D20 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	$t_R = 1.63$ min, (95%) LRMS: Anal. Calcd. for $C_{36}H_{38}F_2N_7O_3$ 652.28; found: 652.29 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{36}H_{38}F_2N_7O_3$ 652.2848; found: 652.2858 (M + H) ⁺ .

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Section D			
Entry	Compound Name	Structure	**Data
D28	5,5'-(4-methoxy-3,4'-biphenyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)		$t_R = 1.53$ min, (98.2%) LRMS: Anal. Calcd. for $C_{27}H_{31}N_6O$ 455.26; found: 455.26 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{27}H_{31}N_6O$ 455.2559; found: 455.2576 (M + H) ⁺ .
D29	5,5'-(3-fluoro-4,4'-biphenyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole) tetraacetate		$t_R = 1.55$ min, (95%) LRMS: Anal. Calcd. for $C_{26}H_{28}FN_6$ 443.24; found: 443.24 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{26}H_{28}FN_6$ 443.2359; found: 443.2371 (M + H) ⁺ .
D30			$t_R = 1.72$ min, (77.5%) LRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$ 461.23; found: 461.25 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$ 461.2265; found: 461.2272 (M + H) ⁺ .

Prepared from entry D9
(in lieu of 152j-27) using
experimental conditions
outlined in Example 152k-1

Prepared from entry 10 (in
lieu of 152j-27) using
experimental conditions
outlined in Example 152k-1.

Prepared from entry D12
(in lieu of 152j-27) using
experimental
conditions outlined in
Example 152k-1.

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Section D			
Entry	Compound Name	Structure	**Data
D31	5,5'-(2,5'-difluoro-4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)		$t_R = 1.67$ min, (95%) LRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$: 461.23; found: 461.23 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$: 461.2265; found: 461.2287 (M + H) ⁺ .
D32	2-(3-fluoro-4-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)pyrimidine		$t_R = 1.63$ min, (95%) LRMS: Anal. Calcd. for $C_{32}H_{32}FN_8$: 445.23; found: 445.23 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{32}H_{32}FN_8$: 445.2264; found: 445.2268 (M + H) ⁺ .
D33	(1R,1'R)-2,2'-(4-methoxy-3,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)		$t_R = 1.71$ min, (95%) LRMS: Anal. Calcd. for $C_{40}H_{43}N_8O_3$: 777.42; found: 777.41 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{40}H_{43}N_8O_3$: 777.4241; found: 777.4254 (M + H) ⁺ .

Prepared from entry D11
(in lieu of 152j-27) using
experimental
conditions outlined in
Example 152k-1.

Prepared from entry D13
(in lieu of 152j-27) using
experimental
conditions outlined in
Example 152k-1.

Prepared from entry D28
(in lieu of 148e) and Cap-
1 using experimental
conditions outlined in
Example 148.

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Entry	Compound Name	Structure	Section D	**Data
D34	dimethyl ((4-methoxy-3,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl((2S)-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyil))biscarbamate		Section D	$t_R = 2.09$ min, (95%) LRMS: Anal. Calcd. for $C_{37}H_{39}N_9O_7$: 837.37; found: 837.34 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{37}H_{39}N_9O_7$: 837.3724; found: 837.3690 (M + H) ⁺ .
D35	methyl ((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazo-5-yl)-3-fluoro-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		Section D	$t_R = 1.85$ min, (97.2%) LRMS: Anal. Calcd. for $C_{43}H_{54}FN_9O_4$: 789.43; found: 789.43 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{43}H_{54}FN_9O_4$: 789.4252; found: 789.4225 (M + H) ⁺ .

Prepared from entry D28
(in lieu of 148e) and Cap-
4 using experimental
conditions outlined in
Example 148.

Prepared from entry D25
(in lieu of 148e) and Cap-51
using experimental
conditions outlined in
Example 148.

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Entry	Compound Name	Structure	Section D	**Data
D36	methyl (1S)-2-((2S)-2-(5-(4'-(2-(2S)-1-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenyl)-1H-imidazol-2-yl)-1-methyl-2-oxoethyl)carbamate			$t_R = 1.76$ min, (97.9%) LRMS: Anal. Calcd. for $C_{43}H_{50}FN_9O_4$ 761.39; found: 761.26 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{43}H_{50}FN_9O_4$ 761.3939; found: 761.3967 (M + H) ⁺
D37	methyl (1R)-2-((2S)-2-(5-(4'-(2-(2S)-1-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenyl)-1H-imidazol-2-yl)-1-phenylethyl)carbamate		Prepared from entry D25 (in lieu of 148e) and Cap- 52 using experimental conditions outlined in Example 148.	$t_R = 1.90$ min, (98.6%) LRMS: Anal. Calcd. for $C_{48}H_{52}FN_9O_4$ 823.41; found: 823.42 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{48}H_{52}FN_9O_4$ 823.4096; found: 823.4102 (M + H) ⁺

Prepared from entry D25
 (in lieu of 148e) and Cap-
 4 using experimental
 conditions outlined in
 Example 148.

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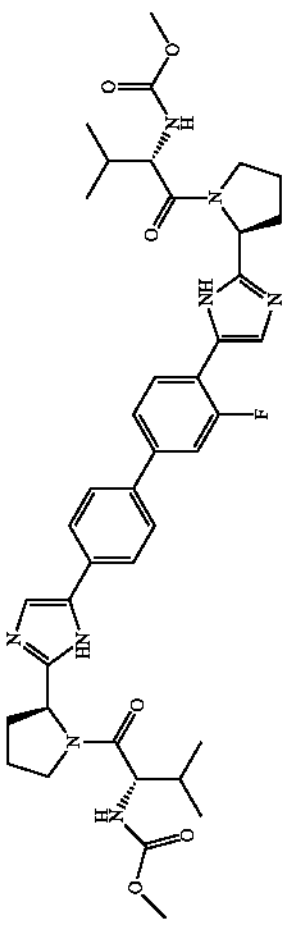
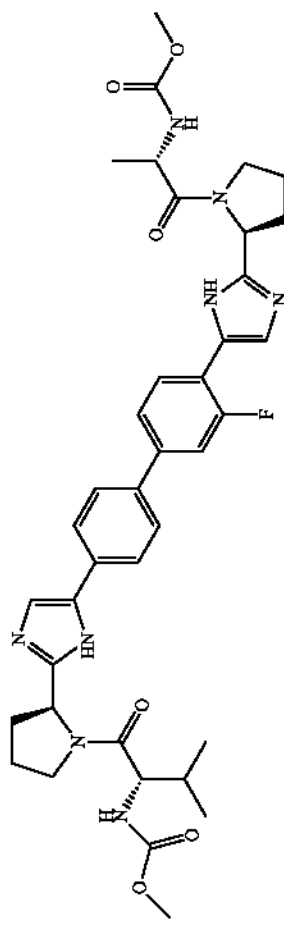
Section D			
Entry	Compound Name	Structure	**Data
D38	methyl (1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-(2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-1-phenylethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbamate		$t_R = 1.89$ min, (98.2%) LRMS: Anal. Calcd. for $C_{47}H_{49}N_9O_7$, 763.34; found: 763.32 ($M + H$) ⁺ . HRMS: Anal. Calcd. for $C_{47}H_{49}N_9O_7$, 763.3368; found: 763.3358 ($M + H$) ⁺ .
		Prepared from entry D23 (in lieu of 148e) and Cap-52 using experimental conditions outlined in Example 148.	
D39	methyl (1R)-2-((2S)-2-(5-(4'-(2-(2S)-1-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbamate		$t_R = 1.88$ min, (98.7%) LRMS: Anal. Calcd. for $C_{48}H_{52}FN_9O_4$, 823.41; found: 823.39 ($M + H$) ⁺ . HRMS: Anal. Calcd. for $C_{48}H_{52}FN_9O_4$, 823.4096; found: 823.4127 ($M + H$) ⁺ .
		Prepared from entry D23 (in lieu of 148e) and Cap-2 using experimental conditions outlined in Example 148.	

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Section D			
Entry	Compound Name	Structure	**Data
D40	methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-((2S)-1-((2S)-2-((methoxycarbonyl)-amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		$t_R = 1.97$ min, (98.4%) LRMS: Anal. Calcd. for $C_{40}H_{50}FN_6O_6$: 757.38; found: 757.32 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{40}H_{50}FN_6O_6$: 757.3837; found: 757.3815 (M + H) ⁺ .
		Prepared from entry D29 (in lieu of 148e) and Cap-51 using experimental conditions outlined in Example 148.	
D41	methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		$t_R = 1.82$ min, (95.0%) LRMS: Anal. Calcd. for $C_{39}H_{48}FN_6O_6$: 729.35; found: 729.29 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{39}H_{48}FN_6O_6$: 729.3524; found: 729.3523 (M + H) ⁺ .
		Prepared from entry D24 (in lieu of 148e) and Cap-52 using experimental conditions outlined in Example 148.	

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Section D

Entry	Compound Name	Structure	**Data
D42	methyl ((1S,2R)-1-((2S)-2-(5-(3-fluoro-4-(2-(2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbamate		$t_R = 1.91$ min, (94.0%) LRMS: Anal. Calcd. for $C_{40}H_{50}FN_9O_7$: 773.38; found: 773.31 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{40}H_{50}FN_9O_7$: 773.3786; found: 773.3759 (M + H) ⁺ .
			$t_R = 1.72$ min, (97.6%) LRMS: Anal. Calcd. for $C_{40}H_{52}FN_9O_4$: 727.41; found: 727.35 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{40}H_{52}FN_9O_4$: 727.4096; found: 727.4091 (M + H) ⁺ .

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Section D			
Entry	Compound Name	Structure	**Data
D44	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenyl)-1-pyrrolidinyl)carboxyl)-2-methylpropyl)carbamate		$t_R = 1.83$ min, (96.9%) LRMS: Anal. Calcd. for $C_{43}H_{54}FN_8O_4$: 789.43; found: 789.36 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{43}H_{54}FN_8O_4$: 789.4252; found: 789.4225 (M + H) ⁺ .
		Prepared from entry D24 (in lieu of 148e) and Cap-2 using experimental conditions outlined in Example 148.	
D45	methyl ((1S)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbamate		$t_R = 1.69$ min, (97.7%) LRMS: Anal. Calcd. for $C_{38}H_{42}FN_8O_6$: 701.32; found: 701.30 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{38}H_{42}FN_8O_6$: 701.3222; found: 701.3211 (M + H) ⁺ .
		Prepared from entry D29 (in lieu of 148e) and Cap-52 using experimental conditions outlined in Example 148.	

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Section D		Section D	
Entry	Compound Name	Structure	**Data
D46	dimethyl (3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazo[5,2-d]pyrrolidin-2-yl)-2-oxo-1-phenyl-2,1-ethanediyl)biscarbamate		$t_R = 2.05$ min, (99.9%) LRMS: Anal. Calcd. for $C_{46}H_{46}FN_6O_6$ 825.35; found: 825.35 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{46}H_{46}FN_6O_6$ 825.3524; found: 825.3522 (M + H) ⁺ .
		Prepared from entry D29 (in lieu of 148e) and Cap- 4 using experimental conditions outlined in Example 148.	
D47	(1R,1'R)-2,2'-(3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazo[5,2-d]pyrrolidin-2-yl)-bis-(N,N-diethyl-2-oxo-1-phenylethanamine)		$t_R = 1.72$ min, (99.5%) LRMS: Anal. Calcd. for $C_{50}H_{50}FN_6O_2$ 821.47; found: 821.44 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{50}H_{50}FN_6O_2$ 821.4667; found: 821.4636 (M + H) ⁺ .
		Prepared from entry D29 (in lieu of 148e) and Cap- 2 using experimental conditions outlined in Example 148.	

-continued

Section D			
Entry	Compound Name	Structure	**Data
D48	methyl ((1R)-2-((2S)-2-(5-(4-(2-(2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.76$ min, (99.7%) LRMS: Anal. Calcd. for $C_{43}H_{50}FN_9O_4$: 761.39; found: 761.27 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{43}H_{50}FN_9O_4$: 761.3939; found: 761.3952 (M + H) ⁺ .
		Prepared from entry D23 (in lieu of 148e) and Cap-69b using experimental conditions outlined in Example 148.	
D49	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4-(2-(2S)-1-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		$t_R = 1.92$ min, (98.7%) LRMS: Anal. Calcd. for $C_{43}H_{52}FN_9O_4$: 787.41; found: 787.36 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{43}H_{52}FN_9O_4$: 787.4096; found: 787.4074 (M + H) ⁺ .
		Prepared from entry D25 (in lieu of 148e) and Cap-54b using experimental conditions outlined in Example 148.	

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Section D			
Entry	Compound Name	Structure	**Data
D50	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3-fluoro-4-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		$t_R = 1.94$ min, (99.0%) LRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_7$ 755.37; found: 755.32 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{40}H_{48}FN_8O_6$ 755.3681; found: 755.3670 (M + H) ⁺
		Prepared from entry D24 (in lieu of 148e) and Cap-54b using experimental conditions outlined in Example 148.	
D51	methyl ((1R)-2-((2S)-2-(5-(4-(2-(N,N-diethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.92$ min, (98.3%) LRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.39; found: 761.35 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.3939; found: 761.3956 (M + H) ⁺
		Prepared from entry D23 (in lieu of 148e) and Cap-69b using experimental conditions outlined in Example 148.	

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Section D			
Entry	Compound Name	Structure	**Data
D52	methyl ((1S)-2-((2S)-2-(5-(2',5'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-methyl-2-oxoethyl)carbamate		$t_R = 1.69$ min, (99.2%) LRMS: Anal. Calcd. for $C_{39}H_{41}F_2N_9O_6$ 719.31; found: 719.29 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{39}H_{41}F_2N_9O_6$ 719.3117; found: 719.3109 (M + H) ⁺
		Prepared from entry D31 (in lieu of 148e) and Cap-52 using experimental conditions outlined in Example 148.	
D53	dimethyl ((2,5-difluoro-4'-(biphenyldiyl)bis(1H-imidazo[5,2-d]pyrrolidin-2-yl)-2-oxo-1-phenyl-2,1-ethanediyl))biscarbamate		$t_R = 2.08$ min, (100.0%) LRMS: Anal. Calcd. for $C_{46}H_{43}F_2N_9O_6$ 843.34; found: 843.34 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{46}H_{43}F_2N_9O_6$ 843.3430; found: 843.3458 (M + H) ⁺
		Prepared from entry D31 (in lieu of 148e) and Cap-4 using experimental conditions outlined in Example 148 of 10889PSP.	

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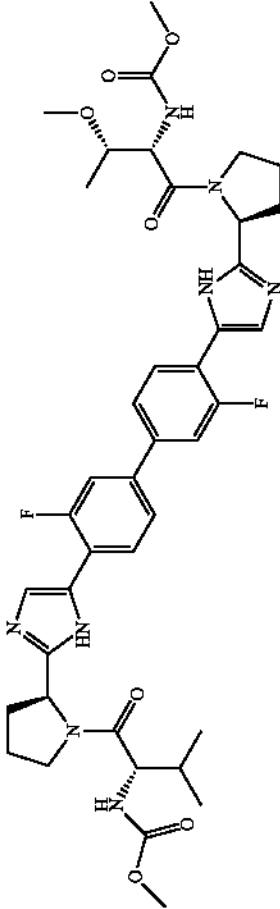
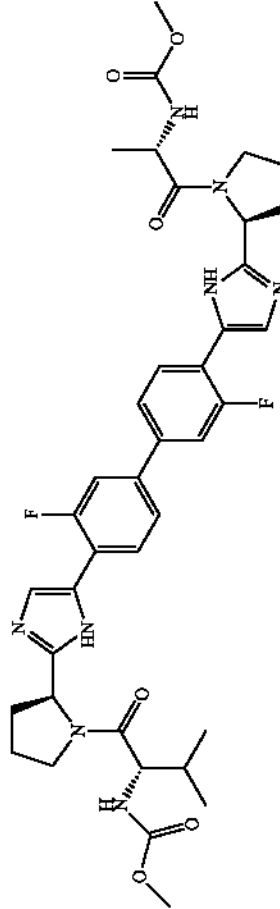
Section D			
Entry	Compound Name	Structure	**Data
D54	(1R,1'R)-2,2'-(2,5-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis-(N,N-diethyl-2-oxo-1-phenylethanamine)		$t_R = 1.76$ min, (99.8%) LRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.46; found: 839.43 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.4573; found: 839.4585 (M + H) ⁺
		Prepared from entry D31 (in lieu of 148e) and Cap-2 using experimental conditions outlined in Example 148.	
D55	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3,3'-difluoro-4'-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl))-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		$t_R = 1.93$ min, (98.5%) LRMS: Anal. Calcd. for $C_{60}H_{60}F_2N_{10}O_6$ 773.36; found: 773.31 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{60}H_{60}F_2N_{10}O_6$ 773.3567; found: 773.3587 (M + H) ⁺
		Prepared from entry D26 (in lieu of 148e) and Cap-54b using experimental conditions outlined in Example 148.	

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Section D		Section D	
Entry	Compound Name	Structure	**Data
D56	methyl ((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carboxyl)-2-methoxypropyl)carbamate		$t_R = 2.00$ min, (98.0%) LRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_9O_7$ 791.37; found: 791.32 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_9O_7$ 791.3692; found: 791.3682 (M + H) ⁺
		Prepared from entry D26 (in lieu of 148e) and Cap-86 using experimental conditions outlined in Example 148.	
D57	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carboxyl)-2-methoxypropyl)carbamate		$t_R = 1.86$ min, (95.6%) LRMS: Anal. Calcd. for $C_{39}H_{43}F_2N_9O_6$ 747.34; found: 747.30 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{39}H_{43}F_2N_9O_6$ 747.3430; found: 747.3425 (M + H) ⁺
		Prepared from entry D26 (in lieu of 148e) and Cap-52 using experimental conditions outlined in Example 148.	

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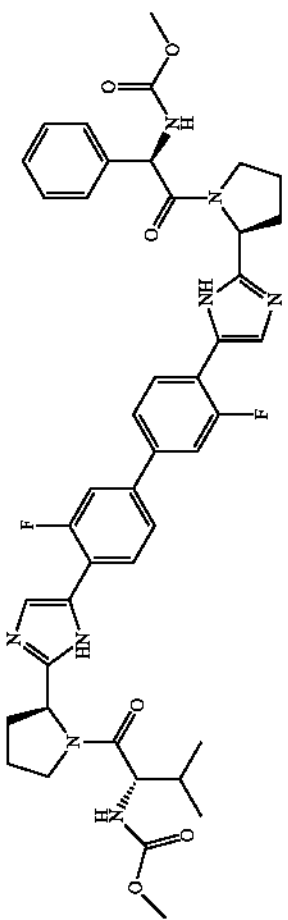
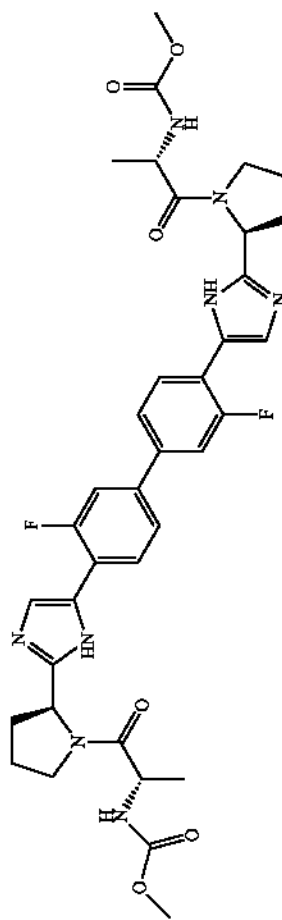
Section D			
Entry	Compound Name	Structure	**Data
D58	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-(2S)-1-((methoxycarbonyl)-amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbamate methylpropyl)carbamate		$t_R = 2.02$ min, (96.3%) LRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_6$ 775.37; found: 775.31 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_6$ 775.3743; found: 775.3734 (M + H) ⁺ .
		Prepared from entry D26 (in lieu of 148e) and Cap-51 using experimental conditions outlined in Example 148.	
D59	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-(2S)-1-(N,N-diethylpyrrolidinyl)-2-imidazol-5-yl)-3,3'-difluoro-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbamate methylpropyl)carbamate		$t_R = 1.78$ min, (98.2%) LRMS: Anal. Calcd. for $C_{40}H_{51}F_2N_8O_4$ 745.40; found: 745.34 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{40}H_{51}F_2N_8O_4$ 745.4001; found: 745.4008 (M + H) ⁺ .
		Prepared from entry D26 (in lieu of 148e) and Cap-69b using experimental conditions outlined in Example 148.	

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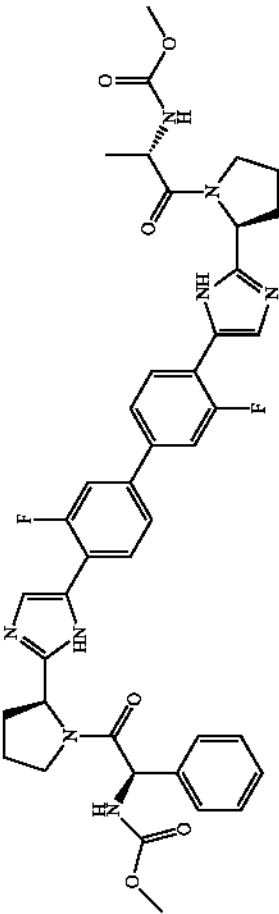
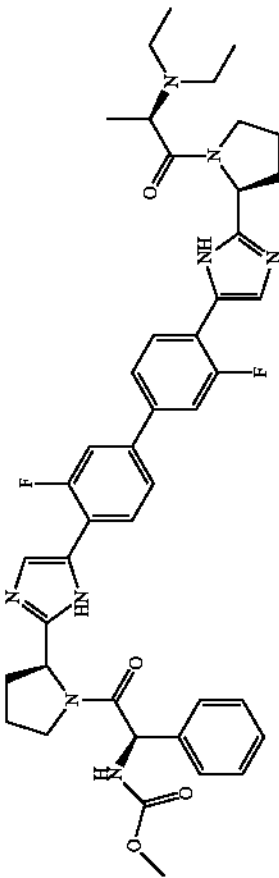
Section D			
Entry	Compound Name	Structure	**Data
D60	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-(2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		$t_R = 2.08$ min, (99.1%) LRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_6$ 809.36; found: 809.29 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_6$ 809.3587; found: 809.3568 (M + H) ⁺ .
		Prepared from entry D26 (in lieu of 148e) and Cap-4 using experimental conditions outlined in Example 148.	
D61	methyl ((1S)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-(2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		$t_R = 1.71$ min, (94.3%) LRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_6$ 719.31; found: 719.19 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_6$ 719.3117; found: 719.3115 (M + H) ⁺ .
		Prepared from entry D30 (in lieu of 148e) and Cap-52 using experimental conditions outlined in Example 148.	

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Section D		Section D	
Entry	Compound Name	Structure	**Data
D62	methyl ((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.94$ min, (98.3%) LRMS: Anal. Calcd. for $C_{41}H_{43}F_2N_8O_6$: 781.33; found: 781.26 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{41}H_{43}F_2N_8O_6$: 781.3274; found: 781.3264 (M + H) ⁺ .
		Prepared from entry D27 (in lieu of 148e) and Cap-52 using experimental conditions outlined in Example 148.	
D63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-(N,N-diethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$t_R = 1.44$ min, (99.0%) LRMS: Anal. Calcd. for $C_{43}H_{49}F_2N_8O_4$: 779.38; found: 779.32 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{43}H_{49}F_2N_8O_4$: 779.3845; found: 779.3842 (M + H) ⁺ .
		Prepared from entry D27 (in lieu of 148e) and Cap-69b using experimental conditions outlined in Example 148.	

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Section D

Entry	Compound Name	Structure	**Data
D66	methyl (1S)-1-cyclopropyl-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		$t_R = 2.01$ min, (99.5%) LRMS: Anal. Calcd. for $C_{43}H_{43}F_2N_9O_6$ 807.34; found: 807.29 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{43}H_{43}F_2N_9O_6$ 807.3430; found: 807.3409 (M + H) ⁺
D67	methyl (1S)-2-((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		$t_R = 1.58$ min, (91.1%) LRMS: Anal. Calcd. for $C_{34}H_{40}FN_{10}O_6$ 703.31; found: 703.27 (M + H) ⁺ HRMS: Anal. Calcd. for $C_{34}H_{40}FN_{10}O_6$ 703.3116; found: 703.3101 (M + H) ⁺

Prepared from entry D27
(in lieu of 148e) and Cap-
54b using experimental
conditions outlined in
Example 148.

Prepared from entry D32
(in lieu of 148e) and Cap-
52 using experimental
conditions outlined in
Example 148.

-continued

Section D

Entry	Compound Name	Structure	**Data
D68	methyl ((1S)-1-((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-(2S)-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbamate 2-methylpropyl)carbamate		$t_R = 1.95$ min, (99.3%) LRMS: Anal. Calcd. for $C_{39}H_{49}FN_{10}O_6$: 759.37; found: 759.30 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{39}H_{49}FN_{10}O_6$: 759.3742; found: 759.3715 (M + H) ⁺ .
D69	methyl ((1R)-2-(2S)-2-(5-(2-fluoro-4-(5-(2-((2R)-2-(methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)2-oxo-1-phenylethyl)carbamate		$t_R = 2.05$ min, (99.3%) LRMS: Anal. Calcd. for $C_{44}H_{44}FN_{10}O_6$: 827.34; found: 827.27 (M + H) ⁺ . HRMS: Anal. Calcd. for $C_{44}H_{44}FN_{10}O_6$: 827.3429; found: 827.3407 (M + H) ⁺ .

Prepared from entry D32
(in lieu of 148e) and Cap-
51 using experimental
conditions outlined in
Example 148.

Prepared from entry D32
(in lieu of 148e) and Cap-
4 using experimental
conditions outlined in
Example 148.

-continued

Entry	Compound Name	Structure	Section D	**Data
D70	methyl ((1S,2R)-1-((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbamate		Section D	t _R = 1.79 min, (93.0%) LRMS: Anal. Calcd. for C ₃₉ H ₄₉ FN ₁₀ O ₈ 791.36; found: 791.31 (M + H) ⁺ . HRMS: Anal. Calcd. for C ₃₉ H ₄₉ FN ₁₀ O ₈ 791.3641; found: 791.3636 (M + H) ⁺ .

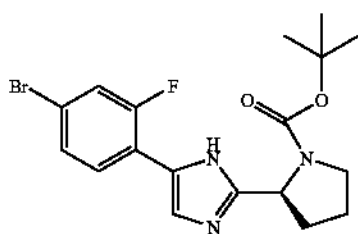
Prepared from entry D32
(in lieu of 148e) and Cap-
86 using experimental
conditions outlined in
Example 148.

**LCMS conditions: Phenomenex-Luna 4.6 × 50 mm S10, 0 to 100% B over 3 min, 4 min stop time, 4 mL/min, 220 nm, A: 10% MeOH-90% H₂O - 0.1% TFA; B: 90% MeOH-10% H₂O-0.1% TFA

Example D5

(S)-tert-butyl 2-(5-(4-bromo-2-fluorophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[1214]



D5

[1215] Bromine (0.54 mL, 10.6 mmol) was added dropwise to a cold (0° C.) solution of 4-bromo-2-fluoroacetophenone (2.30 g, 10.6 mmol) in dioxane (80 mL) and tetrahydrofuran (80 mL). The mixture was stirred for 1 h at 0° C. and warmed to RT for 15 h. The mixture was diluted with ethyl acetate, washed with saturated NaHCO₃ solution, 5% sodium thiosulfate solution and brine prior to drying (Na₂SO₄). 2-Bromo-1-(4-bromo-2-fluorophenyl)ethanone (D1) was isolated as a colorless film which solidified upon further concentration under high vacuum. This solid was dissolved into anhydrous acetonitrile (50 mL) and treated with N-Boc-L-proline (2.28 g, 10.6 mmol) and diisopropylethylamine (1.85 mL, 10.6 mmol). After being stirred for 3 h at RT, the solvent was removed in vacuo and the residue was partitioned into ethyl acetate and water. The organic phase was washed with 0.1N hydrochloric acid, saturated NaHCO₃ solution and brine prior to drying (Na₂SO₄), filtration, and concentration. This residue was taken up in xylenes (50 mL) and treated to solid NH₄OAc (4.1 g, 53.0 mmol). The mixture was heated at 140° C. for 2 hr in a thick-walled, screw-top flask before it was cooled to ambient temperature, diluted with ethyl acetate and washed with saturated NaHCO₃ solution and brine prior to drying (Na₂SO₄) and concentration. Purification of the residue by Biotage™ flash chromatography on silica gel (65M column, preequilibration with 16% B for 1800 mL followed by gradient elution with 16% B to 16% B for 450 mL, 16% B to 50% B for 2199 mL and finally 50% B to 100% B for 2199 mL) afforded title compound (D5) (3.61 g, 83%) as a brownish/caramel-colored oil. A small portion (40 mg) of the title compound was further purified by preparative HPLC (20% B to 100% B over 14 min where B is 10 mM NH₄OAc in 10:90 H₂O/ACN and A is 10 mM NH₄OAc in 95:5 H₂O/CAN using a Phenomenex-Gemini 30x100 mm S10 column flowing at 40 mL/min) to afford pure title compound (31.8 mg) as a white solid.

[1216] ¹H NMR (500 MHz, DMSO-d₆) δ 12.13-11.95 (m, 1H), 7.94 (br s, 1H), 7.54 (d, J=10.7 Hz, 1H), 7.42 (d, J=7.9 Hz, 1H), 7.36-7.34 (m, 1H), 4.86-4.77 (2m, 1H), 3.54 (m, 1H), 3.38-3.32 (m, 1H), 2.28-2.14 (2m, 1H), 2.05-1.78 (2m, 3H), 1.39 and 1.14 (2s, 9H).

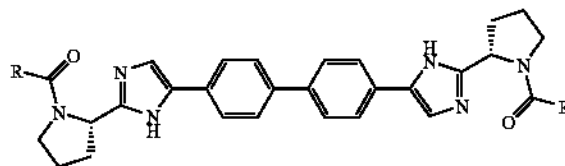
[1217] HPLC Phenomenex LUNA C-18 4.6x50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.27 min, 95% homogeneity index.

[1218] LRMS: Anal. Calcd. for C₁₈H₂₂BrFN₃O₂ 410.09 and 412.09; found: 410.08 and 412.08 (M+H)⁺.

[1219] HRMS: Anal. Calcd. for C₁₈H₂₂BrFN₃O₂ 410.0879; found: 410.0893 (M+H)⁺.

Examples M1-M27

[1220]



[1221] Example M1-M27 were prepared from 1e and the respective acids using the method described for Example 1. The products were prepared as TFA salts, unless noted otherwise. LC Conditions were as follows:

Condition 1

Column=Phenomenex-Luna 3.0x50 mm S10

Start % B=0

Final % B=100

[1222] Gradient time=2 min

Stop time=3 min

Flow Rate=4 mL/min

Wavelength=220 nm

[1223] Solvent A=0.1% TFA in 10% methanol/90% H₂O

Solvent B=0.1% TFA in 90% methanol/10% H₂O

Condition 2

Column=Phenomenex-Luna 4.6x50 mm S10

Start % B=0

Final % B=100

[1224] Gradient time=2 min

Stop time=3 min

Flow Rate=5 mL/min

Wavelength=220 nm

[1225] Solvent A=0.1% TFA in 10% methanol/90% H₂O

Solvent B=0.1% TFA in 90% methanol/10% H₂O

Condition 3

Column=HPLC XTERRA C18 3.0x50 mm S7

Start % B=0

Final % B=100

[1226] Gradient time=3 min

Stop time=4 min

Flow Rate=4 mL/min

Wavelength=220 nm

[1227] Solvent A=0.1% TFA in 10% methanol/90% H₂O

Solvent B=0.1% TFA in 90% methanol/10% H₂O

Condition M1

Column: Luna 4.6x50 mm S10

Start % B=0

Final % B=100

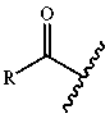
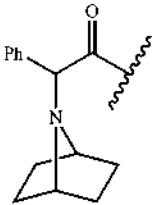
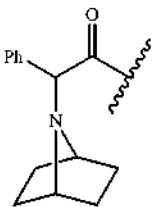
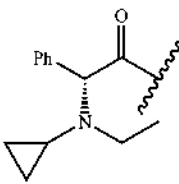
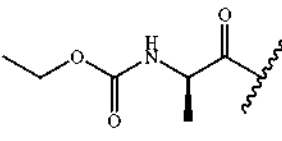
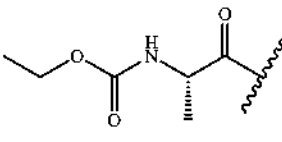
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Stop time=4 min

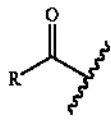
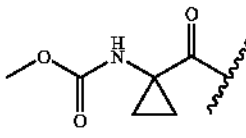
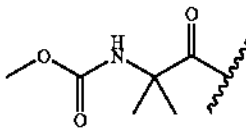
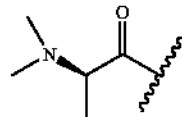
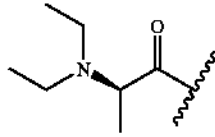
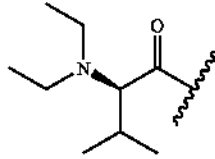
Flow rate=4 mL/min

Solvent A:=95% H₂O: 5% CH₃CN, 10 mM Ammonium acetate

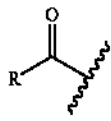
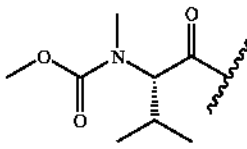
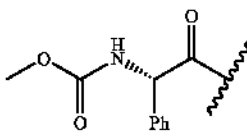
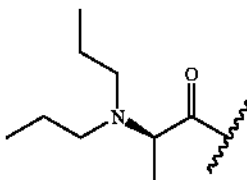
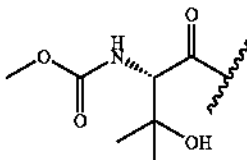
Solvent B:=5% H₂O: 95% CH₃CN; 10 mM Ammonium acetate

Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data; ¹ H NMR data
M1	7,7'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediy))bis(7-azabicyclo[2.2.1]heptane)	 (Cap-77a)	1.04 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₄ H ₅₉ N ₉ O ₂ : 851.48; found 851.55; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₄ H ₅₉ N ₉ O ₂ : 851.4761; found 851.4780
M2	7,7'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediy))bis(7-azabicyclo[2.2.1]heptane)	 (Cap-77b)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₄ H ₅₉ N ₉ O ₂ : 851.48; found 851.57; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₄ H ₅₉ N ₉ O ₂ : 851.4761; found 851.4792
M3	N,N'-(4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy))bis(N-ethylcyclopropanamine)	 (Cap-78)	1.13 min (Cond. 1); >95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₂ H ₅₉ N ₉ O ₂ : 827.48; found 827.69; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₂ H ₅₉ N ₉ O ₂ : 827.4761; found 827.4782
M4	ethyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(ethoxycarbonyl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-59a)	1.20 min (Cond. 1); >97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₈ O ₆ : 711.36; found 711.46; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₈ O ₆ : 711.3619; found 711.3638
M5	ethyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(ethoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-59b)	1.16 min (Cond. 1); 97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₈ O ₆ : 711.36; found 711.48; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₈ O ₆ : 711.3619; found 711.3621

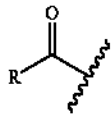
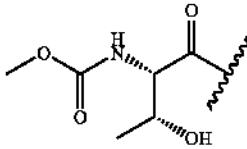
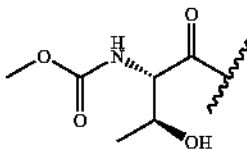
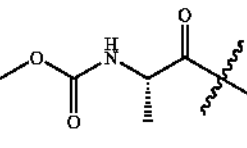
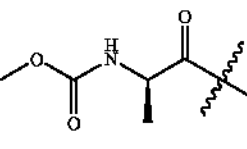
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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data; ¹ H NMR data
M6	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl-1,1-cyclopropanediyl))biscarbamate	 (Cap-60)	1.12 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₃ N ₉ O ₆ : 707.33; found 707.45; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₃ N ₉ O ₆ : 707.3306; found 707.3309
M7	methyl (2-((2S)-2-(5-(4'-((2S)-1-(2-(methoxycarbonyl)amino)-2-methylpropanoyl)-2-pyrrolidinediyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinediyl)-1,1-dimethyl-2-oxoethyl)carbamate	 (Cap-61)	1.21 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₉ O ₆ : 711.36; found 711.53; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₉ O ₆ : 711.3619; found 711.3652
M8	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-2-propanamine)	 (Cap-83)	0.91 min (Cond. 1); >80%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₇ N ₉ O ₂ : 623.38; found 623.46; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₇ N ₉ O ₂ : 623.3822; found 623.3819
M9	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-1-oxo-2-propanamine)	 (Cap-69a)	1.00 min (Cond. 1); >95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₅ N ₉ O ₂ : 623.38; found 679.67; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₅ N ₉ O ₂ : 679.4448; found 679.4432
M10	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-3-methyl-1-oxo-2-butanamine)	 (Cap-72)	1.03 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₆₃ N ₉ O ₂ : 735.51; found 735.76; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₆₃ N ₉ O ₂ : 735.5074; found 735.5060

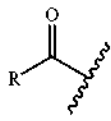
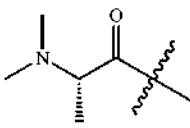
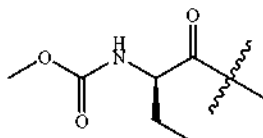
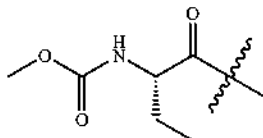
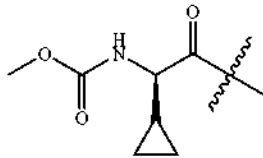
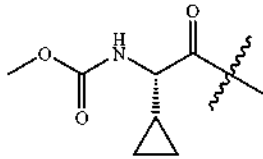
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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data; ¹ H NMR data
M11	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)(methyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate	 (Cap-62)	1.46 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₅ N ₉ O ₂ : 767.42; found 767.38; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₅ N ₉ O ₂ : 767.4245; found 767.4252
M12	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-phenyl-2,1-ethanediy)))biscarbamate	 (Cap-82)	1.32 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₄₇ N ₉ O ₆ : 807.36; found 807.32; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₄₇ N ₉ O ₆ : 807.3619; found 807.3651
M13	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-1-oxo-1,2-propanediyl)))bis(N-propyl-1-propanamine)	 (Cap-70a)	1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₆₃ N ₉ O ₂ : 735.51; found 735.46; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₆₃ N ₉ O ₂ : 735.5074; found 735.5063
M14	methyl ((1S)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate	 (Cap-65)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₁ N ₉ O ₈ : 771.38; found 771.21

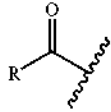
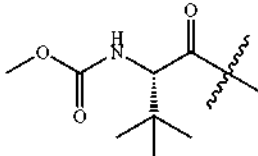
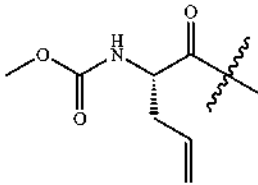
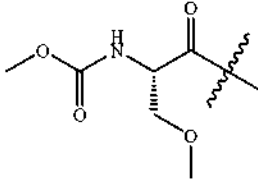
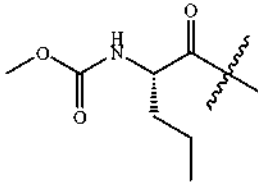
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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data; ¹ H NMR data
M15	methyl ((1S,2R)-2-hydroxy-1-(((2S)-2-(5-(4'-((2S)-1-((2S,3R)-3-hydroxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl) carbamate	 (Cap-66)	1.10 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₉ O ₈ : 743.35; found 753.23; ¹ H NMR (DMSO-d ₆ , δ = 2.5 ppm, 400 MHz), ~14.5 (br s, 4 H), 8.15 (s, 2 H), 7.97 (d, J = 8.5, 4 H), 7.89 (d, J = 8.4, 4 H), 7.10/7.05 (two overlapping d, J = 8.0, 8.4, 1.82 H), 6.57 (app br s, 0.18 H), 5.78 (br d, J = 7.9, 0.18 H), 5.16 (m, 1.82 H), 4.27 (dd, J = 8.0, 5.3, 1.82 H), 4.10 (m, 0.18 H), 3.96-3.81 (m, 6 H), 3.55 (s, 5.46 H), 3.37 (s, 0.54 H), 2.41 (m, 2 H), 2.17-2.00 (m, 6 H), 1.10 (d, J = 6.3, 0.54 H), 1.04 (d, J = 6.3, 5.46 H).
M16	methyl ((1S,2S)-2-hydroxy-1-(((2S)-2-(5-(4'-((2S)-1-((2S,3S)-3-hydroxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl) carbamate	 (Cap-67)	1.11 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₉ O ₈ : 743.35; found 743.23
M17	methyl ((1S)-2-((2S)-2-(5-(4'-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-52)	1.64 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₃ N ₉ O ₆ : 683.33; found 683.30; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₃ N ₉ O ₆ : 683.3306; found 683.3305.
M18	methyl ((1R)-2-((2S)-2-(5-(4'-((2S)-1-(N-(methoxycarbonyl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-85)	1.70 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₃ N ₉ O ₆ : 683.33; found 683.32; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₃ N ₉ O ₆ : 683.3306; found 683.3318.

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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data; ¹ H NMR data
M19	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)bis(N,N-dimethyl-1-oxo-2-propanamine)	 (Cap-13)	1.43 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₇ N ₉ O ₂ : 623.38; found 623.43; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₇ N ₉ O ₂ : 623.3822; found 623.3837.
M20	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)((2R)-1-oxo-1,2-butanediyl))biscarbamate	 (Cap-53a)	1.82 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₉ O ₆ : 711.36; found 711.35; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₉ O ₆ : 711.3619; found 711.3649.
M21	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)((2S)-1-oxo-1,2-butanediyl))biscarbamate	 (Cap-53b)	1.81 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₉ O ₆ : 711.36; found 711.35; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₉ O ₆ : 711.3619; found 711.3643.
M22	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)((1R)-1-cyclopropyl-2-oxo-2,1-ethandiyl))biscarbamate	 (Cap-54a)	1.83 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₇ N ₉ O ₆ : 735.36; found 735.44; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₇ N ₉ O ₆ : 735.3619; found 735.3614.
M23	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl)((1S)-1-cyclopropyl-2-oxo-2,1-ethandiyl))biscarbamate	 (Cap-54b)	1.81 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₇ N ₉ O ₆ : 735.36; found 735.43; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₇ N ₉ O ₆ : 735.3619; found 735.3651.

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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data; ¹ H NMR data
M24	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-(2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-(pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate		2.11 min (Cond. 2); >99% LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₅ N ₈ O ₆ ; 767.42; found 767.58; HRMS: Anal. Calcd. for C ₄₂ H ₅₅ N ₈ O ₆ ; 767.4245; found 767.4230.
M25	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((4S)-5-oxo-1-penten-5,4-diyl))biscarbamate	 (Cap-55)	1.91 min (Cond. 2); 98% LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₇ N ₈ O ₆ ; 735.36; found 735.47; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₇ N ₈ O ₆ ; 735.3619; found 735.3630.
M26	methyl ((1S)-2-(2-(5-(4'-(2-(2S)-1-(N-(methoxycarbonyl)-O-methyl-L-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-(pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate	 (Cap-56)	1.72 min (Cond. 2); 97% LC/MS; Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₈ O ₈ ; 743.35; found 743.49; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₈ O ₈ ; 743.3517; found 743.3489.
M27	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-(2S)-1-((2S)-2-((methoxycarbonyl)amino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-(pyrrolidinyl)carbonyl)butyl)carbamate	 (Cap-57)	1.98 min (Cond. 2); 98% LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₁ N ₈ O ₆ ; 736.39; found 739.52; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₁ N ₈ O ₆ ; 739.3932; found 739.3904.

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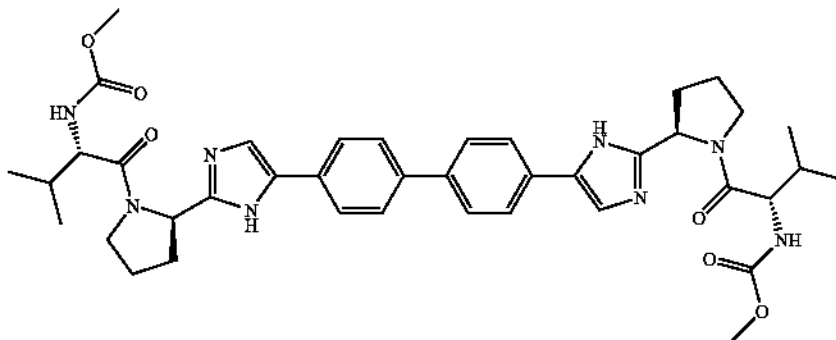
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Example M28

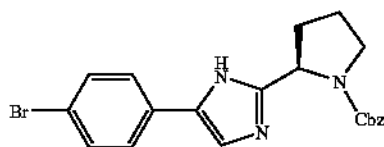
methyl ((1S)-1-(((2R)-2-(5-(4'-((2R)-1-((2S)-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1229]



Example M28, Step a

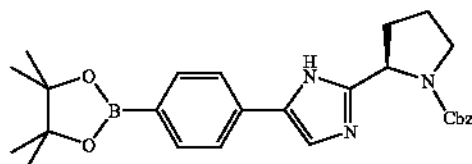
[1230]



[1231] Bromide M28a was prepared from D-Proline according to the procedure described for its enantiomer 28b.

Example M28, Step b

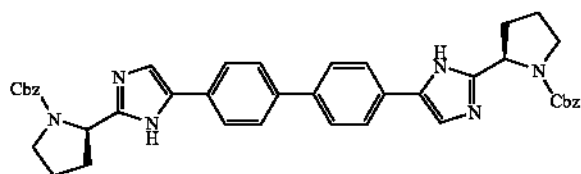
[1232]



[1233] Boronate ester M28b was prepared from bromide M28a according to the procedure described for intermediate 1c. LC: RT=1.57 min (Cond. 1); LC/MS: Anal. Calcd. for [M+H]⁺ C₂₇H₃₃BN₃O₄: 474.26; found 474.24.

Example M28, Step c

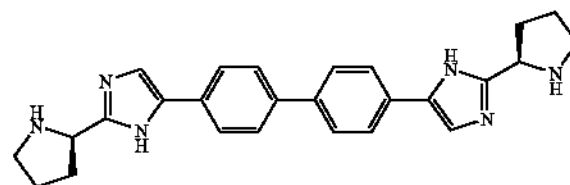
[1234]



[1235] Biphenyl M28c was prepared from bromide M28a and boronate M28b according to the procedure described for intermediate 1d. LC: RT=1.43 min (Cond. 1); LC/MS: Anal. Calcd. for [M+H]⁺ C₄₂H₄₁N₆O₄: 693.32; found 693.38.

Example M28, Step d

[1236]



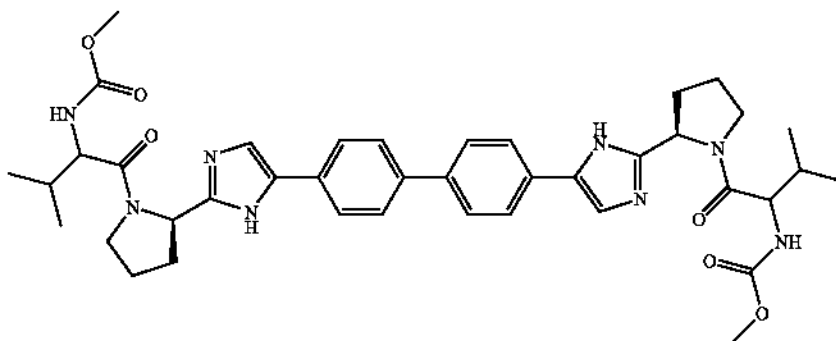
[1237] Pyrrolidine M28d was prepared from carbamate M28c according to the procedure described for intermediate 28d. ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.80 (d, J=8.3, 4H), 7.66 (d, J=8.3, 4H), 7.46 (br s, 2H), 4.16 (app t, J=7.2, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Note: in the region between 3.2-2.6 ppm there is a broad base-line signal that is believed to be that of the pyrrolidine NH]. LC: RT=1.02 min (Cond. 1); LC/MS: Anal. Calcd. for [M+H]⁺ C₂₆H₂₉N₆: 425.25; found 425.27.

Example M28

[1238] Example M28 was prepared as TFA salt from intermediate M28d and Cap-51 according to the procedure described for Example 1. LC: RT=1.33 min (Cond. 1); 96% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₀H₅₁N₈O₆: 739.32; found 739.43; HRMS: Anal. Calcd. for [M+H]⁺ C₄₀H₅₁N₈O₆: 739.3932; found 739.3907.

Example M28-1

[1239]



[1240] The TFA salt of Example M28-1 was prepared as a mixture of three stereoisomers from intermediate M28d and racemic version of Cap-51 according to the procedure described for Example 1. Three peaks with a retention time of 21.74 min, 22.62 min, and 23.40 min, and exhibiting the correct molecular weight, were observed when the sample was analyzed under the following condition:

Waters Acquity HPLC with Micromass ZQ MS (electrospray probe) and Waters 2996 PDA detection. (UV detection (315 nm))

Column: Acquity HPLC; BEH C18; 1.7 μ m; 100 \times 2.1 mm ID; (at approx. 30 C)

Mobile phase A: water, 25 mM ammonium acetate at pH=5

Mobile phase B: acetonitrile

Flow rate: 0.50 ml/min

10-50% B 0-35.0 min

50-98% B 35.0-45.0 min

Hold 98% B 45.0-48.0 min

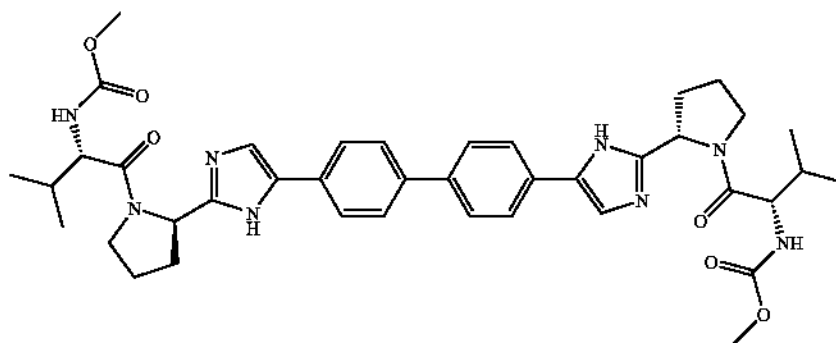
98% B-100% B 48.0-48.5 min

Hold 100% B 48.5-50.0 min

Example M28-2

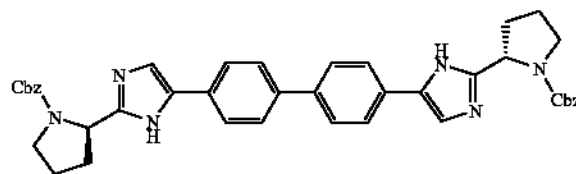
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1241]



Example M28-2, Step a

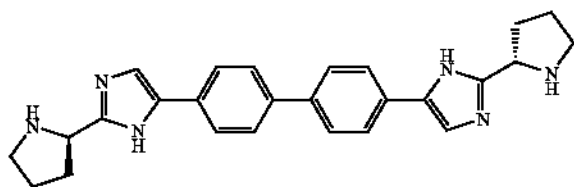
[1242]



[1243] Carbamate M28-2a was prepared from boronate ester M28b and bromide 28b according to the procedure described for intermediate 1d. ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 12.25/12.01/11.93 (three br s, 2H), 7.86-6.98 (m, 20H), 5.13-4.88 (m, 6H), 3.63 (m, 2H), 3.47 (m, 2H), 2.35-1.84 (M, 8H). LC: RT=1.46 min (Cond. 1); LC/MS: Anal. Calcd. for [M+H]⁺ C₄₂H₄₁N₆O₄: 693.32; found 693.34.

Example M28-2, Step b

[1244]



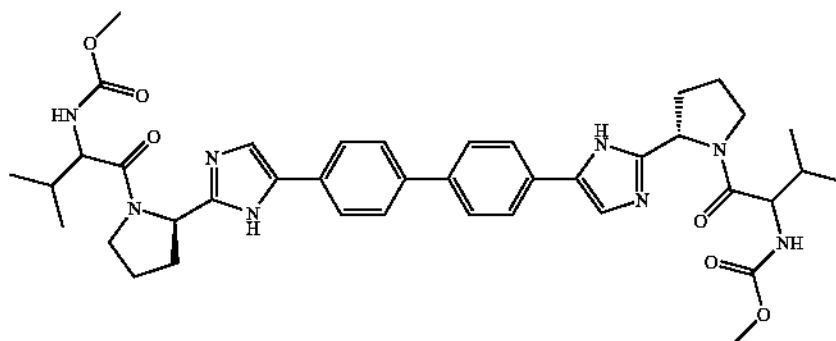
[1245] Pyrrolidine M28-2b was prepared from carbamate M28-2a according to the procedure described for intermediate 28d. ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 11.84 (br s, 2H), 7.80 (d, J=8.3, 4H), 7.66 (d, J=8.3, 4H), 7.46 (br s, 2H), 4.87 (m, 0.05H), 4.16 (app t, J=7.2, 1.95H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Note: in the region between -3.1-2.6 ppm there is a broad base-line signal that is believed to be that of the pyrrolidine NH]. LC: RT=0.96 min (Cond. 1); LC/MS: Anal. Calcd. for [M+H]⁺ C₂₆H₂₉N₆: 425.25; found 425.28.

Example M28-2

[1246] Example M28-2 was prepared as TFA salt from intermediate M28-2b and Cap-51 according to the procedure described for Example 1. LC: RT=1.96 minutes (Cond. 2); 98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₀H₅₁N₈O₆: 739.39; found 739.47.

Example M28-3

[1247]

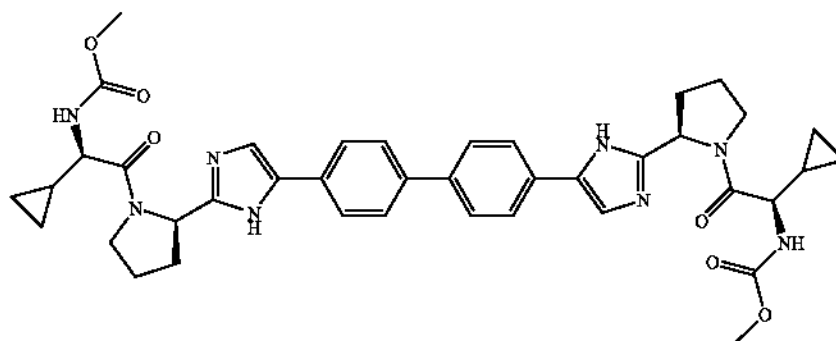


[1248] The TFA salt of Example M28-3 was prepared as a mixture of four stereoisomers from intermediate M28-2b and racemic version of Cap-51 according to the procedure described for Example 1. Three peaks with a retention time of 21.28 min, 22.19 min, and 23.01 min, and exhibiting the correct molecular weight, were observed when the sample was analyzed under the LC/MS condition described for Example M28-1.

Example M29

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2R)-2,1-pyrrolidinediyl((1R)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate

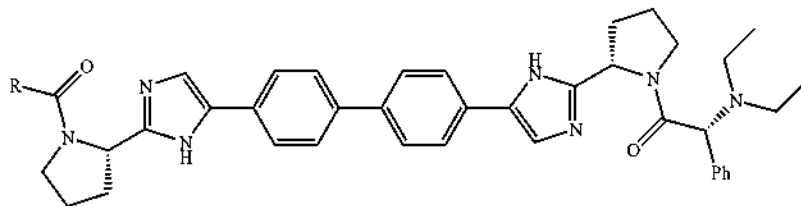
[1249]



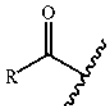
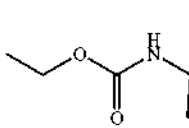
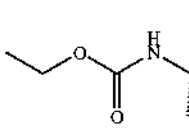
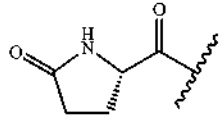
[1250] Example M29 was prepared as TFA salt from intermediate M28d and Cap-54a according to the procedure described for Example 1. LC: RT=1.21 min (Cond. 1); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; found 735.3598.

Example M30-M62

[1251]



[1252] Example M30-M62 were prepared as TFA salts from CJ-24 and the respective caps using the same method described for Example 28.

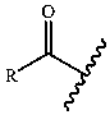
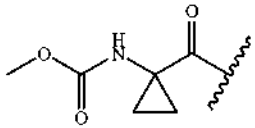
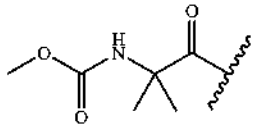
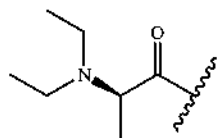
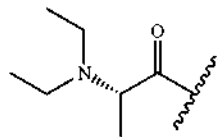
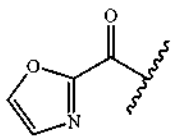
Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M30	ethyl ((1R)-2-((2S)-2-(5-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-59a)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; found 757.50; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4181
M31	ethyl ((1S)-2-((2S)-2-(5-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-59b)	1.07 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; found 757.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4225
M32	(5S)-5-(((2S)-2-(5-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-pyrrolidinone		1.02 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_3$: 725.39; found 725.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_3$: 725.3928; found 725.3926

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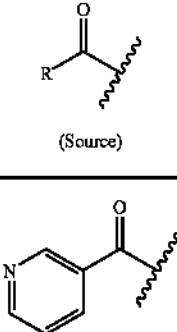
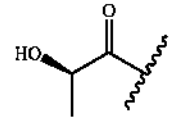
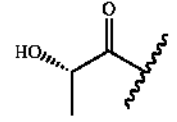
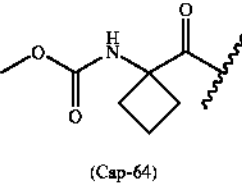
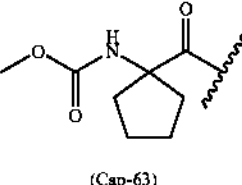
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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M33	methyl 1-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopropyl carbamate	 (Cap-60)	1.12 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₁ N ₈ O ₄ : 755.40; found 755.61; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₁ N ₈ O ₄ : 755.4033; found 755.4066
M34	methyl 2-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate	 (Cap-61)	1.16 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₄ : 757.42; found 757.63; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₄ : 757.4190; found 757.4164
M35	(2R)-1-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine	 (Cap-69a)	1.06 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₇ N ₈ O ₂ : 741.46; found 741.64; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₇ N ₈ O ₂ : 741.4604; found 741.4597
M36	(2S)-1-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine	 (Cap-69b)	1.04 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₇ N ₈ O ₂ : 741.46; found 741.63; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₇ N ₈ O ₂ : 741.4604; found 741.4581
M37	(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-((2S)-1-((1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.11 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₅ N ₈ O ₃ : 709.36; found 709.51; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₅ N ₈ O ₃ : 709.3615; found 709.3615

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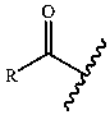
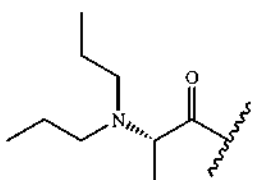
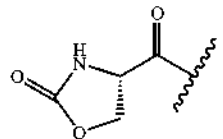
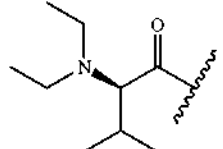
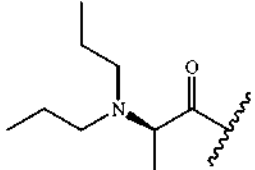
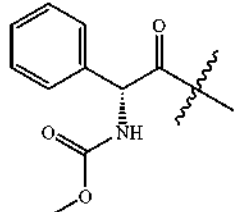
Example	Compound Name	(Source)	RT (LC-Cond.); % homogeneity index; MS data
M38	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-((2S)-1-(3-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₇ N ₉ O ₃ : 719.38; found 719.51; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₇ N ₉ O ₃ : 719.3822; found 719.3829
M39	(2R)-1-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol		1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₈ N ₇ O ₃ : 686.38; found 686.58; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₈ N ₇ O ₃ : 686.3819; found 686.3843
M40	(2S)-1-((2S)-2-(5-(4'-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol		1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₈ N ₇ O ₃ : 686.38; found 686.57; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₈ N ₇ O ₃ : 686.3819; found 686.3832
M41	methyl 1-(((2S)-2-(5-(4'-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclobutyl carbamate	 <p data-bbox="740 1556 806 1577">(Cap-64)</p>	1.19 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₃ N ₉ O ₄ : 769.42; found 769.66; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₃ N ₉ O ₄ : 769.419; found 469.4155
M42	methyl 1-(((2S)-2-(5-(4'-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl carbamate	 <p data-bbox="740 1829 806 1850">(Cap-63)</p>	1.25 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₅ N ₉ O ₄ : 783.43; found 783.69; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₅ N ₉ O ₄ : 783.4346; found 783.4357

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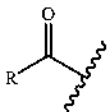
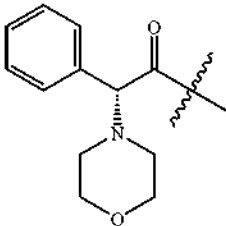
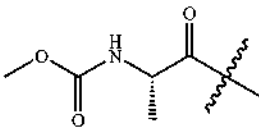
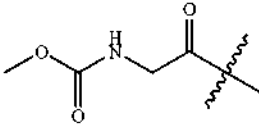
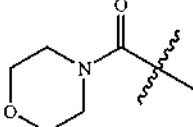
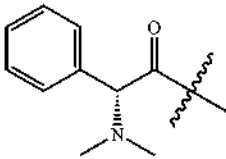
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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M43	N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-N-propyl-1-propanamine	 (Cap-70b)	1.10 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₇ H ₆₁ N ₈ O ₂ : 769.49; found 769.69; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₇ H ₆₁ N ₈ O ₂ : 769.4917; found 769.4925
M44	(4S)-4-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-oxazolidin-2-one	 (Cap-81)	1.08 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₄ : 727.37; found 727.56; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₄ : 727.3720; found 727.3740
M45	(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-3-methyl-1-oxo-2-butanamine	 (Cap-72)	1.08 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₇ H ₆₁ N ₈ O ₂ : 769.49; found 769.73; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₇ H ₆₁ N ₈ O ₂ : 769.4917; found 769.4898
M46	N-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-N-propyl-1-propanamine	 (Cap-70a)	1.12 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₇ H ₆₁ N ₈ O ₂ : 769.49; found 769.45; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₇ H ₆₁ N ₈ O ₂ : 769.4917; found 769.4915
M47	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (Cap-4)	1.85 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₅₃ N ₈ O ₄ : 805.42; found 805.4; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₅₃ N ₈ O ₄ : 805.4190; found 805.4196.

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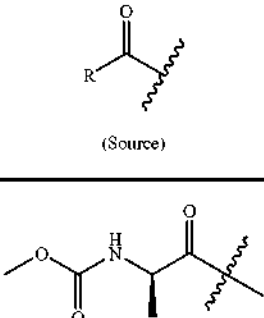
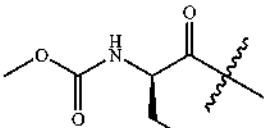
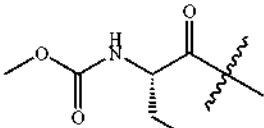
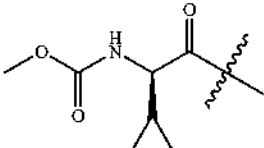
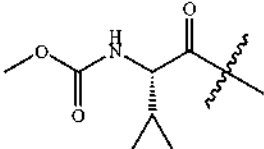
Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M48	(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morpholinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	 (Cap-6)	1.69 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₇ N ₈ O ₃ : 817.45; found 817.48; HRMS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₇ N ₈ O ₃ : 817.4554; found 817.4589.
M49	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-52)	1.67 min (Cond. 2); 92%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₁ N ₈ O ₄ : 743.40; found 743.42; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₁ N ₈ O ₄ : 743.4033; found 743.4053.
M50	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 (Cap-52)	1.63 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₉ N ₈ O ₄ : 729.39; found 729.39; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₉ N ₈ O ₄ : 729.3877; found 729.3888.
M51	(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	 (Cap-1)	1.67 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₁ N ₈ O ₃ : 727.41; found 727.40; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₁ N ₈ O ₃ : 727.4084; found 727.4117.
M52	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine	 (Cap-1)	1.65 min (Cond. 2); 92%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₅₅ N ₈ O ₂ : 775.44; found 775.48; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₅₅ N ₈ O ₂ : 775.4448; found 775.4433.

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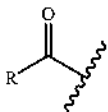
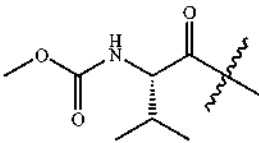
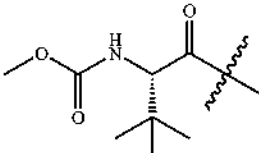
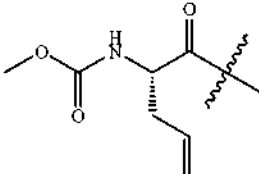
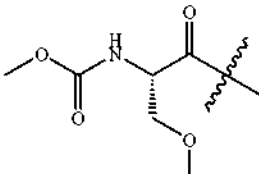
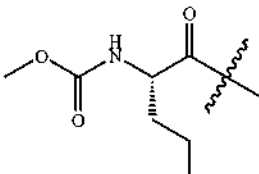
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Example	Compound Name	(Source)	RT (LC-Cond.); % homogeneity index; MS data
M53	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 <p data-bbox="740 735 806 756">(Cap-85)</p>	1.68 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₁ N ₈ O ₄ ; 743.40; found 743.42; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₁ N ₈ O ₄ ; 743.4033; found 743.4055.
M54	methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	 <p data-bbox="740 1016 806 1037">(Cap-53a)</p>	1.78 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₄ ; 757.42; found 757.42; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₄ ; 757.4190; found 757.4216.
M55	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	 <p data-bbox="740 1289 806 1310">(Cap-53b)</p>	1.74 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₄ ; 757.42; found 757.41; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₄ ; 757.4190; found 757.4212.
M56	methyl ((1R)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 <p data-bbox="740 1583 806 1604">(Cap-54a)</p>	1.74 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₃ N ₈ O ₄ ; 769.42; found 769.52; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₃ N ₈ O ₄ ; 769.4190; found 769.4188.
M57	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 <p data-bbox="740 1856 806 1877">(Cap-54b)</p>	1.72 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₃ N ₈ O ₄ ; 769.42; found 769.53; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₃ N ₈ O ₄ ; 769.4190; found 769.4218.

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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M58	methyl ((1S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-51)	1.76 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₅ N ₈ O ₄ : 771.43; found 771.54; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₃ N ₈ O ₄ : 771.4346; found 771.4379.
M59	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate	 (Cap-52)	1.92 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₇ N ₈ O ₅ : 785.45; found 785.63; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₇ N ₈ O ₄ : 785.4503; found 785.4515.
M60	methyl ((1S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-buten-1-yl)carbamate	 (Cap-55)	1.81 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₃ N ₈ O ₄ : 769.42; found 769.55; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₃ N ₈ O ₄ : 769.4190; found 769.4157.
M61	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate	 (Cap-56)	1.73 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₅ : 773.41; found 773.55; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₅ : 773.4139; found 773.4107.
M62	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate	 (Cap-57)	1.73 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₅ N ₈ O ₄ : 771.43; found 771.56 (M + H) ⁺ ; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₅ N ₈ O ₄ : 771.4346; found 771.4315.

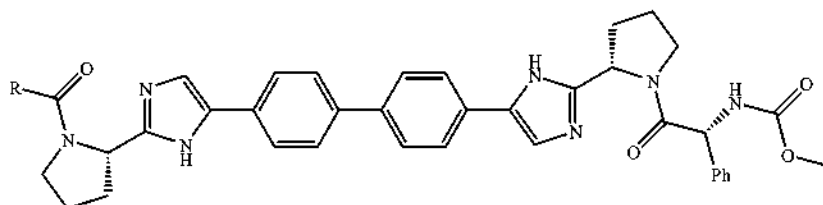
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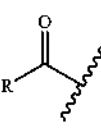
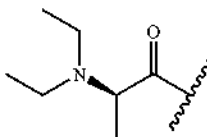
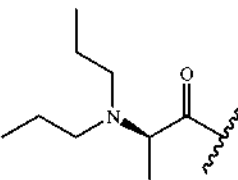
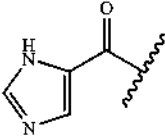
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Example M63-M66

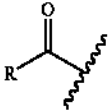
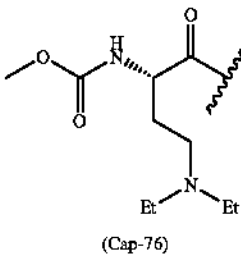
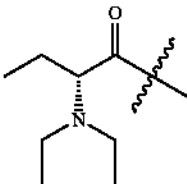
[1253]



[1254] Example M63-M66x were prepared from 28f and the respective acids using the method described for Example 28. Products were prepared as TFA salts unless noted otherwise.

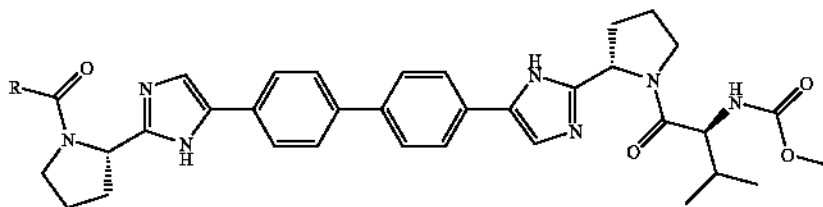
Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (Cap-69a)	1.17 min (Cond. 1); >98%; LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₁ N ₈ O ₄ ; 743.40; found 743.41; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₁ N ₈ O ₄ ; 743.4033; found 743.4017
M64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (Cap-70a)	1.22 min (Cond. 1); >98%; LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₅ N ₈ O ₄ ; 771.43; found 771.39; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₅ N ₈ O ₄ ; 771.4346; found 771.4361
M65	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.15 min (Cond. 1); >90%; LC/MS; Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₀ N ₉ O ₄ ; 710.32; found 710.31; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₀ N ₉ O ₄ ; 710.3203; found 710.3180

-continued

Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M66a & M66b	M66a: methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(diethylamino)-2-(methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (Cap-76)	Two fractions enriched with one of two compounds exhibiting very similar spectral data were isolated. M66a: 1.19 min (Cond. 1); 97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₆ N ₉ O ₆ : 830.44; found 830.39. M66b: 1.21 min (Cond. 1); >97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₆ N ₉ O ₆ : 830.44; found 830.39; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₆ H ₅₆ N ₉ O ₆ : 830.4354; found 830.4316.
M66x (AcOH)	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond. 2); (98%); LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₄ : 757.42; found 757.48; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₄ : 757.4190; found 757.4156.

Example M67-M91

[1255]



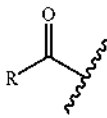
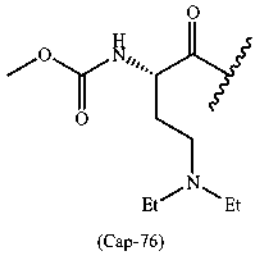
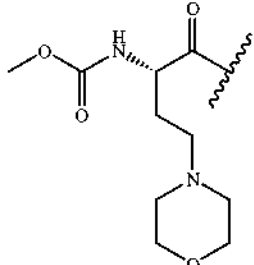
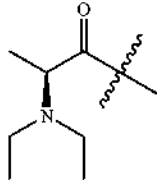
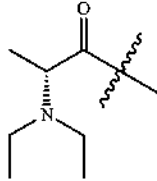
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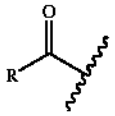
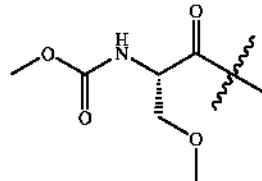
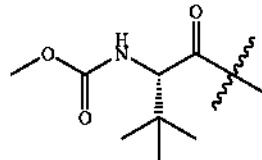
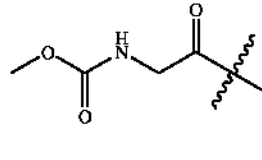
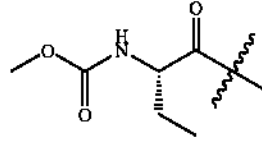
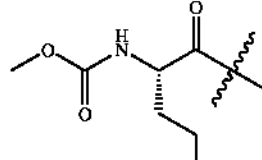
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[1256] Example M67-M91y were prepared from 28d and the respective acids using the method described for Example

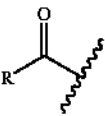
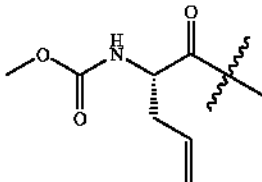
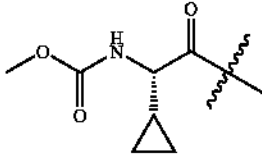
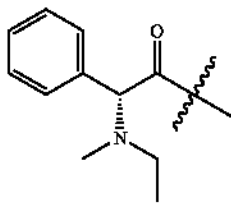
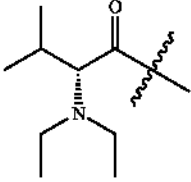
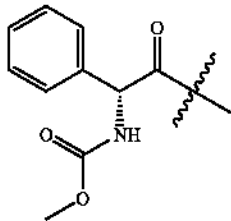
28. Final products were prepared as TFA salts, unless noted otherwise.

Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M67a & M67b	M67a: methyl ((1S)-1-(((2S)-2-(5-(4'-((2S)-1-(4-(diethylamino)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-76)	Two fractions enriched with one of two compounds exhibiting very similar spectral data were isolated M67a: 1.16 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ : C ₄₃ H ₅₈ N ₉ O ₆ ; 796.45; found 796.40 M67b: 1.17 min (Cond. 1); >96%; LC/MS: Anal. Calcd. for [M + H] ⁺ : C ₄₃ H ₅₈ N ₉ O ₆ ; 796.45; found 796.40; HRMS: Anal. Calcd. for [M + H] ⁺ : C ₄₃ H ₅₈ N ₉ O ₆ ; 796.4510; found 796.4537
M68 (*AcOH)	methyl ((1S)-1-(((2S)-2-(5-(4'-((2S)-1-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-(4-morpholinyl)propyl)carbamate	 (Cap-79)	1.10 min (Cond. 1); >96%; LC/MS: Anal. Calcd. for [M + H] ⁺ : C ₄₃ H ₅₆ N ₉ O ₇ ; 810.43; found 810.44; HRMS: Anal. Calcd. for [M + H] ⁺ : C ₄₃ H ₅₆ N ₉ O ₇ ; 810.4303; found 810.4333
M69	methyl ((1S)-1-(((2S)-2-(5-(4'-((2S)-1-(N,N-diethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-69b)	1.72 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ : C ₄₀ H ₅₃ N ₈ O ₄ ; 709.42; found 709.56; HRMS: Anal. Calcd. for [M + H] ⁺ : C ₄₀ H ₅₃ N ₈ O ₄ ; 709.4190; found 709.4219.
M70	methyl ((1S)-1-(((2S)-2-(5-(4'-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-69a)	1.75 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ : C ₄₀ H ₅₃ N ₈ O ₄ ; 709.42; found 709.55; HRMS: Anal. Calcd. for [M + H] ⁺ : C ₄₀ H ₅₃ N ₈ O ₄ ; 709.4190; found 709.4184.

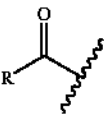
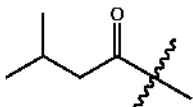
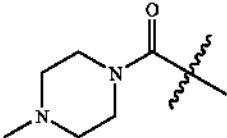
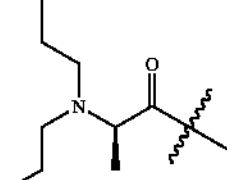
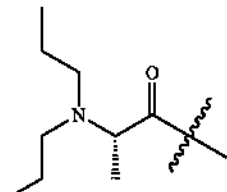
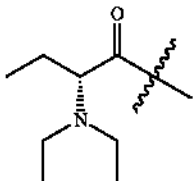
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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M71	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate	 (Cap-56)	1.81 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₉ N ₈ O ₇ : 741.37; found 741.48; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₉ N ₈ O ₇ : 741.3724; found 741.3738.
M72	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-53b)	2.07 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₃ N ₈ O ₆ : 753.41; found 753.53; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₃ N ₈ O ₆ : 753.4088; found 753.4111.
M73	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 (Cap-53b)	1.80 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₇ H ₄₅ N ₈ O ₆ : 697.35; found 697.32; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₇ H ₄₅ N ₈ O ₆ : 697.3462; found 697.3443.
M74	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-53b)	1.90 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₉ N ₈ O ₆ : 725.37; found 725.36; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₉ N ₈ O ₆ : 725.3775; found 725.3742.
M75	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate	 (Cap-57)	1.96 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₁ N ₈ O ₆ : 739.39; found 739.37; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₁ N ₈ O ₆ : 739.3932; found 739.3953.

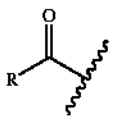
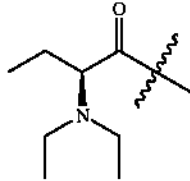
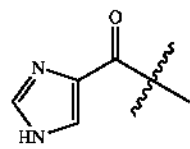
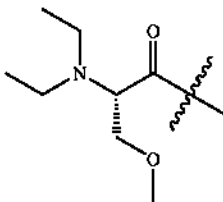
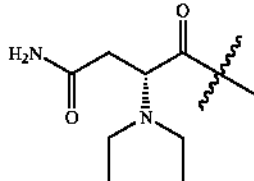
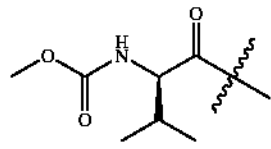
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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M76	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-buten-1-yl)carbamate	 (Cap-55)	1.91 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₉ N ₈ O ₆ : 737.38; found 737.38; HRMS: Anal. Calcd. C ₄₀ H ₄₉ N ₈ O ₆ : 737.3775; found 737.3744.
M77	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-54b)	1.90 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₉ N ₈ O ₆ : 737.38; found 737.34; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₉ N ₈ O ₆ : 737.3775; found 737.3764.
M78	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(ethyl(methyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-3)	1.82 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₄ : 757.42; found 757.42; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₃ N ₈ O ₄ : 757.4190; found 757.4188.
M79	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-72)	1.78 min (Cond. 2); 94%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₇ N ₈ O ₄ : 737.45; found 737.45; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₇ N ₈ O ₄ : 737.4503; found 737.4488.
M80	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-4)	2.05 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₉ N ₈ O ₆ : 773.37; found 773.40; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₄₉ N ₈ O ₆ : 773.375; found 773.3759.

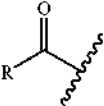
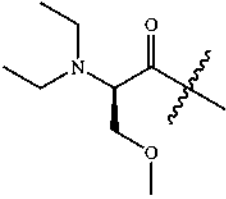
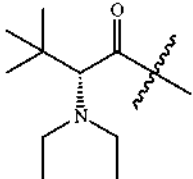
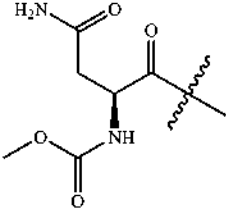
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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M81	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		2.05 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₈ N ₇ O ₄ 666.38; found 666.37; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₈ N ₇ O ₄ 666.3768; found 666.3785.
M82	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(4-methyl-1-piperazinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		1.75 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₅₀ N ₉ O ₄ 708.40; found 708.38; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₅₀ N ₉ O ₄ 708.3986; found 708.3974.
M83	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-70a)	1.81 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₇ N ₈ O ₄ 737.45; found 737.47; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₇ N ₈ O ₄ 737.4503; found 737.4480.
M84	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-70b)	1.78 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₇ N ₈ O ₄ 737.45; found 737.47; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₇ N ₈ O ₄ 737.4503; found 737.4491.
M85	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(2R)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-71a)	1.76 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₅ N ₈ O ₄ 723.43; found 723.47; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₅ N ₈ O ₄ 723.4346; found 723.4335.

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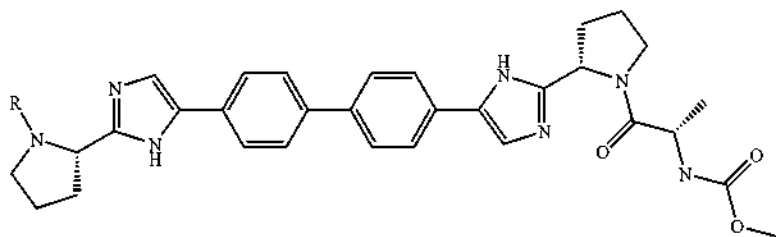
Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M86	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-71b)	1.73 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₅ N ₉ O ₄ 723.43; found 723.47; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₅ N ₉ O ₄ 723.4346; found 723.4343.
M87	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		1.67 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₇ H ₄₂ N ₉ O ₄ 676.34; found 676.45; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₇ H ₄₂ N ₉ O ₄ 676.3360; found 676.3344.
M88	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-O-methyl-L-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-73)	1.67 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₅ N ₉ O ₅ 739.43; found 739.54; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₅ N ₉ O ₅ 739.4295; found 739.4327.
M89	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N ² ,N ² -diethyl-D-asparaginyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-74)	1.76 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₄ N ₉ O ₅ 752.42; found 752.43; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₄ N ₉ O ₅ 752.4248; found 752.4263.
M90	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-1-((2R)-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-84)	2.00 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₁ N ₈ O ₆ 739.39; found 739.46; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₁ N ₈ O ₆ 739.3932; found 739.3901.

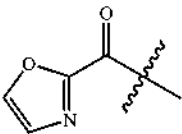
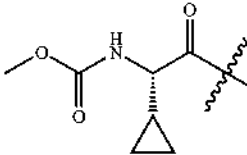
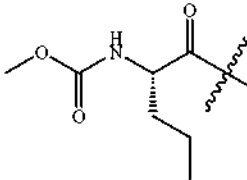
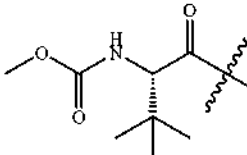
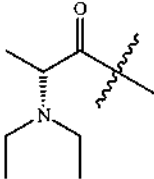
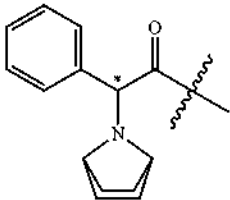
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Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M91	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-O-methyl-D-eryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (Cap-75)	1.73 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₅ N ₈ O ₅ 739.43; found 739.39; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₅₅ N ₈ O ₅ 739.4295; found 739.4277.
M91x	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-3-methyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		1.78 minutes (Cond. 2); (97%); LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₉ N ₈ O ₄ 751.47; found 751.50; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₃ H ₅₉ N ₈ O ₄ 751.4659; found 751.4648.
M91y	methyl ((1S)-3-amino-1-(((2S)-2-(5-(4'-(2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-oxopropyl)carbamate (non-preferred name)	 (Cap-58)	1.92 min (Cond. 2); (>97%); LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₈ N ₉ O ₇ 754.37; found 754.42; HRMS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₈ N ₉ O ₇ 754.3677; found 754.3676.

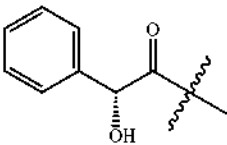
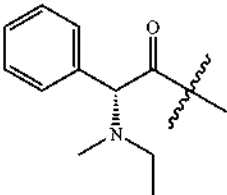
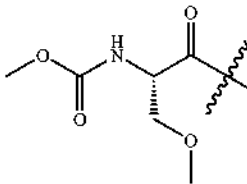
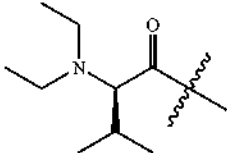
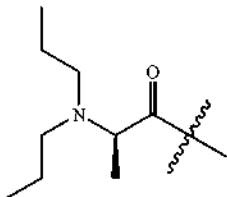
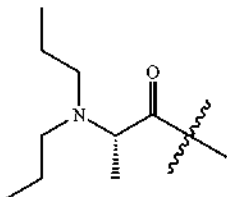
Example M92-M103

[1257] Example M92-M103 were prepared from 28d and the respective acids using the method described for Example 28. Final products were prepared as TFA salts, unless noted otherwise.



Example	Compound Name	R (Source)	Analytical Data
M92	methyl ((1S)-1-methyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.70 min (Cond. 2); 95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₅ H ₃₇ N ₈ O ₅ 649.29; found 649.41; HRMS: Anal. Calcd for [M + H] ⁺ C ₃₅ H ₃₇ N ₈ O ₅ 649.2887; found 649.2867
M93	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 (Cap-54b)	1.76 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₅ N ₈ O ₆ 709.35; found 709.50; HRMS: Anal. Calcd for [M + H] ⁺ C ₃₈ H ₄₇ N ₈ O ₆ 709.3462; found 709.3478
M94	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(2S)-2-(methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate	 (Cap-57)	1.84 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₈ O ₆ 711.36; found 711.54; HRMS: Anal. Calcd for [M + H] ⁺ C ₃₈ H ₄₇ N ₈ O ₆ 711.3619; found 711.3590.
M95	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate	 (Cap-57)	1.91 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₉ N ₈ O ₆ 725.37; found 725.54; HRMS: Anal. Calcd for [M + H] ⁺ C ₃₉ H ₄₉ N ₈ O ₆ 725.3775; found 725.3809.
M96	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-69a)	1.61 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₉ N ₈ O ₄ 681.39; found 681.54; HRMS: Anal. Calcd for [M + H] ⁺ C ₃₈ H ₄₉ N ₈ O ₄ 681.3877; found 681.3867.
M97	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(7-azabicyclo[2.2.1]hept-7-yl(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-77b)	1.72 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₅ H ₅₁ N ₈ O ₄ 767.40; found 767.59; HRMS: Anal. Calcd for [M + H] ⁺ C ₄₅ H ₅₁ N ₈ O ₄ 767.4033; found 767.4067.

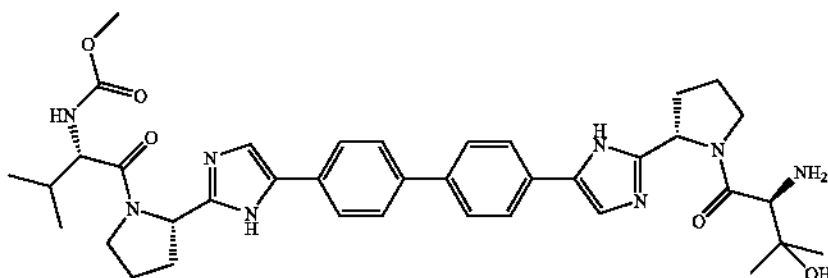
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Example	Compound Name	R (Source)	Analytical Data
M98	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		1.80 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₉ H ₄₂ N ₇ O ₅ 688.32; found 688.48; HRMS: Anal. Calcd for [M + H] ⁺ C ₃₉ H ₄₂ N ₇ O ₅ 688.3247; found 688.3263.
M99	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(ethyl(methyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-3)	1.70 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₉ N ₈ O ₄ 729.39; found 729.56; HRMS: Anal. Calcd for [M + H] ⁺ C ₄₂ H ₄₉ N ₈ O ₄ 729.3877; found 729.3887.
M100	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate	 (Cap-56)	1.75 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₇ H ₄₅ N ₈ O ₇ 713.34; found 713.34; HRMS: Anal. Calcd for [M + H] ⁺ C ₃₇ H ₄₅ N ₈ O ₇ 713.3411; found 713.3386.
M101	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-72)	1.66 min (Cond. 2); 94%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₃ N ₈ O ₄ 709.42; found: 709.42; HRMS: Anal. Calcd for [M + H] ⁺ C ₄₀ H ₅₃ N ₈ O ₄ 709.4190; found 709.4166.
M102	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-70a)	1.71 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₃ N ₈ O ₄ 709.42; found 709.48; HRMS: Anal. Calcd for [M + H] ⁺ C ₄₀ H ₅₃ N ₈ O ₄ 709.4190; found 709.4191.
M103	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (Cap-70b)	1.66 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₃ N ₈ O ₄ 709.42; found 709.42; HRMS: Anal. Calcd for [M + H] ⁺ C ₄₀ H ₅₃ N ₈ O ₄ 709.4190; found 709.4198.

Example M104

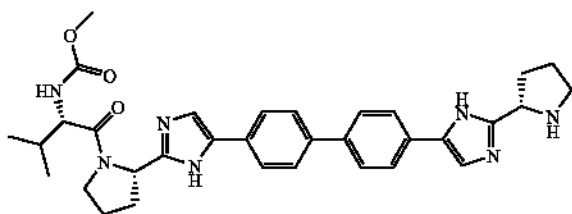
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-hydroxy-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1258]



Example M104, Step a

[1259]



thylbutanoic acid (65.8 mg, 0.282 mmol) and *i*-Pr₂EtN (180 μ L, 1.03 mmol), and the reaction mixture was stirred at ambient condition for 35 min. The volatile component was removed in vacuo, and the residue was purified with a reverse phase HPLC (MeOH/H₂O/TFA), and the fractions were concentrated in vacuo. The resultant residue was treated with 25% TFA/CH₂Cl₂ (6.0 mL) and stirred for 3.25 hr. The volatile component was removed in vacuo and the residue was free-based (MCX; MeOH wash; 2.0 M NH₃/MeOH elution) to afford Example M104 as an off-white foam (107 mg). LC (Cond. 2): RT=1.03 min; >95% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₃₈H₄₉N₈O₅=697.38; found 697.28.

[1260] Pyrrolidine M104a was prepared from intermediate 28d and Cap-51 according to the procedure described for the synthesis of pyrrolidine 28f

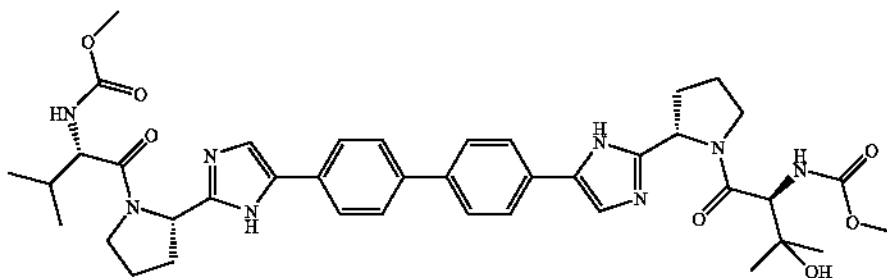
Example M104

[1261] HATU (96.3 mg, 0.253 mmol) was added to a DMF (5.0 mL) solution of pyrrolidine M104a (150 mg, 0.217 mmol), (S)-2-(tert-butoxycarbonylamino)-3-hydroxy-3-me-

Example M105

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1262]



[1263] Methyl chloroformate (20 μ L, 0.258 mmol) was added to a THF (2.0 mL) solution of Example M104 (82.9 mg, 0.119 mmol) and *i*-Pr₂EtN (50 μ L, 0.287 mmol) and stirred for 65 min. The mixture was then treated with 2.0 M NH₃/MeOH (3 mL), stirred for 2.75 hr, and the volatile component was removed in vacuo. The resultant residue was

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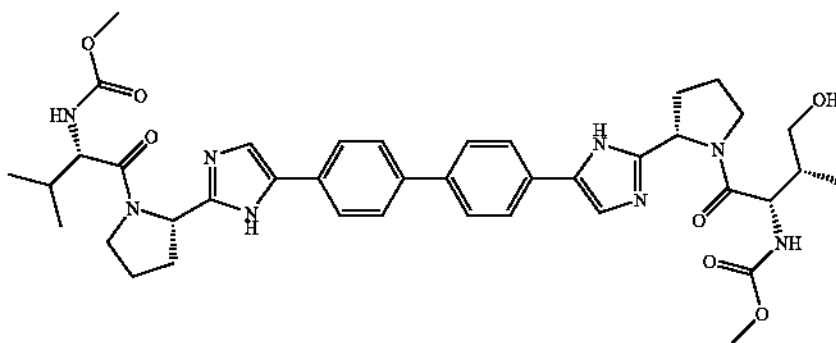
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purified with a reverse phase HPLC (MeOH/H₂O/TFA) to afford the TFA salt of Example M105 as a white foam (64.1 mg). LC (Cond. 2): RT=1.17 min; >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₀H₅₁N₈O₇=755.39; found 755.25.

Example M106

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-4-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1264]



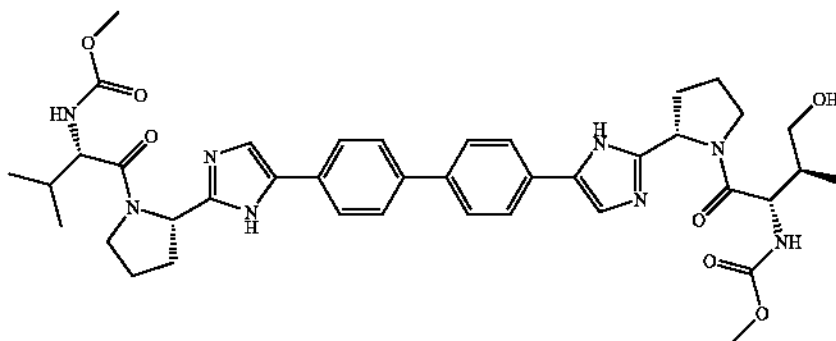
[1265] HATU (69 mg, 0.181 mmol) was added to a DMF (3.0 mL) solution of pyrrolidine M104a (101 mg, 0.173 mmol), Cap-80b (55.9 mg, ~0.183 mmol) and *i*-Pr₂EtN (90 μ L, 0.515 mmol), and the reaction mixture was stirred at ambient condition for 70 min. The volatile component was removed in vacuo and the residue was purified with a reverse phase HPLC (H₂O/MeOH/TFA) to retrieve the dominant signal. The collected fraction was allowed to stand at ambient condition for a few hours and then the volatile component was removed in vacuo, at which time total desilylation of the coupled product was achieved. The resultant product was submitted to a reverse phase HPLC purification (ACN/H₂O/NH₄OAc) to afford Example M106 as an off-white foam

(32.2 mg). LC (Cond. 2): RT=1.19 min; >95% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₀H₅₁N₈O₇=755.39; found 755.85.

Example M107

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-4-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1266]



[1267] Example M107 was prepared from pyrrolidine M104a and Cap-80a according to the procedure described for the synthesis of Example M106. LC (Cond. 2): RT=1.20 min; ~95% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₀H₅₁N₈O₇=755.39; found 755.78.

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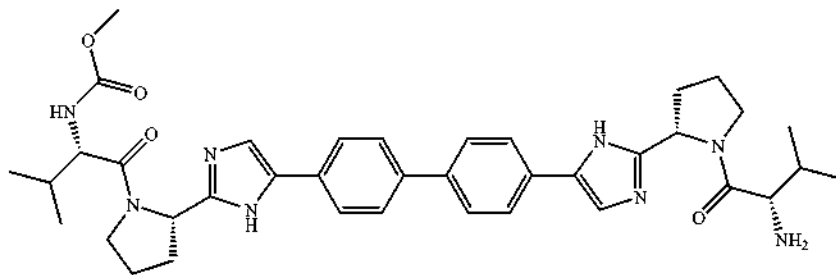
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Example M108

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-L-valyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

[1268]



[1269] HATU (70.1 mg, 0.184 mmol) was added to a DMF (3.0 mL) solution of pyrrolidine M104a (100.7 mg, 0.173 mmol), (L)-Boc-Valine (49.6 mg, 0.228 mmol) and *i*-Pr₂EtN (70 μ L, 0.40 mmol), and the reaction mixture was stirred at ambient condition for 65 min. The volatile component was removed in vacuo and the residue was purified with a Biotage (60-100% EtOAc/hexanes) to afford 116.6 mg of the coupled product.

[1270] The above product (112 mg) was treated with 25% TFA/CH₂Cl₂ (2 mL) and the reaction mixture was stirred for 6 hr. The volatile component was removed in vacuo and the crude material was purified with a combination of MCX resin (MeOH wash; 2.0 M NH₃/MeOH elution) and reverse phase HPLC (H₂O/MeOH/TFA) to afford the TFA salt of Example M108 as a white foam (98.5 mg). LC (Cond. 2): RT=1.14 min; >98% homogeneity index; LC/MS: Anal. Calcd. for

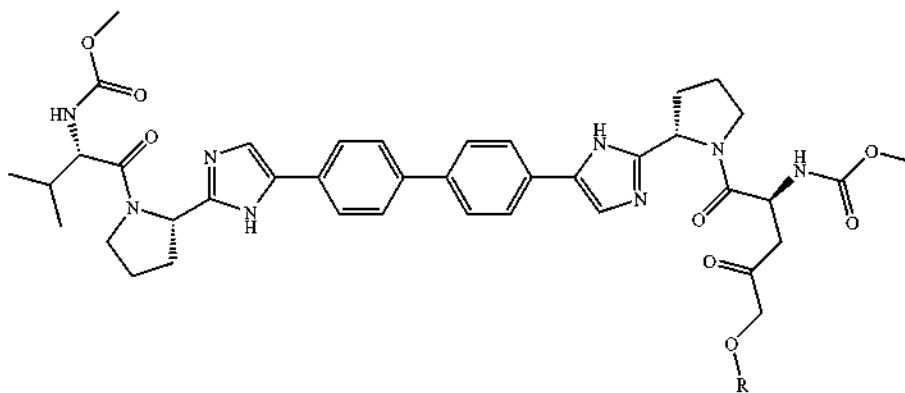
[M+H]⁺ C₃₈H₄₉N₈O₄=681.39; found 681.36. HRMS Calcd. for [M+H]⁺ C₃₈H₄₉N₈O₄: 681.3877; found 681.3865.

Example M109 (R=Bn) & M110 (R=Me)

M109: benzyl (3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoate

M110: methyl (3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoate

[1271]



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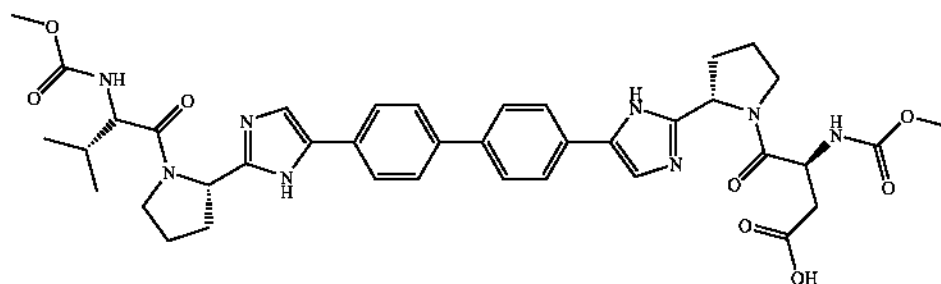
[1272] HATU (109 mg, 0.287 mmol) was added to DMF (1.5 ml) solution of pyrrolidine M104a (151 mg, 0.260 mmol), Cap-68 (109 mg, 387 mmol), and *i*-Pr₂EtN (100 μ l, 0.574 mmol), and the reaction mixture was stirred at ambient condition for 3 hr. The volatile component was removed in vacuo and crude material was purified with a combination of MCX resin (MeOH wash; 2.0 M NH₃/MeOH elution) and reverse phase HPLC (H₂O/MeOH/TFA) to afford the TFA salt Example M109 (88.0 mg) and Example M110 (90.2 mg). Example M109: LC (Cond. 2): RT=2.16; 97% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₆H₅₃N₈O₈: 845.40; found 845.51. HRMS Calcd. for [M+H]⁺ C₄₆H₅₃N₈O₈:

845.3986; found 845.3983. Example M110: LC (Cond. 2): RT=1.92; 97% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₀H₄₉N₈O₄: 769.47; found 769.46. HRMS Calcd. for [M+H]⁺ C₄₀H₄₉N₈O₄: 769.3673; found 769.3682.

Example M111

(3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoic acid

[1273]

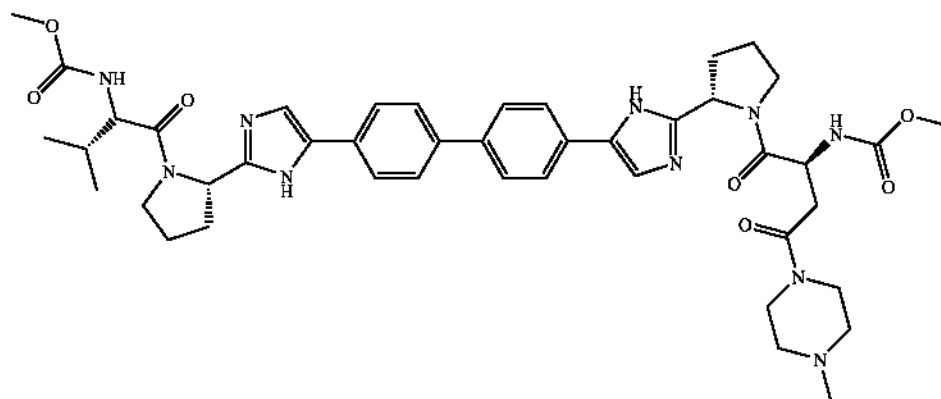


[1274] A mixture of Example M109 (69.7 mg, 0.082 mmol) and 10% Pd/C (10 mg) in methanol (5 ml) was stirred at room temperature under a balloon of H₂ for 1.5 h. The reaction was filtered through diatomaceous earth (Celite®) and concentrated in vacuo, and the resultant material was purified with a reverse phase HPLC (H₂O/MeOH/TFA) to afford the TFA salt of Example M111 as an off-white foam (54.0 mg). LC (Cond. 2): RT=1.18; 99% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₃₉H₄₇N₈O₈: 755.35; found 755.32. HRMS Calcd. for [M+H]⁺ C₃₉H₄₇N₈O₈: 755.3517; found 755.3525.

Example M112

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(2S)-2-((methoxycarbonyl)amino)-4-(4-methyl-1-piperazinyl)-4-oxobutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1275]



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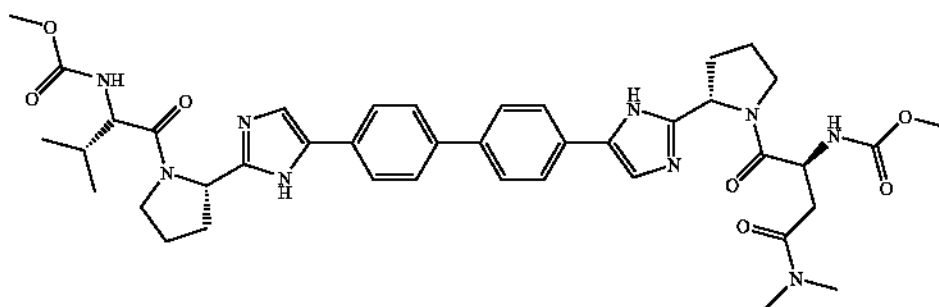
[1276] HATU (30.6 mg, 0.080 mmol) was added to a DMF (1.5 ml) solution of Example M111 (55.3 mg, 0.0733 mmol), N-methyl piperazine (11.0 mg, 0.11 mmol) and i-Pr₂EtN (25 μ l, 0.14 mmol), and the reaction mixture was stirred at ambient condition for 1.5 h. All volatile components were removed in vacuo, and the residue was purified with a combination of MCX resin and a reverse phase HPLC (H₂O/MeOH/TFA) to afford the TFA salt of Example M112 as an off-white foam (51.4 mg). LC (Cond. 2): RT=1.75; 91% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₄H₅₇N₁₀O₇: 837.44;

found 837.59. HRMS Calcd. for [M+H]⁺ C₄₄H₅₇N₁₀O₇: 837.4412; found 837.4453.

Example M113

methyl ((1S)-3-(dimethylamino)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-oxopropyl)carbamate

[1277]

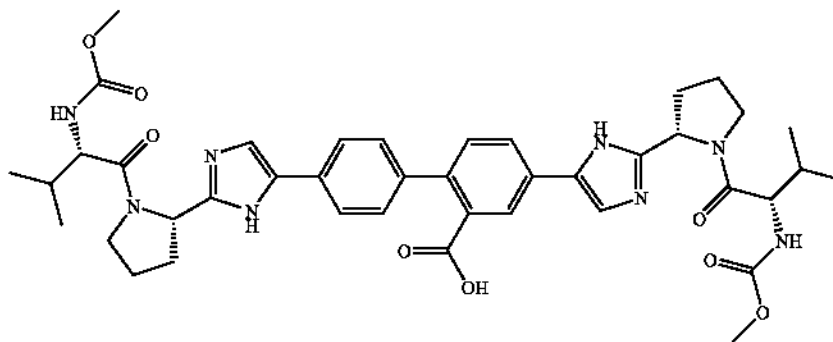


[1278] Example M118 was prepared from Example M111 and Me₂NHCl according to the procedure described for Example M112. LC (Cond. 2): RT=1.89; 99% homogeneity index. LC/MS: Anal. Calcd. for [M+H]⁺ C₄₁H₅₂N₉O₇: 782.40; found 782.47. HRMS Calcd. for [M+H]⁺ C₄₁H₅₂N₉O₇: 782.3990; found 782.4008.

Example M114

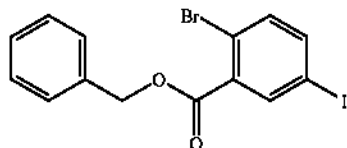
4,4'-bis(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid

[1279]



Example M114, Step a

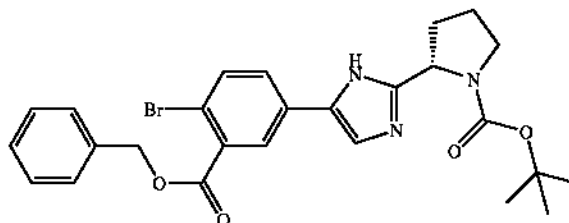
[1280]



Example M114, Step b-d

[1281] DMF (20 mL) was added to mixture of KHCO_3 (1.84 g, 18.4 mmol) and 2-bromo-5-iodobenzoic acid (4.99 g, 15.3 mmol) and the resulting mixture was stirred for 15 min. Benzyl bromide (2.4 mL, 20.2 mmol) was added drop-wise over 5 min and stirring was continued at ambient condition for ~20 hr. Most of the volatile component was removed in vacuo and the residue was partitioned between CH_2Cl_2 (50 mL) and water (50 mL), and the organic layer was washed with water (50 mL), dried (MgSO_4), filtered, and concentrated. The resulting crude material was purified with flash chromatography (7% EtOAc/hexanes) to afford ester M114a as a colorless viscous oil (6.01 g). ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.5$ ppm, 400 MHz): δ 8.07 (d, $J=2.0$, 1H), 7.81 (dd, $J=8.4$, 2.1, 1H), 7.53 (d, $J=8.4$, 1H), 7.48 (m, 2H), 7.43-7.34 (m, 3H), 5.34 (s, 2H). LC (Cond. 1): RT=2.1 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{Na}]^+ \text{C}_{14}\text{H}_{10}\text{BrINaO}_2$: 438.88; found 438.83.

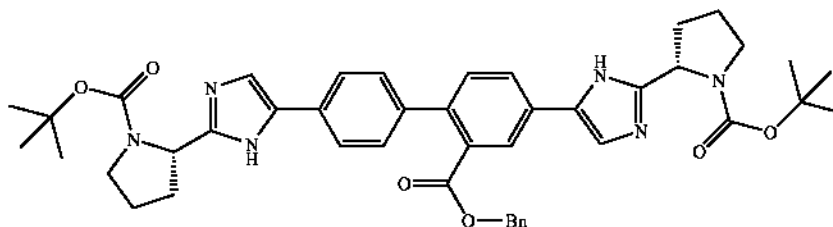
[1282]



[1283] Ester M114a was elaborated to ester M114d by employing a three step protocol employed in the synthesis of bromide 121c from 1-bromo-4-iodo-2-methylbenzene. M114d: ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.5$ ppm, 400 MHz): δ 12.04/11.97 (br s, 1H), 8.12 (d, $J=2.0$, 0.92H), 7.99 (app br s, 0.08H), 7.81 (dd, $J=8.3$, 2.0, 0.92H), 7.74-7.62 (m, 2.08H), 7.50 (app br d, $J=7.0$, 2H), 7.44-7.35 (m, 3H), 5.38 (s, 2H), 4.79 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.24-1.79 (m, 4H), 1.39/5.11 (two s, 9H). LC (Cond. 1): RT=1.66 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{26}\text{H}_{29}\text{BrN}_3\text{O}_4$: 526.13; found 526.16.

Example M114, Step e

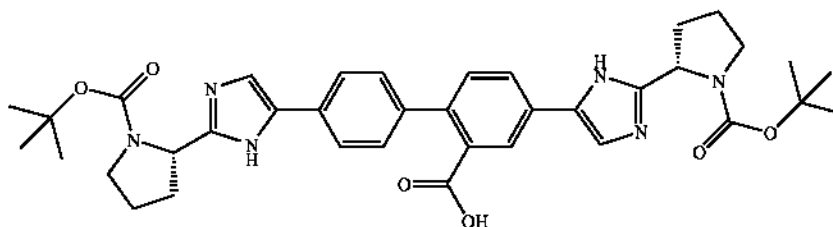
[1284]



[1285] Ester M114e was prepared from bromide M114d and boronate 1c according to the preparation of dimer 1d. ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.5$ ppm, 400 MHz): δ 12.18/12.00/11.91/11.83 (four br s, 2H), 8.11-7.03 (m, 14H), 5.10 (s, 2H), 4.85-4.78 (m, 2H), 3.55 (app br s, 2H), 3.37 (m, 2H), 2.29-1.80 (m, 8H), 1.41/1.16 (two s, 18H). LC (Cond. 1): RT=1.54 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+ \text{C}_{44}\text{H}_{51}\text{N}_6\text{O}_6$: 759.39; found 759.63.

Example M114, Step f

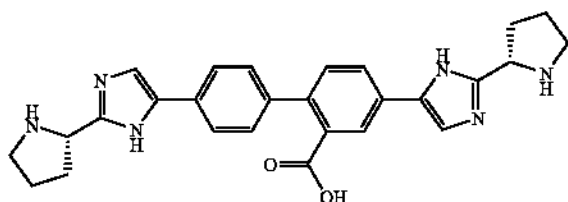
[1286]



[1287] A mixture of benzyl ester M114e (1.005 g, 1.325 mmol) and 10% Pd/C (236 mg) in MeOH (20 mL) was stirred under a balloon of H₂ for 5 hr. The reaction mixture was then treated with a 1:1 mixture of MeOH and CH₂Cl₂, filtered through a pad of diatomaceous earth (Celite®-521), and the filtrate was rotovaped to afford acid M114f (840 mg), contaminated with Ph₃PO which was a carryover from the Suzuki coupling step. ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz): δ 12.17/11.98/11.89/11.81 (four app br s, 2H), 8.04-7.31 (m, 9H), 4.85-4.78 (m, 2H), 3.55 (app br s, 2H), ~3.37 (m, 2H, overlapped with water signal) 2.27-1.84 (m, 8H), 1.41/1.16 (two s, 18H). LC (Cond. 1): RT=1.37 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₃₇H₄₅N₆O₆: 669.34; found 669.53.

Example M114, Step g

[1288]



[1289] 4N HCl/dioxane (8.0 mL) and CH₂Cl₂ (2.0 mL) were sequentially added to carbamate M114f (417 mg, 0.623 mmol), the mixture was vigorously stirred 5.5 hr, and then the volatile component was removed in vacuo to afford the HCl (0.4x) salt of pyrrolidine M114g (487 mg), contaminated with Ph₃PO impurity. ¹H NMR (DMSO-d₆, δ=2.5 ppm, 400 MHz) after D₂O exchange: δ 8.23 (d, J=1.7, 1H), 8.09-8.04 (m, 3H), 7.92 (d, J=8.3, 2H), 7.53 (d, J=8.1, 1H), 7.48 (d,

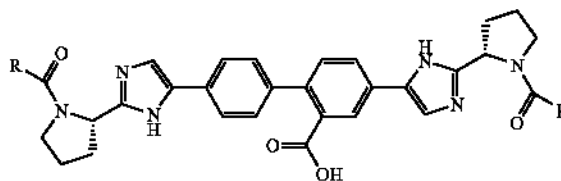
J=8.3, 2H), 5.00 (app br t, J=8.3, 1H), 4.90 (app br t, J=8.4, 1H), 3.6-3.3 (m, 4H), 2.5-1.99 (m, 8H). LC (Cond. 1): RT=0.92 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₂₇H₂₉N₆O₂: 469.24; found 469.31.

Example M114

[1290] HATU (79.9 mg, 0.21 mmol) was added to a DMF (3.0 mL) solution of pyrrolidine M114g. 4HCl (80 mg, 0.13 mmol), Cap-51 (92.4 mg, 0.527 mmol) and i-Pr₂EtN (160 μL, 0.919 mmol), and the reaction mixture was stirred at ambient condition for 2 hr. The volatile component was removed in vacuo and the residue was purified with a combination of MCX (MeOH wash; 2.0 M NH₃/MeOH elution) and a reverse phase HPLC (CH₃CN/H₂O/NH₄OAc) to afford the acetic acid salt of Example M114. LC (Cond. 1): RT=1.20 min; >98 homogeneity index. LC/MS: Anal. Calcd. for [M+H]⁺ C₄₁H₅₁N₈O₈: 783.38; found 783.34. HRMS Calcd. for [M+H]⁺ C₄₁H₅₁N₈O₈: 783.3830; found 783.3793.

Example M115-M116

[1291] Examples M115-M116 were prepared using the same method as described for Example M114 and by substituting the appropriate acids for Cap-51. The products were isolated as either the acetic acid or TFA salt depending on the nature of the mobile phase of the HPLC purification step.



Example	Compound Name	(Source)	RT (LC-Cond.); % homogeneity index; MS data
M115 (AcOH)	4,4'-bis(2-((2S)-1-((2R)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid	 (Cap-54a)	1.17 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₈ : 779.35; found 779.33; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₈ : 779.3517; found 779.3498
M116 (2.TFA)	4,4'-bis(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid	 (Cap-54b)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₈ : 779.35; found 779.33; HRMS: Anal. Calcd. for [M + H] ⁺ C ₄₁ H ₄₇ N ₈ O ₈ : 779.3517; found 779.3551

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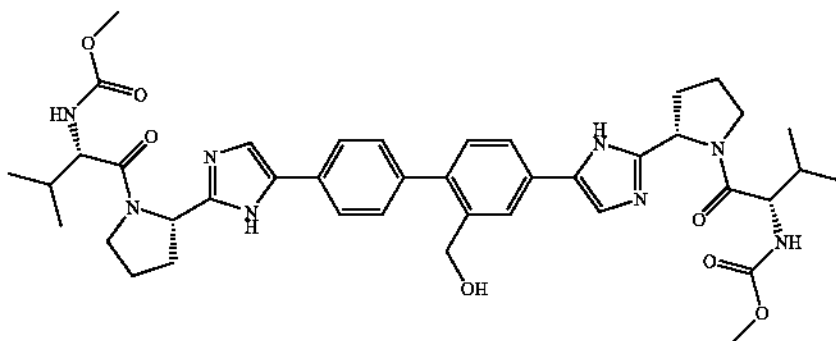
Example M118

[1295] The TFA salt of Example 118 was prepared from intermediate M118a and Cap-51 according to the procedure described for Example 1. LC (Cond. 1): RT=1.16 min; 97% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.40; found 782.40. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.3990; found 782.3979.

Example M19

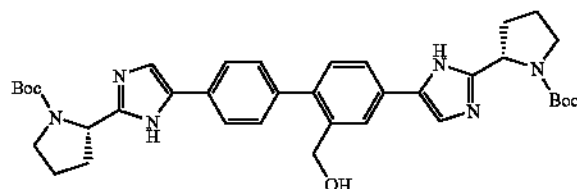
methyl ((1S)-1-(((2S)-2-(5-(2-(hydroxymethyl)-4'-(2-((2S)-1-((2S)-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1296]



Example M119, Step a

[1297]

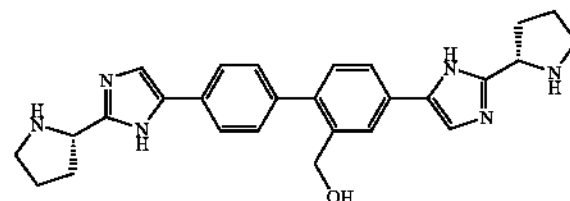


[1298] DIBAL-H (8.0 mL of 1.0 M/ CH_2Cl_2 , 8.0 mmol) was added drop-wise to an ice-water cooled CH_2Cl_2 (20 mL) solution of benzyl ester M114e (1.216 g, 1.60 mmol), and the reaction mixture was stirred for 1 hr and an additional DIBAL-H (0.5 mL of 1.0 M/ CH_2Cl_2 , 0.5 mmol) was added and stirring was continued for ~2.5 hr. The reaction was quenched with excess saturated NH_4Cl solution and the mixture was diluted with water and extracted with CH_2Cl_2 (3x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude material was purified with a Biotage (100 g silica gel; 2-6% MeOH/ $EtOAc$) to afford alcohol M119a as an off-white foam (610 mg). 1H NMR ($DMSO-d_6$, $\delta=2.5$ ppm, 400 MHz): δ 12.23 (br s, 0.19H), 12.17 (br s, 0.19H), 11.89 (br s, 0.81H), 11.82 (br s, 0.81H), 7.97 (s, 0.81H), 7.84 (s, 0.19H), 7.78 (d, J=8.1, 1.62H), 7.69-7.20 (m, 6.38H), 5.21-5.15 (m, 1H), 4.86-4.78 (m, 2H), 4.49-4.45 (m, 2H), ~3.54 (m, 2H), 3.40-3.34 (m,

2H), 2.30-1.80 (m, 8H), 1.41/1.17 (two s, 18H). LC (Cond. 1): RT=1.36 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{47}N_6O_5$: 655.36; found 655.34.

Example M119, Step b

[1299]



[1300] 25% TFA/ CH_2Cl_2 (3.0 mL) was added to carbamate M119a (105 mg, 0.160 mmol) and the mixture was stirred at ambient condition for 4.5 hr. The volatile component was removed in vacuo and the residue was free-based (MCX; MeOH wash; 2.0 M NH_3 /MeOH elution) to afford pyrrolidine M119b, contaminated with its trifluoroacetylated derivative of unknown regiochemistry. The sample was dissolved in MeOH (1.5 mL) and treated with 1.0 M NaOH/ H_2O (300 μ L, 0.3 mmol) and the mixture was stirred for 2.75 hr. It was then directly submitted to MCX purification (MeOH wash; 2.0 M NH_3 /MeOH elution) to afford M119b as a film of white solid (63.8 mg). 1H NMR ($DMSO-d_6$, $\delta=2.5$ ppm, 400 MHz): δ 11.82 (br s, 2H), 7.96 (s, 1H), 7.77 (d, J=8.0, 2H), 7.66 (d, J=8.0, 1H), 7.46 (br s, 1H), 7.42 (br s, 1H), 7.36 (d, J=8.0, 2H), 7.21 (d, J=8.0, 1H), 5.16 (app br s, 1H), 4.46 (s, 2H), 4.16 (app t, J=7.1, 2H), 3.00-2.82 (two m, 4H); there is a broad base line signal in this region from the pyrrolidine NH that was not included in the integration), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). LC (Cond. 1): RT=0.78 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{31}N_6O$: 455.26; found 455.27.

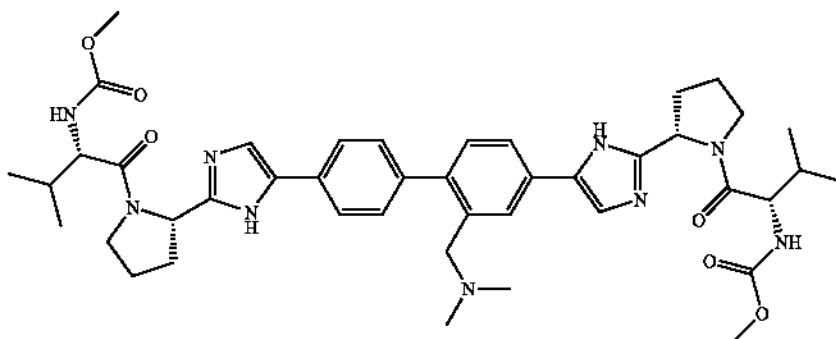
Example M119

[1301] Example M119 was prepared from M119b and Cap-51 according to the procedure described for Example 1, with the exception that a reverse phase HPLC with ACN/ H_2O / NH_4OAc solvent system was employed for the purification step. LC (Cond. 1): RT=1.15 min; 98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_9O_7$: 769.40; included in the integration), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). LC (Cond. 1): RT=0.78 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{31}N_6O$: 455.26; found 455.27.

Example M120

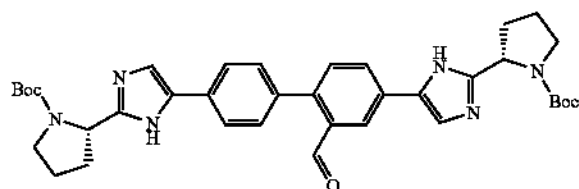
methyl ((1S)-1-(((2S)-2-(5-(2-((dimethylamino)methyl)-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1302]



Example M120, Step a

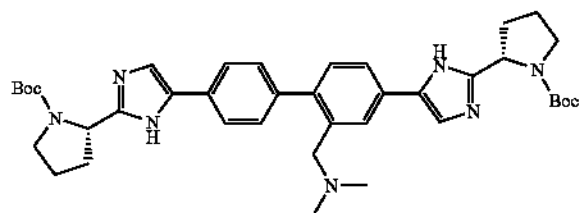
[1303]



[1304] CH_2Cl_2 (6.0 mL) was added to a mixture alcohol M119a (501 mg, 0.765 mmol), TPAP (29.1, 0.083 mmol) and 4-methylmorpholine N-oxide (135.8 mg, 1.159 mmol), and the resultant heterogeneous mixture was vigorously stirred at ambient condition for 14.5 hr. Additional TPAP (11.0 mg, 0.031 mmol) and 4-methylmorpholine N-oxide (39 mg, 0.33 mmol) were added and stirring was continued for an additional 24 hr. The mixture was filtered through diatomaceous earth (Celite®), the filtrate was rotavaped and the resulting crude material was purified with a Biotage (2% MeOH/EtOAc) to afford aldehyde M120a as a yellow viscous oil (195.6 mg). LC (Cond. 1): RT=1.37 min. LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{37}\text{H}_{45}\text{N}_6\text{O}_5$: 653.35; found 653.40.

Example M120, Step b

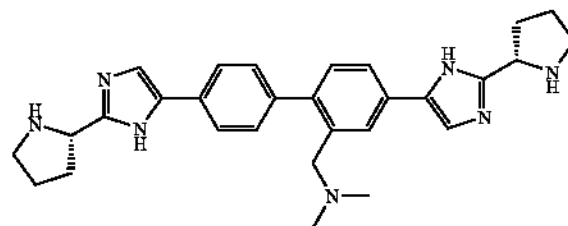
[1305]



[1306] NaCNBH_3 (33 mg, 0.50 mmol) was added in one batch to a MeOH (3.0 mL) solution of aldehyde M120a (195.6 mg, 0.30 mmol) and Me_2NH (200 μL of 40% solution in H_2O), and the reaction mixture was stirred for 4 hr. The volatile component was removed in vacuo and the residue was purified with a flash chromatography (sample was loaded as a silica gel mesh; 3-15% MeOH/ CH_2Cl_2) to afford amine M120b as an off-white foam (120 mg). LC (Cond. 1): RT=1.32 min. LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{35}\text{H}_{52}\text{N}_7\text{O}_4$: 682.41; found 682.42.

Example M120, Step c

[1307]



[1308] Carbamate M120b was converted to M120c by employing the protocol described for the preparation of 1e from 1d. ^1H NMR ($\text{DMSO}-d_6$, δ =2.5 ppm, 400 MHz): δ 11.82 (br s, 2H), 7.87 (s, 1H), 7.77 (d, J =8.0, 2H), 7.65 (d, J =7.8, 1H), 7.45/7.43 (overlapping two br s, 2H), 7.37 (d, J =7.8, 2H), 7.21 (d, J =7.8, 1H), 4.87 (m, 0.1H), 4.17 (m, 1.90H), ~3.3 (signal of Me_2NCH_2 overlapped with that of water), 3.01-2.94 (m, 2H), 2.89-2.83 (m, 2H), 2.10 (s, 6H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.81-1.67 (m, 4H). LC (Cond. 1): RT=0.79 min. LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{29}\text{H}_{36}\text{N}_7$: 482.30; found 482.35.

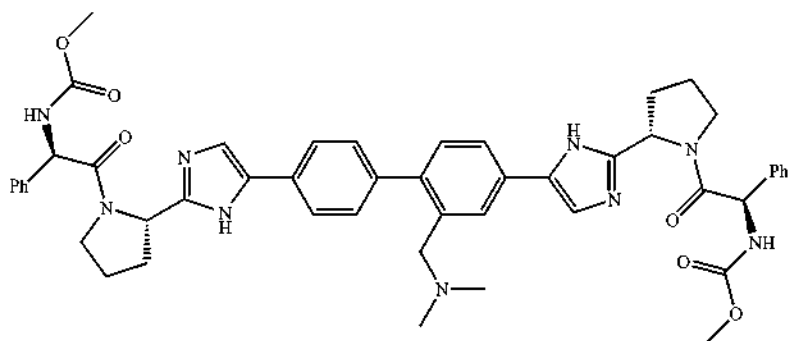
Example M120

[1309] The TFA salt of Example M120 was prepared from pyrrolidine M120c and Cap-51 according to the procedure described for Example 1. LC (Cond. 1): RT=1.06 min; 96% homogeneity index. LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{43}\text{H}_{58}\text{N}_9\text{O}_6$: 796.45; found 796.48. HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{43}\text{H}_{58}\text{N}_9\text{O}_6$: 796.4510; found 796.4515.

Example M121

dimethyl ((2-((dimethylamino)methyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)))biscarbamate

[1310]

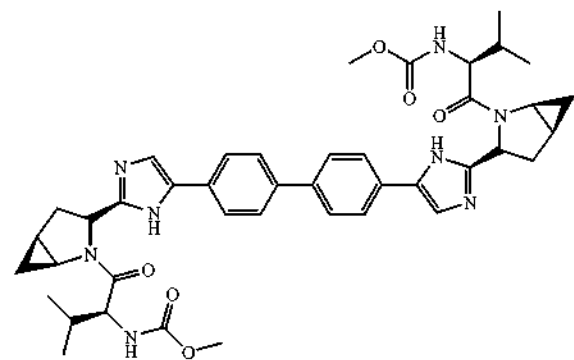


[1311] The TFA salt of Example M121 was prepared from M120c and Cap-4 according to the procedure described for Example 1. LC (Cond. 1): RT=1.15 min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{54}N_{10}O_6$: 796.45; found 864.46. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{54}N_{10}O_6$: 864.4197; found 864.4222.

Example M122

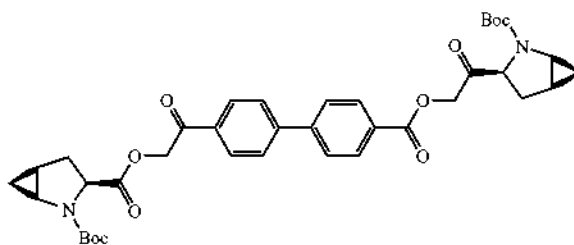
methyl ((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[1312]



Example M122, Step a

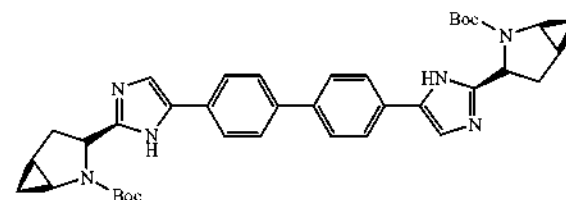
[1313]



[1314] Diisopropyl ethylamine (1.81 mL, 10.4 mmol) was slowly added to acetonitrile (20 mL) solution of (1S,3S,5S)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (2.36 g, 10.4 mmol) and (2-(4'-(2-bromoacetyl)biphenyl-4-yl)-2-oxoethyl)bromonium (2.0 g, 5.05 mmol), and the reaction mixture was stirred at ambient conditions for 16 hr. The solvent was evaporated and the residue was partitioned between ethyl acetate and water (1:1, 40 mL each). The organic layer was washed with Sat. $NaHCO_3$ (2x10 mL), brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford ketoester M122a (3.58 g) as a viscous amber oil, which solidified upon storage in a refrigerator. 1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): δ 8.20 (m, 4H), 7.97 (d, J=8.5, 4H), 5.71-5.48 (m, 4H), 4.69 (m, 2H), 3.44 (m, 2H), 3.3 (m, 2H), 2.76-2.67 (m, 2H), 2.27 (m, 2H), 1.60 (m, 2H), 1.44/1.38 (two s, 18H), 0.78 (m, 2H), 0.70 (m, 2H). LC (Cond. 1): RT=1.70 min; LC/MS: the molecular ion was not picked up.

Example M122, Step b

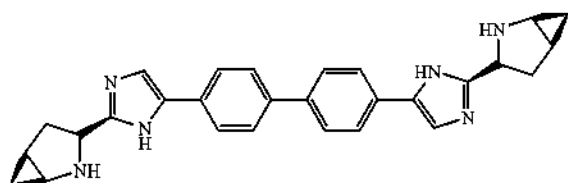
[1315]



[1316] Ammonium acetate (2.89 g, 37.5 mmol) was added to a toluene (20 mL) solution of ketoester M122a (2.58 g, 3.75 mmol), and the resulting mixture was heated at 120°C for 4.5 hr, while azeotroping the water that is formed with a Dean-Stark set-up. The reaction mixture was cooled to room temperature and the volatile component was removed in vacuo. Sat. $NaHCO_3$ solution (10 mL) was added to the solid and the mixture was stirred for 30 min, and the solid was filtered, dried in vacuo and submitted to a Biotage purification (28-100% EtOAc/hexanes) to afford imidazole M122b as light yellow solid (0.6 g). LC (Cond. 1): RT=1.52 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{45}N_6O_4$: 649.35; found 649.78.

Example M1122, Step c

[1317]



[1318] 4 N HCl in dioxane (5 mL) was added to a ice-water cooled dioxane (16 mL) solution of carbamate M122b (0.8 g, 1.2 mmol), the ice-water bath was removed and the mixture was stirred at ambient condition for 4 hr. Big chunks of solid that formed during the reaction were broken up with a spatula. Removal of the volatile component in vacuo afforded pyrrolidine M122c (0.4HCl) as yellow solid (0.73 g).

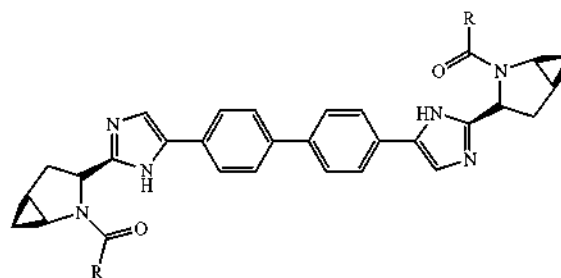
[1319] ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): δ 7.90 (d, J =8.3, 4H), 7.84 (br s, 2H), 7.79 (d, J =8.3, 4H), 5.24 (m, 2H), 3.38 (m, 2H), 2.71 (m, 2H), ~2.50 (2H, overlapped with solvent signal), 1.93 (m, 2H), 1.38 (m, 2H), 0.96 (m, 2H). LC (Cond. 1): RT=1.03 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{28}\text{H}_{29}\text{N}_6$: 449.25; found 449.59.

Example M122

[1320] The TFA salt of Example M122 was prepared from M122c and Cap-51 according to the procedure described for Example 1. LC (Cond. 1): RT=1.34 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{42}\text{H}_{51}\text{N}_8\text{O}_6$: 763.39; found 763.73.

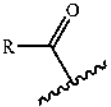
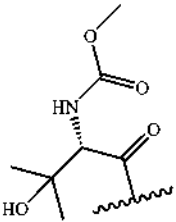
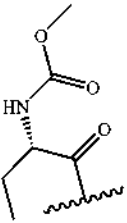
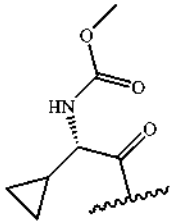
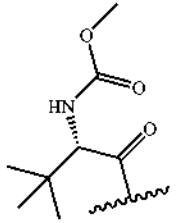
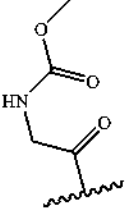
Example M123-M130

[1321] Example M123-M130 were prepared according to the procedure described for Example M122. Example M123-M129 were prepared as TFA salts, where as Example M130 was prepared as a free base.

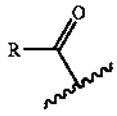
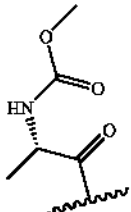


Example	Compound Name	(Source)	RT (LC-Cond.); % homogeneity index; MS data
M123	methyl ((1R)-1-(((1S,3S,5S)-3-(5-(4'-(2-(t(1S,3S,5S)-2-(t(2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate	 (Cap-84)	1.372 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[\text{M} + \text{H}]^+$ $\text{C}_{42}\text{H}_{51}\text{N}_8\text{O}_6$: 763.39; found 763.73
M124	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediy)))biscarbamate	 (Cap-4)	2.28 minutes (Cond. M1); >98%; LC/MS: Anal. Calcd. for $[\text{M} + \text{H}]^+$ $\text{C}_{48}\text{H}_{47}\text{N}_8\text{O}_6$: 831.36; found 831.36

-continued

Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M125	methyl ((1S)-2-hydroxy-1-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-3-hydroxy-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate	 (Cap-65)	1.76 minutes (Cond. M1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₁ N ₈ O ₈ : 795.38; found 795.37
M126	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate	 (Cap-53b)	1.25 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₇ N ₈ O ₆ : 735.36; found 735.68
M127	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate	 (Cap-54b)	1.27 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₄₇ N ₈ O ₆ : 759.36; found 759.72
M128	methyl ((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-(methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2,2-dimethylpropyl)carbamate	 (Cap-54b)	2.48 minutes (Cond. M1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₅ N ₈ O ₆ : 791.42; found 791.41
M129	methyl (2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)oxoethyl)carbamate	 (Cap-54b)	1.10 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₃₉ N ₈ O ₆ : 679.74; found 679.77

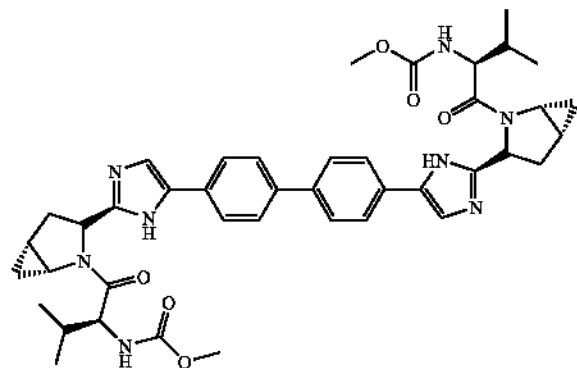
-continued

Example	Compound Name	 (Source)	RT (LC-Cond.); % homogeneity index; MS data
M130	methyl ((1S)-2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(N-(methoxycarbonyl)-L-alanyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-1-methyl-2-oxoethyl)carbamate	 (Cap-52)	1.16 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₃ N ₈ O ₆ : 707.33; found 707.69

Example M131

methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[1322]

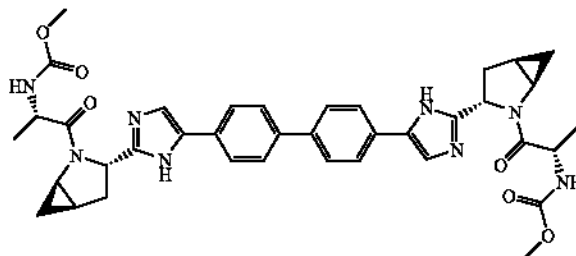


[1323] Example M131 was prepared according to the procedure described for its diastereomer Example M122 starting from (1R,3S,5R)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid, which was in turn synthesized by employing a literature protocol (Hanessian et al., *Angew. Chem., Int. Ed. Engl.* 1997, 36, 1881-1884). LC (Cond. D): RT=1.273 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₄₂H₅₀N₈O₆: 763.39; found 763.94.

Example M132

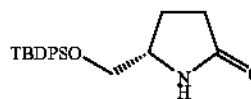
methyl ((1S)-2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(N-(methoxycarbonyl)-L-alanyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-1-methyl-2-oxoethyl)carbamate

[1324]



Example M132, Step a

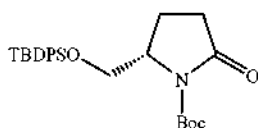
[1325]



[1326] To a solution of (S)-5-(hydroxymethyl)pyrrolidin-2-one (10 g, 87 mmol) in CH₂Cl₂ (50 mL) was added tert-butylchlorodiphenylsilane (25.6 g, 93 mmol), triethylamine (12.1 mL, 87 mmol) and DMAP (1.06 g, 8.7 mmol). The mixture was stirred at room temperature for 5 hours, treated with CH₂Cl₂ (50 mL) and washed with water (50 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo. The crude product was purified with a flash chromatography (30 to 100% of EtOAc/hexanes) to afford ether M132a as colorless oil (22.7 g, 74% yield). ¹H NMR (DMSO-d₆, δ=2.50, 400 MHz): 7.69 (br s, 1H), 7.64-7.61 (m, 4H), 7.50-7.42 (m, 6H), 3.67-3.62 (m, 1H), 3.58-3.51 (m, 2H), 2.24-2.04 (m, 3H), 1.89-1.78 (m, 1H), 1.00 (s, 9H).

Example M132, Step b

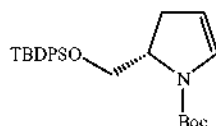
[1327]



[1328] Di-tert-butyl dicarbonate (28.0 g, 128 mmol) was added slowly to a cooled (ice/water) CH_2Cl_2 (120 mL) solution of ether M132a (22.7 g, 64.2 mmol), triethylamine (8.95 mL, 64.2 mmol), and DMAP (7.84 g, 64.2 mmol). At the end of addition, the cooling bath was removed and stirring continued at ambient condition for 20 hours. The volatile component was removed in vacuo, and the crude material was submitted to a flash chromatography (20 to 50% EtOAc/hexanes) to afford carbamate M132b as off-white solid (29 g, 99% yield). ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz): 7.61-7.54 (m, 4H), 7.50-7.38 (m, 6H), 4.19-4.16 (m, 1H), 3.90 (dd, $J=10.4$, 3.6, 1H), 3.68 (dd, $J=10.4$, 2.1, 1H), 2.68-2.58 (m, 1H), 2.40-2.33 (m, 1H), 2.22-2.12 (m, 1H), 2.01-1.96 (m, 1H), 1.35 (s, 9H), 0.97 (s, 9H).

Example M132, Step c

[1329]

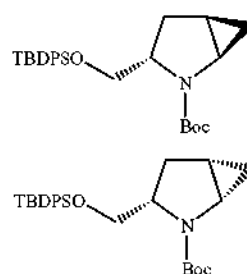


[1330] A three-necked flask equipped with a thermometer and a nitrogen inlet was charged with carbamate M132b (10.054 g, 22.16 mmol) and toluene (36 mL), and lowered into -55°C . cooling bath. When the internal temperature of the mixture reached $\sim -50^\circ\text{C}$, Superhydride (23 mL of 1.0 M in THF, 23.00 mmol) was added dropwise over 30 minutes while maintaining the internal temperature between -50 and -45°C , and stirred for 35 minutes while maintaining the temperature between -50 and -45°C . Hunig's Base (16.5 mL, 94 mmol) was added dropwise over 10 minutes. Then DMAP (34 mg, 0.278 mmol) was added in one batch, followed by the addition of trifluoroacetic anhydride (3.6 mL, 25.5 mmol) over 15 minutes, while maintaining the internal temperature between -50 and -45°C . The bath was removed 10 minutes later, and the reaction mixture was stirred for 14 hours while allowing it to thaw to ambient temperature. It was then diluted with toluene (15 mL), cooled with ice-water bath, and treated slowly with water (55 mL) over 5 minutes. At the end of addition, the phases were separated, and the organic layer was washed with water (50 mL, 2 \times) and then concentrated in vacuo. The crude material was purified with a flash chromatography (5% EtOAc/hexanes) to afford carbamate M132c as a colorless viscous oil (7.947 g, 82%). ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz): 7.62-7.58 (m, 4H), 7.49-7.40 (m, 6H), 6.47 (br m, 1H), 5.07-5.01 (br m, 1H), 4.18 (br m,

1H), 3.89 (br m, 0.48H), 3.69 (br m, 1.52H), 2.90-2.60 (br m, 2H), 1.40/1.26 (two overlapping s, 9H), 0.98 (s, 9H).

Example M132, Step d

[1331]



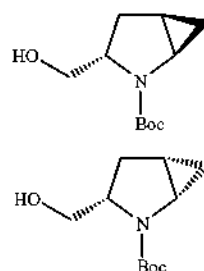
M132d-i

M132d-ii

[1332] Diethylzinc (19 mL of ~ 1.1 M in toluene, 20.90 mmol) was added dropwise over 15 minutes to a cooled (-30°C .) toluene (27 mL) solution of carbamate M132c (3.94 g, 9.0 mmol). Then chloriodomethane (97%, stabilized over copper; 3 mL, 41.2 mmol) was added dropwise over 10 minutes, and stirred while maintaining the bath temperature around -25°C . for 1 hour and around -21°C . for 18.5 hours. The reaction was then opened to air and quenched by a slow addition of 50% saturated NaHCO_3 solution (40 mL), and then removed from the cooling bath and stirred at ambient condition for 20 minutes. It was filtered through a filter paper and the white cake was washed with 50 mL of toluene. The organic phase of the filtrate was separated, and washed with water (40 mL, 2 \times), dried (MgSO_4), filtered, and concentrated in vacuo. The resulting crude material was purified with a Biotage system (350 g silica gel; sample was loaded with 7% EtOAc/hexanes; eluted with 7-20% EtOAc/hexanes) to afford methanopyrrolidine M132d as a colorless viscous oil, mainly as the trans isomer (3.691 g, 90.7%). [Note: the exact trans/cis ratio has not been determined yet at this stage]. ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz) of M132d-i: 7.62-7.60 (m, 4H), 7.49-7.40 (m, 6H), 3.76 (br m, 1H), 3.67 (br m, 2H), 3.11-3.07 (m, 1H), 2.23 (br m, 1H), 2.03 (br m, 1H), 1.56-1.50 (m, 1H), 1.33 (br s, 9H), 1.00 (s, 9H), 0.80-0.75 (m, 1H), 0.30 (br m, 1H).

Example M132, Step e

[1333]



M132e-i

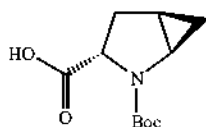
M132e-ii

[1334] TBAF (7.27 mL of 1.0 M in THF, 7.27 mmol) was added dropwise over 5 minutes to a THF (30 mL) solution of

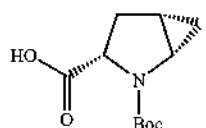
the ether M132d (3.13 g, 6.93 mmol) and the mixture was stirred at ambient condition for 4.75 hours. After it was treated with saturated NH_4Cl solution (5 mL), most of the volatile component was removed in vacuo, and the residue was partitioned between CH_2Cl_2 (70 mL) and 50% saturated NH_4Cl solution (30 mL). The aqueous phase was extracted with CH_2Cl_2 (30 mL), and the combined organic phase was dried (MgSO_4), filtered, concentrated in vacuo, and then exposed to high vacuum overnight. The resulting crude material was purified with a Biotage (40-50% EtOAc/hexanes) to afford alcohol M132e as colorless oil, mainly as the trans isomer, contaminated with traces of lower Rf impurities (1.39 g, 94%). [Note: the exact trans/cis ratio has not been determined yet at this stage]. ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz) of M132e-i: 4.70 (app t, $J=5.7$, 1H), 3.62-3.56 (m, 1H), 3.49-3.44 (m, 1H), 3.33-3.27 (m, 1H), 3.08-3.04 (m, 1H), 2.07 (br m, 1H), 1.93-1.87 (m, 1H), 1.51-1.44 (m, 1H), 1.40 (s, 9H), 0.76-0.71 (m, 1H), 0.26 (br m, 1H).

Example M132, Step f

[1335]

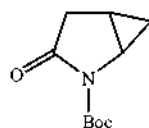


M132f-i



M132f-ii

-continued



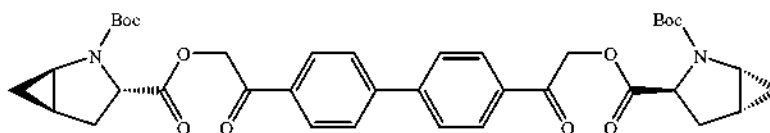
M132f-iii

[1336] A semi-solution of NaIO_4 (6.46 g, 30.2 mmol) in H_2O (31 mL) was added to CH_3CN (20 mL) and CCl_4 (20 mL) solution of alcohol M132e (2.15 g, 10.08 mmol) prepared above, and RuCl_3 (0.044 g, 0.212 mmol) was added immediately and the heterogeneous reaction mixture was

vigorously stirred for 75 minutes. The reaction mixture was diluted H_2O (60 mL) and extracted with CH_2Cl_2 (50 mL, 3 \times). The combined organic phase was treated with 1 mL CH_3OH , allowed to stand for about 5 minutes, and then filtered through a pad of diatomaceous earth (Celite®). The pad was washed with CH_2Cl_2 (50 mL), and the filtrate was rotavaped to afford a light charcoal-colored solid. ^1H NMR of the crude material indicated a 1.00:0.04:0.18 mole ratio among trans acid M132f-i: presumed cis acid M132f-ii: side product M132f-iii. The crude material was dissolved in EtOAc (~10 mL) with heating, and allowed to stand at ambient condition with seeding. About 15 minutes into the cooling phase, a rapid crystal formation was observed. About 1 hour later, hexanes (~6 mL) was added and the mixture was refrigerated overnight (it does not appear that additional compound has precipitated out). The mixture was filtered and washed with ice/water cooled hexanes/EtOAc (2:1 ratio; 20 mL) and dried under high vacuum to afford the first crop of acid M132f-i (off-white crystals, 1.222 g). The mother liquor was rotavaped, and the residue was dissolved in ~3 mL of EtOAc (with heating), allowed to stand at ambient condition for 1 hour, and then 3 mL hexanes was added and stored in a refrigerator for ~15 hours. A second crop of acid M132f-i (grey crystals, 0.133 g) was retrieved similarly. ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz): 12.46 (br s, 1H), 3.88 (br m, 1H), 3.27 (br m, 1H; partially overlapped with the signal of water), 2.28 (br m, 1H), 2.08 (br m, 1H), 1.56 (br m, 1H), 1.40/1.34 (two overlapped br s, 9H), 0.73-0.68 (m, 1H), 0.46-0.43 (m, 1H). Optical rotation (10 mg/mL of CHCl_3): $[\alpha]_D=-216$ for first crop & -212 for the second crop.

Example M132, Step g

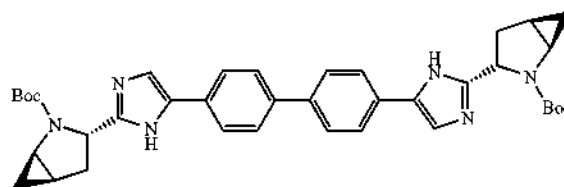
[1337]



[1338] Ketoester M132g was prepared from acid M132f-i and 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) by employing the procedure described for the preparation of ketoester M122a. LC (Cond. I): RT=2.09 minutes. LC/MS: Anal. Calcd. for $[\text{M}+\text{H}-\text{Boc}]^+$ $\text{C}_{33}\text{H}_{37}\text{N}_2\text{O}_8$: 589.26; found 589.29.

Example M132, Step h

[1339]



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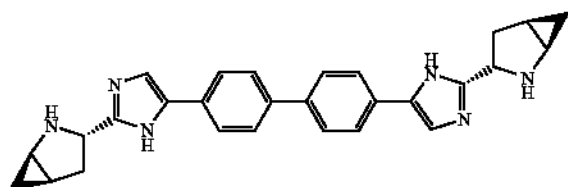
450

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[1340] Carbamate M132h was prepared from ketoester M132g according to the procedure described for the preparation of imidazole 1b from ketoamide 1a, with the exception that 20 mol equiv of NH_4OAc was employed for the thermal cyclization, and that CH_2Cl_2 was employed during the work up step. LC (Cond. I): RT=1.48 minutes. LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{38}\text{H}_{45}\text{N}_6\text{O}_4$: 649.35; found 649.40.

Example M132, Step i

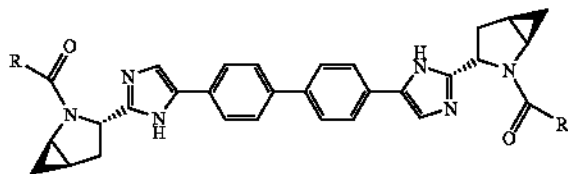
[1341]



[1342] Pyrrolidine M132i (0.4HCl) was prepared from carbamate M132h according to the procedure described for the preparation of pyrrolidine M122c. The crude material was submitted to subsequent acylation step without purification. ^1H NMR ($\text{DMSO}-d_6$, $\delta=2.50$, 400 MHz): 10.5-10.0 (br signal, not integratable), 8.02 (s, 2H), 7.95 (d, $J=8.6$, 4H), 7.85 (d, $J=8.3$, 4H), 4.75 (m, 2H), 3.43 (m, 2H), 2.67-2.50 (m, 4H), 1.95 (m, 2H), 1.11 (m, 2H), 0.86 (m, 2H). RT=1.00 minutes. LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{28}\text{H}_{20}\text{N}_6$: 449.25; found 49.27.

Example M132

[1343] Example M132, along with its analogs Example M133-M137 highlighted in the table below, were prepared as TFA salts from pyrrolidine M132i (0.4HCl) by employing the procedure described for the synthesis of Example M122 and appropriate acids. Example M132: LC (Cond. I): RT=1.14 min; >95% homogeneity index. LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{38}\text{H}_{43}\text{N}_8\text{O}_6$: 707.33; found 707.43.

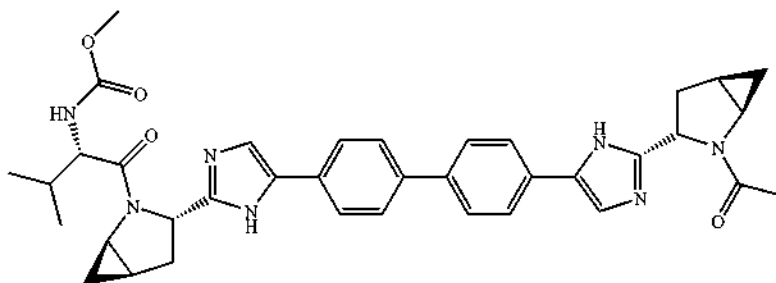


Ex- am- ple	Compound Name		RT (LC- Cond. I); % homogeneity index; MS data
M133	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate		1.22 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[\text{M} + \text{H}]^+$ $\text{C}_{40}\text{H}_{47}\text{N}_8\text{O}_6$: 735.36; found 735.48
M134	methyl (2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate		1.12 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[\text{M} + \text{H}]^+$ $\text{C}_{36}\text{H}_{39}\text{N}_8\text{O}_6$: 679.30; found 679.38
M135	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate		1.25 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[\text{M} + \text{H}]^+$ $\text{C}_{42}\text{H}_{47}\text{N}_8\text{O}_6$: 759.36; found 759.45
M136	methyl (((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate		1.34 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[\text{M} + \text{H}]^+$ $\text{C}_{42}\text{H}_{50}\text{N}_8\text{O}_6$: 763.39; found 763.46
M137	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate		1.38 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[\text{M} + \text{H}]^+$ $\text{C}_{48}\text{H}_{47}\text{N}_8\text{O}_6$: 831.36; found 831.37

Example M138

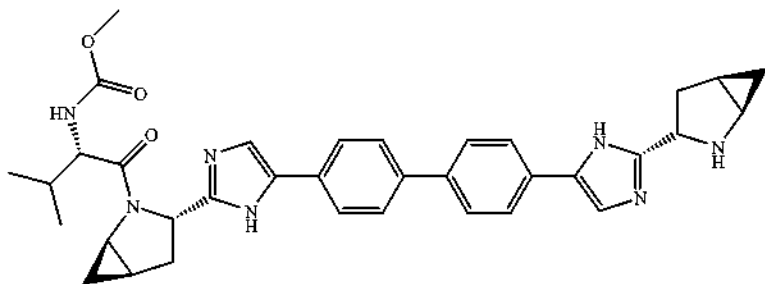
methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-acetyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl) carbamate

[1344]



Example M138, Step a

[1345]



[1346] To a slurry of pyrrolidine M132i (0.4HCl) (0.3 g, 0.32 mmol) in DMF (4 mL), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (97 mg, 0.55 mmol) and *i*-Pr₂EtN (0.26 mL, 1.5 mmol) were added. After the mixture became a clear solution, HATU (0.2 g, 0.53 mmol) was added, and it was stirred at room temperature for 3 hours. The volatile component was removed in vacuo, and the resulting residue (which was a mixture of starting material, and mono- and bis-acylated products) was dissolved in methanol and purified with a reverse phase HPLC (CH₃OH/H₂O/TFA) to isolate the TFA salt of pyrrolidine M138a as white foam (80 mg). LC (Cond. 1): RT=1.17 minutes. LC/MS: Anal. Calcd. for [M+H]⁺ C₃₅H₄₀N₇O₃: 606.32; found 606.36.

Example M138

[1347] Acetic acid (7.6 mg, 0.13 mmol), *i*-Pr₂EtN (32 mg, 0.25 mmol), and HATU (53 mg, 0.14 mmol) were sequentially added to a DMF (2 mL) solution of the TFA salt of pyrrolidine M138a (40 mg, 0.04 mmol), and the reaction mixture was stirred at room temperature for 3 hours. The volatile component was removed in vacuo, and the residue was dissolved in methanol and purified with a reverse phase HPLC (CH₃OH/H₂O/TFA) to afford the TFA salt of Example M138 as white foam (8 mg). LC (Cond. 1): RT=1.20 min; >95% homogeneity index. LC/MS: Anal. Calcd. for [M+H]⁺ C₃₇H₄₂N₇O₄: 648.33; found 648.36.

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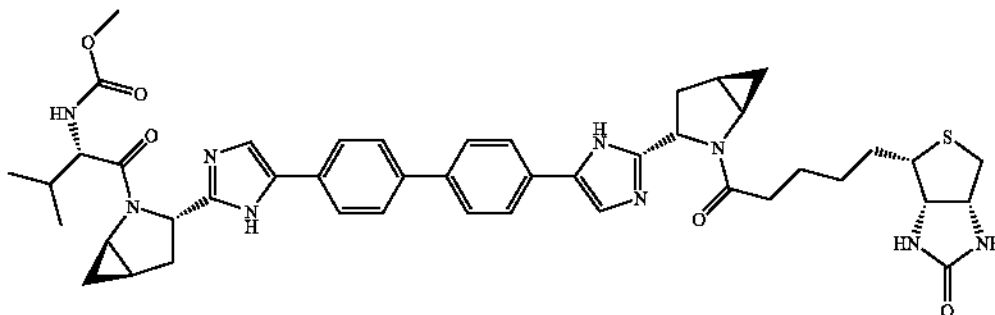
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Example M139

methyl ((1S)-2-methyl-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl-2-methylpropyl)carbamate

[1348]

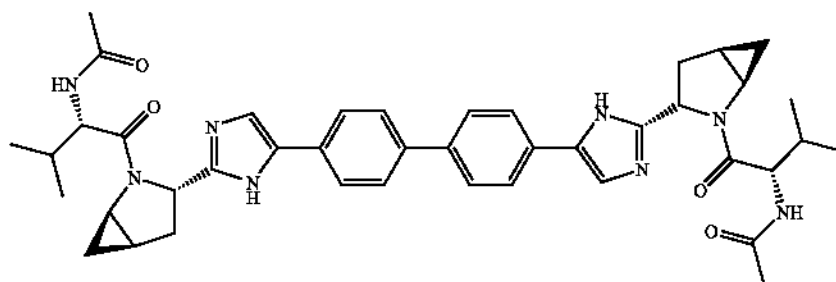


[1349] HATU (53 mg) was added to a mixture of the TFA salt of pyrrolidine M138a (40 mg, 0.042 mmol), d-Biotin (10.3 mg, 0.042 mmol) and *i*-Pr₂EtN (0.044 mL, 0.253 mmol), and the reaction mixture was stirred at room temperature for 3 hours. The volatile component was removed in vacuo, and the residue was dissolved in methanol and purified with a reverse phase HPLC (CH₃OH/H₂O/TFA) to afford the TFA salt of Example M139 as a light yellow solid (7 mg). LC (Cond. I): RT=1.28 min; >95% homogeneity index. LC/MS: Anal. Calcd. for [M+H]⁺ C₄₅H₅₄N₉O₅S: 832.40; found 832.34.

Example M140

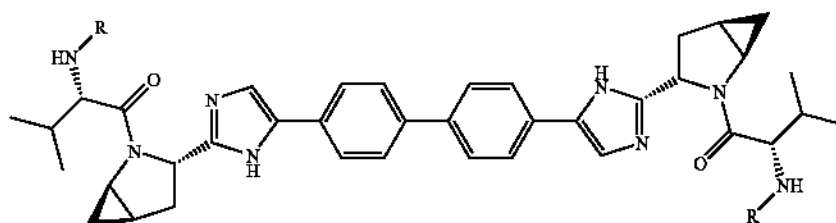
N-(((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-acetamido-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl-2-methylpropyl)acetamide

[1350]



Example M140, Step a

[1351]



M140a-i: R = Boc
M140a-ii: R = H

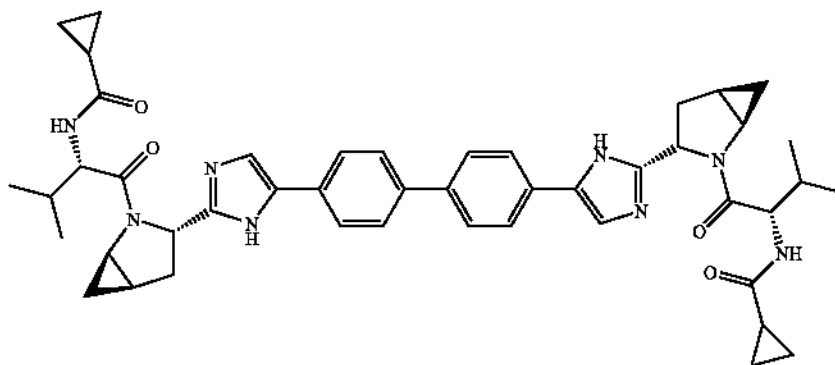
[1352] HATU (852 mg, 2.24 mmol) was added to a DMF (20 mL) solution of pyrrolidine M132i (0.4HCL) (650 mg, 1.09 mmol), Boc-L-Valine (523 mg, 2.41 mmol), *i*-Pr₂EtN (1.15 mL, 6.56 mmol), and the reaction mixture was stirred at room temperature for 1 hour. The volatile component was removed in vacuo, and the crude was dissolved in CH₃OH and purified with a reverse phase HPLC (CH₃OH/H₂O/TFA) to afford 0.96 g of acylated product. A portion of the product (0.72 g) was dissolved in CH₂Cl₂ (4 mL), treated with TFA (0.26 mL, 3.35 mmol), and the resulting mixture was stirred at ambient condition for 4 hours. The volatile component was removed in vacuo to afford the TFA salt of M140a-ii, tert-butyl ((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate, which was used in the next step without purification. LC (Cond. I): RT=0.93 minutes.

condition until completion, as determined by LC/MS analysis. The volatile component was removed in vacuo, and the residue was dissolved in CH₃OH and submitted to a reverse phase HPLC (CH₃OH/H₂O/TFA) to afford the TFA salt of Example M140 as white foam (35 mg). LC (Cond. I): RT=1.18 min; >98% homogeneity index. LC/MS: Anal. Calcd. for [M+H]⁺ C₄₂H₅₁N₈O₄: 731.40; found 731.34.

Example M141

N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((cyclopropylcarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)cyclopropanecarbamate

[1355]



LC/MS: Anal. Calcd. for [M+H]⁺ C₃₈H₄₇N₈O₂: 647.38; found 647.26.

[1353] The free base form of carbamate M140a-i could be isolated at the coupling stage as follows: the HPLC fraction was neutralized with excess 2.0 N NH₃/CH₃OH, the volatile component was removed in vacuo and the residue was partitioned between CH₂Cl₂ and ~5% saturated NaHCO₃ solution. The organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo to afford M140a-i, (2S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-amino-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-3-methyl-1-oxo-2-butanamine, as a light yellow foam. LC (Cond. I): RT=1.64 min; >95% homogeneity index. LC/MS: Anal. Calcd. for [M+H]⁺ C₄₈H₆₃N₈O₆: 847.49; found 847.54.

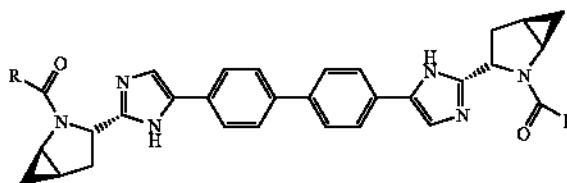
Example M140

[1354] Acetic anhydride (21 mg, 0.204 mmol) and *i*-Pr₂EtN (0.083 mL, 0.476 mmol) were sequentially added to a DMF (3 mL) solution of the TFA salt of M140a-ii (75 mg, 0.068 mmol), and the reaction mixture was stirred at ambient

[1356] Example M141 was prepared as a TFA salt from amine M140a-ii (TFA salt) and cyclopropanecarboxylic acid according to the coupling procedure described for the synthesis of carbamate M140a-i. LC (Cond. I): RT=1.33 min; >95% homogeneity index. LC/MS: Anal. Calcd. for [M+H]⁺ C₄₆H₅₅N₈O₄: 783.42; found 783.36.

Example M142-M143


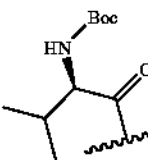
[1357] Example M142 (free base) and Example M143 (TFA salt) were prepared by employing the procedures described for the synthesis of Example M140 and appropriate materials.



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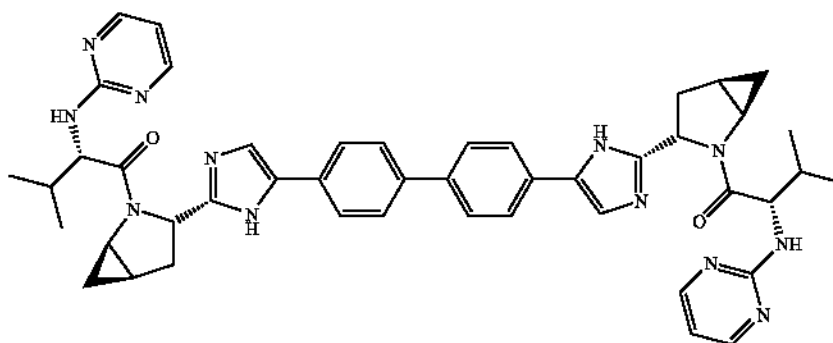
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Ex- am- ple	Compound Name		RT (LC- Cond.); % homogeneity index; MS data	-continued		
				Ex- am- ple	Compound Name	RT (LC- Cond.); % homogeneity index; MS data
M142	tert-butyl (((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((tert)-butoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate		1.65 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₆₃ N ₉ O ₆ : 847.49; found 847.54	M143	N-(((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-acetamido-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)acetamide	1.26 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₁ N ₉ O ₄ : 731.40; found 731.34

Example M144

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl
(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-
3-methyl-1-oxo-1,2-butanediyl)))di(2-pyrimidi-
namine)

[1358]



[1359] A mixture of the TFA salt of amine M140a-ii (75 mg, 0.068 mmol), 2-bromopyrimidine (32.4 mg, 0.204 mmol), and *i*-Pr₂EtN (0.048 mL, 0.272 mmol) in DMSO (0.2 mL)/toluene (1.2 mL) was heated at 90° C. for 20 hours. Additional 2-bromopyrimidine (32.4 mg, 0.204 mmol) was added and heating continued for 8 hours. Most of the volatile component was removed in vacuo and the residue was purified twice by a reverse phase HPLC system, (CH₃OH/H₂O/TFA) followed by (ACN/H₂O/TFA), to afford the TFA salt of

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Example M144, contaminated with unknown minor impurities, as a yellow foam (10 mg). RT=20.9 minutes (see the LC method detail below); >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_{12}O$: 803.43; found 803.70.

Method details for analysis of Example M144:

Instrument: Waters Acquity HPLC with Waters PDA UV-Vis detection and Waters SQ MS (ESI probe)

Column: Waters Acquity BEH C18; 1.7 μ m; 150x2.1 mm ID; (at 35 C)

[1360] Mobile phase A: Water/acetonitrile (97.5/2.5) with 5 mM ammonium formate;

0.05% formic acid at pH 3.3

Mobile phase B: Acetonitrile/Water (97.5/2.5) with 5 mM ammonium formate;

0.05% formic acid

Flow: 0.35 ml/min

Hold 10% B 0-1 min

10-35% B 1-20 min

35-98% B 20-32 min

[1361] hold 98% 32-35 min

98-10% B 35-35.5 min

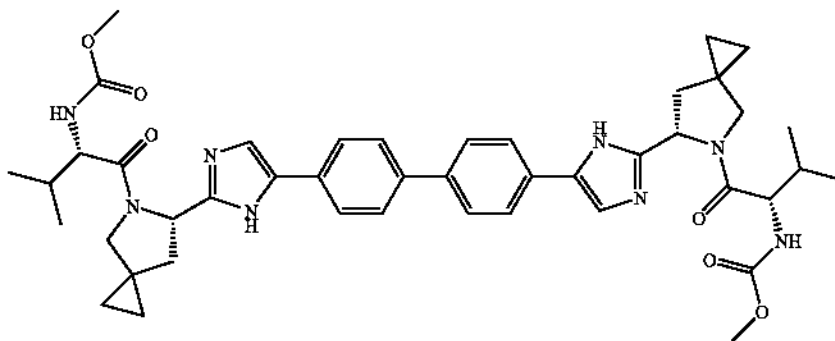
[1362] hold 10% B 35.5-40.0 min

UV detection:@260 nm

Example M145

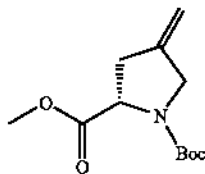
methyl ((1S)-1-(((6S)-6-(4-(4'-((6S)-5-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)carbonyl)-2-methylpropyl)carbamate

[1363]



Example M145, Step a

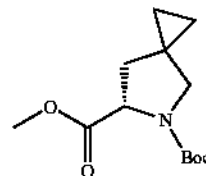
[1364]



[1365] TMSCHN₂ (3.63 mL of 2.0 M/ether, 7.26 mmol) was added dropwise to a CH₃OH (33 mL)/benzene (33 mL) solution of (S)-1-tert-butyl 4-methylenepyrrolidine-1,2-dicarboxylate (1.5 g, 6.60 mmol), and the reaction mixture was stirred at ambient condition for 3.5 hours. Removal of the volatile component in vacuo afforded ester M145a as a tan oil (1.57 g). ¹H NMR (CDCl₃, δ =7.26 ppm, 500 MHz): 5.01-4.98 (m, 2H), 4.50-4.48 (m, 0.5H), 4.39-4.37 (m, 0.5H), 4.07-4.04 (m, 2H), 3.71 (s, 3H), 3.01-2.87 (m, 1H), 2.66-2.55 (m, 1H), 1.46/1.41 (two overlapping s, 9H).

Example M145, Step b

[1366]



[1367] Diethylzinc (5.65 mL of 1.1 M in toluene, 6.22 mmol) was added dropwise over 20 minutes to a cooled (-22° C.) toluene (4 mL) solution of ester M145a (0.50 g, 2.07 mmol). Chloriodomethane (0.90 mL, 12.4 mmol) was added dropwise over 10 minutes, and the reaction mixture was stirred at -22° C. for 18 hours. The reaction was quenched with saturated solution of NaHCO₃ (aq.) (5 mL) at similar temperature and was then allowed to thaw to ambient temperature. The mixture was filtered, and the precipitate was washed with EtOAc (100 mL). The layers of the filtrate were

separated, and the organic phase was dried (MgSO₄), filtered, and concentrated in vacuo. The resulting crude material was purified with a Biotage (10-20% EtOAc/hexanes) to afford ester M145b as colorless oil (0.139 g). ¹H NMR (CDCl₃, δ =7.26 ppm, 500 MHz): 4.47-4.44 (m, 0.5H), 4.47-4.34 (m, 0.5H), 3.73 (s, 3H), 3.39-3.27 (m, 2H), 2.25-2.18 (m, 1H), 1.86-1.84 (m, 0.5H), 1.78-1.75 (m, 0.5H), 1.44/1.40 (two overlapping s, 9H), 0.63-0.48 (m, 4H). LC (Cond. II): RT=2.26 minutes. LC/MS: Anal. Calcd. for $[M+Na]^+$ C₁₂H₁₉NNaO₄: 264.12; found 264.22.

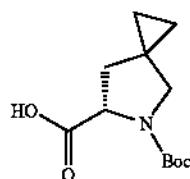
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Example M145, Step c

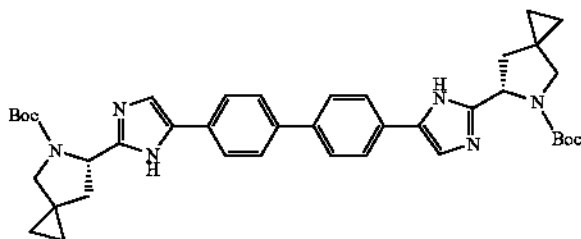
[1368]



[1369] A water (0.61 mL) solution of LiOH (0.016 g, 0.65 mmol) was added to an ethanol (1.2 mL) solution of ester M145b (0.139 g, 0.544 mmol), and the reaction mixture was stirred at ambient condition for 19 hours. The volatile component was removed in vacuo, and the residue was dissolved in water (5 mL), cooled (ice/water), acidified to a pH region of 3.0 with 1N HCl (aq.), and then extracted with EtOAc (50 mL, 3x). The combined organic layer was dried (MgSO₄), filtered, and concentrated in vacuo to afford acid M145c as viscous oil which solidified upon standing (0.129 g). ¹H NMR (CDCl₃, δ=7.26 ppm, 500 MHz): 4.48-4.40 (m, 1H), 3.55-3.05 (m, 2H), 2.37-1.87 (m, 2H), 1.47/1.44 (two overlapping s, 9H), 0.78-0.50 (m, 4H). LC (Cond. II): RT=2.26 minutes. LC/MS: Anal. Calcd. for [M+Na]⁺ C₁₂H₁₉NNaO₄: 264.12; found 264.22.

Example M145, Step d

[1370]

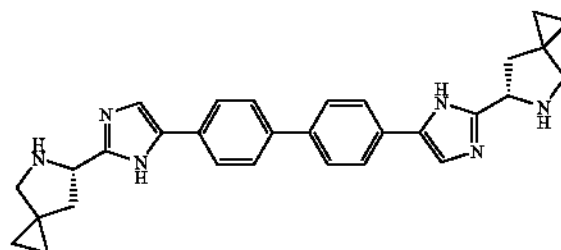


[1371] Carbamate M145d was prepared starting from acid M145c and 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) and employing the general procedure described for the synthesis of M122b with the exception that the ketoester-cyclization step was conducted under microwave conditions (140°

C.; 90 min). LC (Cond. II): RT=2.54 minutes. LC/MS: Anal. Calcd. for [M+H]⁺ C₄₀H₄₉N₆O₄: 677.38; found 677.45.

Example M145, Step e

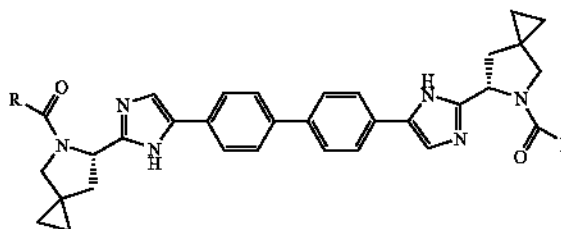
[1372]



[1373] 25% TFA/CH₂Cl₂ (5.3 mL) was added to carbamate M145d (0.718 g, 1.06 mmol) and the resultant mixture was stirred at ambient condition for 5 hours. The volatile component was removed in vacuo, and the residue was free-based with MCX (6 g, CH₃OH washing: 1:1 CHCl₃/2 N NH₃/CH₃OH elution) to afford pyrrolidine M145e as a light yellow solid (406 mg). ¹H NMR (DMSO-d₆, δ=2.5 ppm, 500 MHz): 11.89 (br s, 2H), 7.82 (d, J=7.9, 4H), 7.67 (d, J=7.9, 4H), 7.50 (br s, 2H), 4.37 (m, 2H), 2.92 (app d, J=9.8, 2H), 2.81 (app d, J=10.1, 2H), 2.09-2.05 (m, 2H), 1.98-1.94 (m, 2H), 0.62-0.49 (m, 8H). LC (Cond. II): RT=1.75 minutes. LC/MS: Anal. Calcd. for [M+H]⁺ C₃₀H₃₃N₆: 477.28; found 477.35.

Example M145

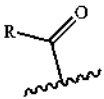
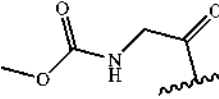
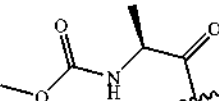
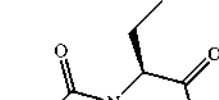
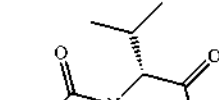
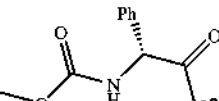
[1374] Example M145, along with its analogs Example M146-M147 highlighted in the table below, were prepared as TFA salts starting from pyrrolidine M145 and appropriate acids, by employing the general HATU coupling condition outlined for Example-1, with the exception that the reaction mixture was diluted with CH₃OH and directly submitted to a reverse phase HPLC (CH₃OH/H₂O/TFA) purification. Example M145: LC (Cond. II), RT=2.27 min; >95% homogeneity index. LC/MS: Anal. Calcd. for [M+H]⁺ =C₄₄H₅₅N₈O₆: 791.42; found 791.44.



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Example	Compound Name		RT (LC-Cond.); % homogeneity index; MS data
M146	methyl 2-((6S)-6-(4-(4'-(2-((6S)-5-((methoxycarbonyl)amino)acetyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)-2-oxoethyl)carbamate		1.97 minutes (Cond. II); >95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₃ N ₈ O ₆ ; 707.33; found 707.36
M147	methyl ((1S)-2-((6S)-6-(4-(4'-(2-((6S)-5-(N-(methoxycarbonyl)-L-alanyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)-1-methyl-2-oxoethyl)carbamate		2.01 minutes (Cond. II); >95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₄₇ N ₈ O ₆ ; 735.36; found 735.41
M148	dimethyl (4,4'-biphenyldiylbis(1H-imidazol-4,2-diyl(6S)-5-azaspiro[2.4]heptane-6,5-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate		2.14 minutes (Cond. II); >95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₁ N ₈ O ₆ ; 763.39; found 763.46
M149	methyl ((1R)-1-(((6S)-6-(4-(4'-(2-((6S)-5-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)carbonyl)-2-methylpropyl)carbamate		2.44 minutes (Cond. II); >95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₅₅ N ₈ O ₆ ; 791.42; found 791.44
M150	dimethyl (4,4'-biphenyldiylbis(1H-imidazol-4,2-diyl(6S)-5-azaspiro[2.4]heptane-6,5-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate		2.52 minutes (Cond. II); >95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₅₀ H ₅₁ N ₈ O ₆ ; 859.39; found 859.42

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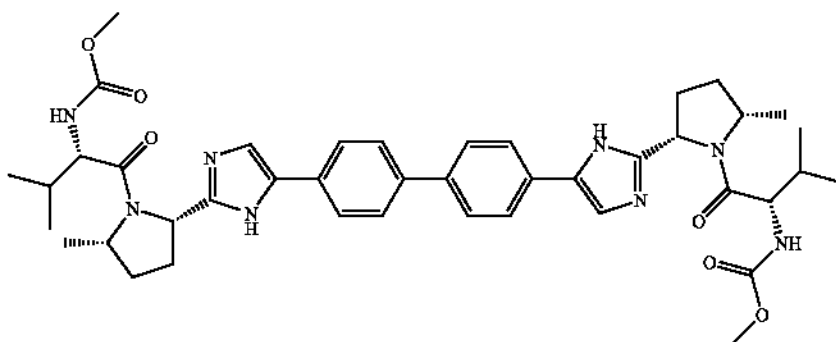
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Example M151

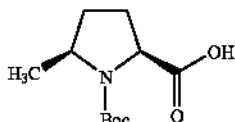
methyl ((1S)-1-(((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[1375]



Example M151, Step a

[1376]

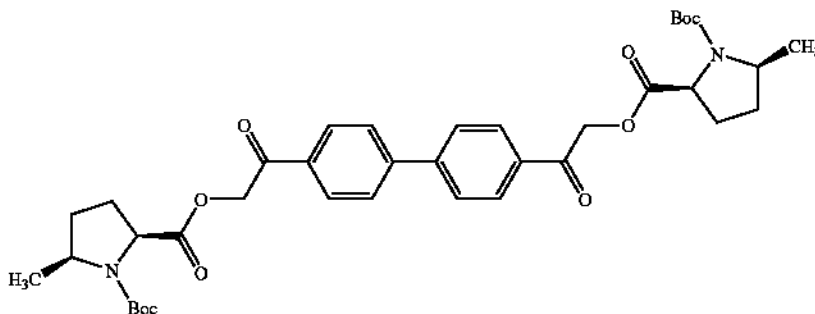


following purification modifications: the crude material (2.7 g) was recrystallized from EtOAc/hexanes at ambient temperature to afford acid M151a as a white crystal (2.2 g). ¹H NMR (CDCl₃, δ=7.24 ppm, 400 MHz): 4.32 (br m, 1H), 3.89 (br m, 1H), 2.40 (br m, 1H), 2.00 (m, 2H), 1.65 (m, 1H), 1.45 (s, 9H), 1.20 (d, J=5.6, 3H). LC (Cond. I): RT=1.40 minutes. LC/MS: Anal. Calcd. for [M+Na]⁺ C₁₁H₂₀NO₄Na: 252.12; found 252.21.

[1377] The title compound was synthesized according to a literature protocol (*J. Med. Chem.*, 2006, 49, 3520) with the

Example M151, Step b

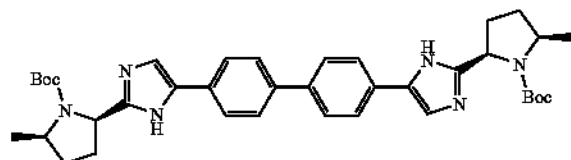
[1378]



[1379] To a mixture of acid M151a and 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (1.85 g, 4.66 mmol) in acetonitrile (50 mL), *i*-Pr₂EtN (1.24 g, 9.6 mmol) was added dropwise, and the reaction was stirred at room temperature for 7 hr. The volatile component was removed in vacuo and the residue was partitioned between ethyl acetate and water (1:1, 100 mL). The organic layer was separated and washed with saturated NaHCO₃ and brine, dried (Na₂SO₄), filtered, and concentrated in vacuo to afford ketoester M151b as white foam (3.19 g), which was used in the next step without purification. ¹H NMR (DMSO-*d*₆, δ=2.5 ppm, 400 MHz): 8.10 (d, J=8.5, 4H), 7.95 (d, J=8.5, 4H), 5.70-5.50 (br m, 4H), 4.40 (br m, 2H), 3.90 (br m, 2H), 2.25 (m, 2H), 2.15 (m, 4H), 1.60 (m, 2H), 1.41 (s, 8H), 1.39 (s, 10H), 1.20 (m, 6H). LC (Cond. I): RT=2.15 minutes. LC/MS: parent ion was not observed.

Example M151, Step c

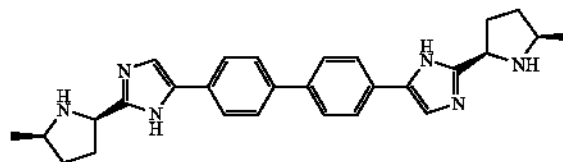
[1380]



[1381] A mixture of ketoester M151b (2.94 g, 4.24 mmol) and ammonium acetate (6.54 g, 85 mmol) in xylene (40 mL) was heated in a sealed tube at 140° C. for 2 hours. The volatile component was removed in vacuo and the residue was partitioned between CH₂Cl₂ (100 mL) and water (50 mL). The organic layer was washed with saturated NaHCO₃ (20 mL), dried (Na₂SO₄), concentrated in vacuo. The resultant crude material was purified with a Biotage (0-100% EtOAc/hexanes) to afford imidazole M151c as light brown solid (1.72 g). LC (Cond. I): RT=1.03 minutes. LC/MS: Anal. Calcd. for [M+H]⁺ C₃₈H₄₉N₆O₄: 653.37; found 653.40.

Example M151, Step d

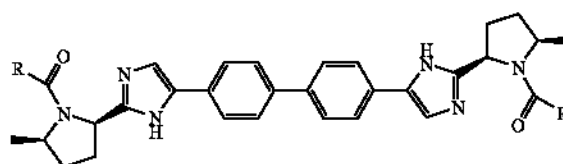
[1382]



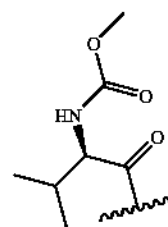
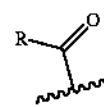
[1383] 4 N HCl in dioxane (14 mL, 56 mmol) was added dropwise to a dioxane (70 mL) solution of carbamate M151c (1.72 g, 2.63 mmol), and the reaction mixture was stirred at room temperature for 4 hours. Removal of the volatile component in vacuo afforded the HCl salt of pyrrolidine M151d as a yellow solid (1.58 g). ¹H NMR (DMSO-*d*₆, δ=2.5 ppm, 400 MHz): δ 9.85 (br s, 1H), 8.80 (br s, 1H), 7.89 (d, J=8.3, 4H), 7.77 (s, 2H), 7.75 (d, J=8.6, 4H), 4.70 (br m, 2H), 3.75 (br m, 2H), 2.45-2.35 (m, 4H), 2.25 (m, 2H), 1.75 (m, 2H), 1.50 (d, J=6.6, 6H). LC (Cond. I): RT=1.03 minutes. LC/MS: Anal. Calcd. for [M+H]⁺ C₂₈H₃₃N₆: 453.28; found 453.28.

Example M151

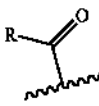
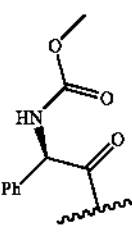
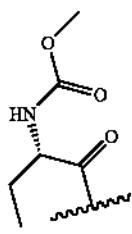
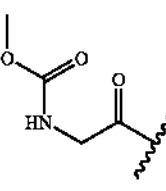
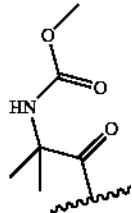
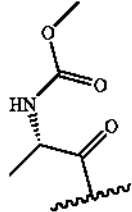
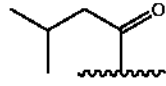
[1384] Example M151, along with its analogs Example M152-M161 highlighted in the table below, were prepared as TFA salts starting from pyrrolidine M151d and appropriate acids, by employing the general HATU coupling condition outlined for Example-1, with the exception that the reaction mixture was diluted with CH₃OH and directly submitted to a reverse phase HPLC purification (CH₃OH/H₂O/TFA). Example M151: LC (Cond. I): RT=1.41 min; >95% homogeneity index. LC/MS: Anal. Calcd. for [M+H]⁺ C₄₂H₅₅N₈O₆: 767.42; found 767.40.



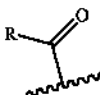
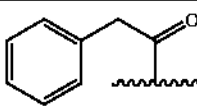
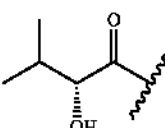
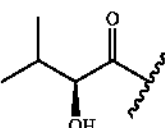
Example	Compound Name		RT (LC-Cond. I); % homogeneity index; MS data
M152	methyl ((1R)-1-(((2S,5S)-2-(4-(4-(2-((2S,5S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		1.38 minutes (Cond. I); >98% LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₅ N ₈ O ₆ : 767.42; found 767.33



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Example	Compound Name		RT (LC-Cond.); % homogeneity index; MS data
M153	dimethyl (4,4'-biphenyldiylbis(1H-imidazol-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediy))))biscarbamate		1.46 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₈ H ₅₁ N ₈ O ₆ : 835.39; found 835.31
M154	dimethyl (4,4'-biphenyldiylbis(1H-imidazol-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((2S)-1-oxo-1,2-butanediyl))))biscarbamate		1.27 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₁ N ₈ O ₆ : 739.39; found 739.28
M155	methyl 2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((methoxycarbonyl)amino)scetyl)-5-methyl-2-pyrrolidiny)-1H-imidazol-4-yl)-4-biphenyly)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidiny)-2-oxoethyl)carbamate		1.19 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₆ H ₄₃ N ₈ O ₆ : 683.33; found 683.32
M156	methyl 2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-2-((methoxycarbonyl)amino)-2-methylpropanoyl)-5-methyl-2-pyrrolidiny)-1H-imidazol-4-yl)-4-biphenyly)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidiny)-1,1-dimethyl-2-oxoethyl)carbamate		1.33 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₁ N ₈ O ₆ : 739.39; found 739.28
M157	methyl ((1S)-2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(N-(methoxycarbonyl)-L-alanyl)-5-methyl-2-pyrrolidiny)-1H-imidazol-4-yl)-4-biphenyly)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidiny)-1-methyl-2-oxoethyl)carbamate		1.21 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₇ N ₈ O ₆ : 711.36; found 711.23
M158	4,4'-(4,4'-biphenyldiylbis(2-((2S,5S)-5-methyl-1-(3-methylbutanoyl)-2-pyrrolidiny)-1H-imidazole)		1.42 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₉ N ₆ O ₂ : 621.39; found 621.28

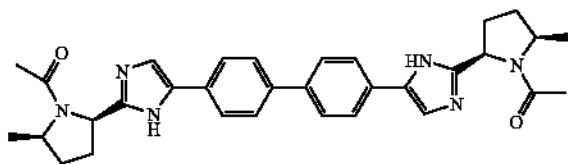
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Example	Compound Name		RT (LC-Cond.); % homogeneity index; MS data
M159	4,4'-(4,4'-biphenyldiyl)bis(2-((2S,5S)-5-methyl-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazole)		1.46 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₄ H ₄₅ N ₆ O ₂ : 689.36; found 689.26
M160	(2R,2'R)-1,1'-(4,4'-biphenyldiyl)bis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol)		1.27 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₉ N ₆ O ₄ : 653.38; found 653.27
M161	(2S,2'S)-1,1'-(4,4'-biphenyldiyl)bis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol)		1.267 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₄₉ N ₆ O ₄ : 653.38; found 653.34

Example M162

2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-4-(4'-(2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole

[1385]

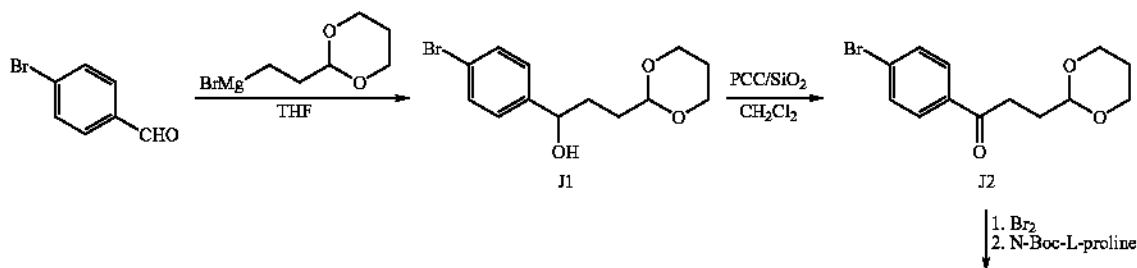


[1386] Acetic anhydride (38.4 mg, 0.376 mmol) and i-Pr₂EtN (0.153 mL, 0.877 mmol) were added to a DMF (3 mL) solution of the HCl salt of pyrrolidine M151d (75 mg, 0.125 mmol), and the mixture was stirred at room temperature for 2 hours. The volatile component was removed in vacuo, and the residue was dissolved in CH₃OH and purified with a reverse phase HPLC (CH₃OH/H₂O/TFA) to afford the TFA salt of M162 as a white foam (55 mg). LC (Cond. I): RT=1.13 min; >95% homogeneity index. LC/MS: Anal. Calcd. for [M+H]⁺ C₃₂H₃₇N₆O₂: 537.30; found 537.21.

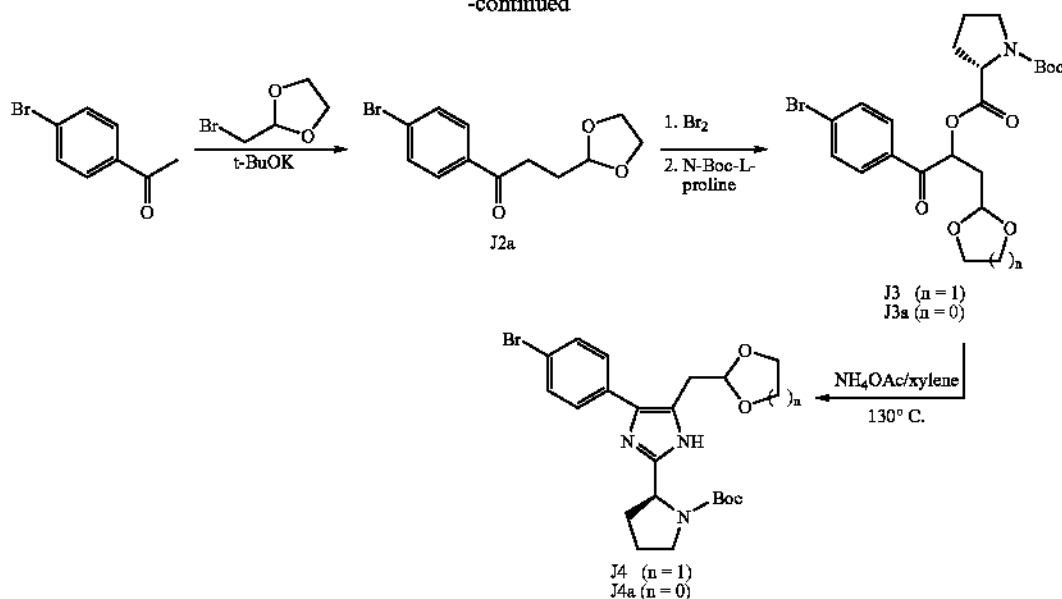
Examples J1-J14.f and E1-E5m

[1387]

Synthetic Scheme 1



-continued

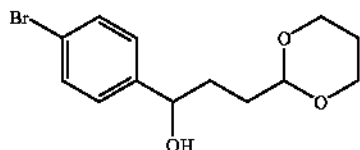


[1388] LCMS conditions 1: Phenomenex-Luna 4.6×50 mm S10, 0 to 100% B over 2 min, 3 min stop time, 4 mL/min, 220 nm, A: 10% CH_3OH —90% H_2O —0.1% TFA; B: 90% CH_3OH —10% H_2O —0.1% TFA.

[1389] LCMS conditions 2: Phenomenex-Luna 4.6×50 mm S10, 0 to 100% B over 3 min, 4 min stop time, 4 mL/min, 220 nm, A: 10% CH_3OH —90% H_2O —0.1% TFA; B: 90% CH_3OH —10% H_2O —0.1% TFA.

[1390] LCMS conditions 3: Luna 4.6×30 mm C18, 0 to 100% B over 2 min, 3 min stop time, 5 mL/min, 220 nm, A: 5% Acetonitrile—90% H_2O —10 mM NH_4OAc ; B: 90% Acetonitrile—10% H_2O —0.1% 10 mM NH_4OAc .

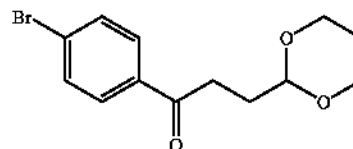
[1391] Reference: *J. Org. Chem.* (1992) 57, 1784.



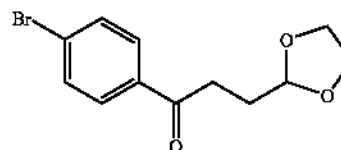
[1392] 108 mL of (1,3-dioxan-2-ylethyl) magnesium bromide (0.5M) was added to a solution of 4-bromobenzaldehyde (10 g, 54.0 mmol) in THF (350 mL) at -78°C under nitrogen and stirred for 2 hours before warming to 0°C . The reaction was quenched with sat NH_4Cl soln, diluted with diethyl ether and washed with brine. The crude product was charged (CH_2Cl_2) to a 40M Biotage silica gel cartridge; Gradient elution 15–100% B over 750 mL (A=Hexanes; B=ethyl acetate) to give Example J1, 1-(4-bromophenyl)-3-(1,3-dioxan-2-yl)propan-1-ol (quantitative yield). ^1H NMR (500 MHz, CDCl_3) δ 7.44 (d, $J=8.5$ Hz, 2H), 7.22 (d, $J=8.5$ Hz, 2H), 4.70–4.66 (m, 1H), 4.57 (t, $J=4.9$ Hz, 1H), 4.12–4.19 (m, 2H), 3.76 (tt, $J=11.9$, 2.7 Hz, 2H), 2.87 (d, $J=3.7$ Hz, 1H), 2.12–2.03 (m, 1H), 1.86–1.87 (m, 2H), 1.74–1.68 (m, 2H),

1.36–1.32 (m, 1H). RT=1.8 minutes (condition 1); LRMS: No parent ion evident.

[1393] Reference: *JOC* (1989) 54 5387.



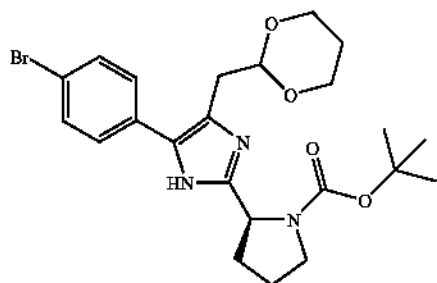
[1394] PCC (8.16 g, 59.8 mmol) was admixed with 9 g SiO_2 and ground (mortar & pestle) and suspended in Dichloromethane (360 mL). To the suspension was added in one portion Example J1, 1-(4-bromophenyl)-3-(1,3-dioxan-2-yl)propan-1-ol (9 g, 29.9 mmol) dissolved in 5 mL of the same solvent. The reaction mixture was stirred for 2 hours and filtered through celite (rinse with CH_2Cl_2). After being concentrated the residue was charged (CH_2Cl_2) to a 40 M Biotage silica gel cartridge. Gradient elution 15–70% B over 750 mL (A=Hexanes; B=ethyl acetate) gave Example J2, 1-(4-bromophenyl)-3-(1,3-dioxan-2-yl)propan-1-one 7.7 g (86%). ^1H NMR (500 MHz, CDCl_3) δ 7.84 (d, $J=8.7$ Hz, 2H), 7.59 (d, $J=8.5$ Hz, 2H), 4.65 (t, $J=4.9$ Hz, 1H), 4.09–4.06 (m, 2H), 3.74 (dt, $J=11.0$, 2.4 Hz, 2H), 3.06 (t, $J=7.3$ Hz, 2H), 2.07–2.01 (m, 3H), 1.35–1.31 (m, 1H). LCMS: RT=1.9 minutes (condition 1); $\text{C}_{13}\text{H}_{15}\text{BrO}_3$ Calcd.: 299; found: 299 ($\text{M}+\text{H}$) $^+$.



[1395] The potassium tert-butoxide (15 mL, 1M in THF) was added dropwise to a solution of 1-(4-bromophenyl)etha-

none (3 g, 15.07 mmol) in DMSO (60 mL) at 0° C. and stirred for 30 min under nitrogen. The enolate was cannulated into a solution of 2-(bromomethyl)-1,3-dioxolane (2.52 g, 15.07 mmol) in DMSO (10 mL) at 0° C. and the reaction allowed to warm to 24° C. and stirred 6 hours. Concentrate to remove solvent (high vacuum rotary evaporation) and charge (CH₂Cl₂) of residue to a 40 (M) Biotage silica gel cartridge and gradient elution 5-35% B over 1 L (A=Hexanes; B=ethyl acetate) gave Example J2a, 1-(4-bromophenyl)-3-(1,3-dioxolan-2-yl)propan-1-one 327 mg (7.6%) and 571 mg of a bis addition product. ¹H NMR (500 MHz, CDCl₃) δ 7.83 (d, J=8.5 Hz, 2H), 7.58 (d, J=8.5 Hz, 2H), 4.97 (t, J=4.3 Hz, 1H), 3.96-3.94 (m, 2H), 3.87-3.84 (m, 2H), 3.08-3.05 (m, 2H), 2.15-2.11 (m, 2H).

[1396] Reference: Bromination *JACS* (1952) 74 6263. Displacement/Cyclization *J. Med. Chem.* (2001) 44 2990.

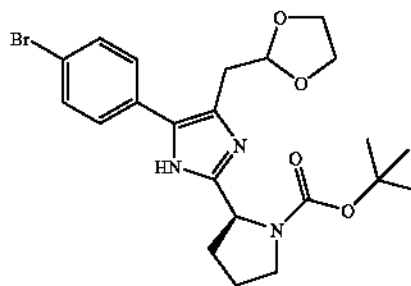


J4

[1397] Bromine (1.3 mL, 25.2 mmol) was added to a solution of Example J2, 1-(4-bromophenyl)-3-(1,3-dioxolan-2-yl)propan-1-one (7.7 g, 25.7 mmol) in diethyl ether (60 mL) and 1,4-dioxane (40 mL) and the solution stirred 30 min at 24° C.

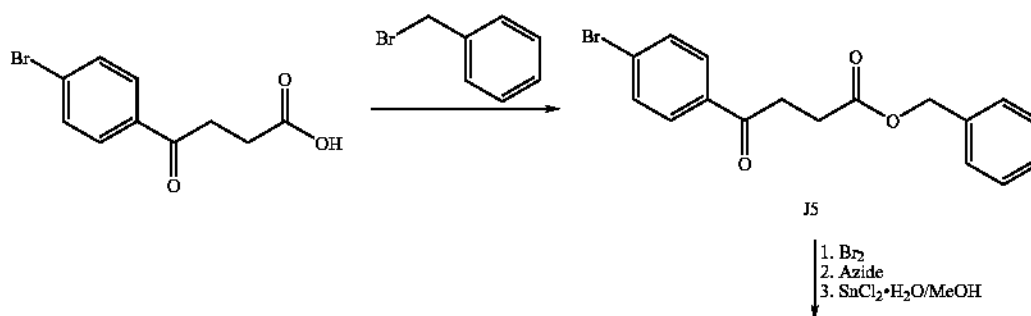
(Until TLC indicated reaction complete). The solvent was removed by rotary evaporation and the residue was taken up in acetonitrile (350 mL). (S)-N-Boc-Proline (5.54 g, 25.7 mmol) was added followed by dropwise addition of Hunig's base (8.5 mL, 51.5 mmol) and the reaction was stirred 6 hours before being concentrated. The crude product was taken up in CH₂Cl₂ and charged to a 40 (M) Biotage silica gel cartridge. Gradient elution 15-100% B over 1 L (A=hexanes; B=ethyl acetate) gave Example J3, 2-(1-(4-bromophenyl)-3-(1,3-dioxolan-2-yl)-1-oxopropan-2-yl) 1-tert-butyl pyrrolidine-1,2-dicarboxylate 13 g (100%). RT=2.2 minutes (condition 1); LCMS: Anal. C₂₃H₃₀BrNO₇ Calcd. 534; found: 534 (M+Na)⁺.

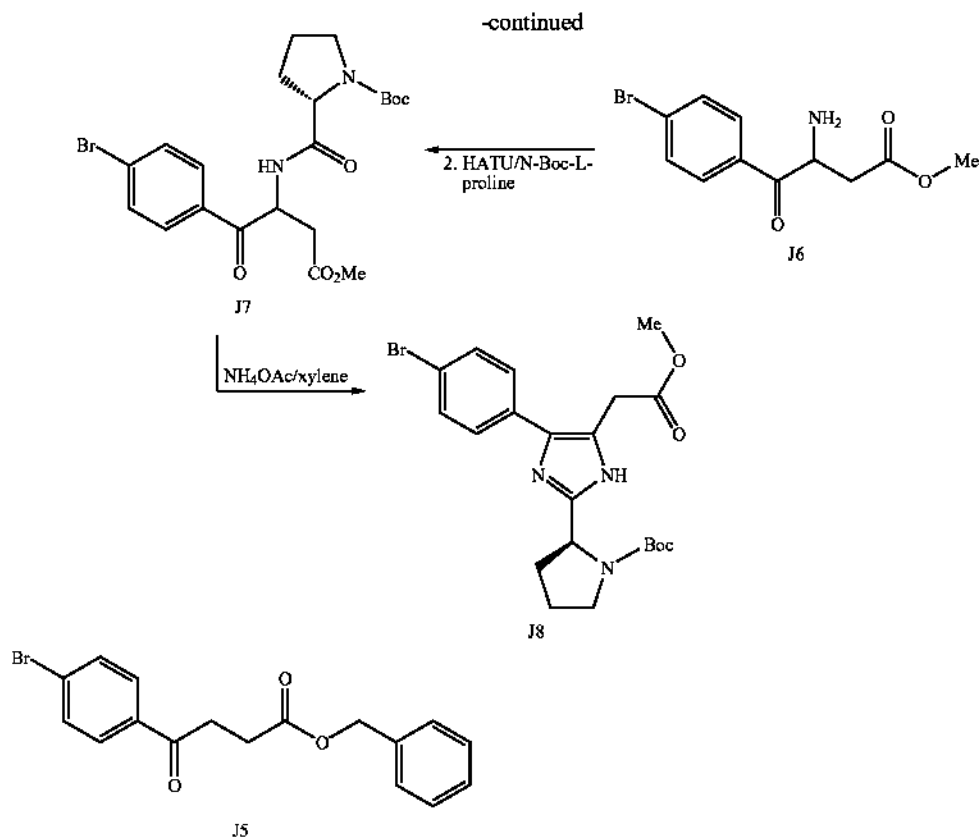
[1398] Ammonium acetate (6.45 g, 107 mmol) was added to a solution of Example J3, 2-(1-(4-bromophenyl)-3-(1,3-dioxolan-2-yl)-1-oxopropan-2-yl) 1-tert-butyl pyrrolidine-1,2-dicarboxylate (5.5 g, 10.7 mmol) in xylene (120 mL) and stirred for 3 hours at 130° C. in a screw capped 500 mL pressure vessel. After being cooled, the reaction mixture was diluted with ethyl acetate (600 mL) and washed with sat NaHCO₃ and brine before being concentrated by rotary evaporation under high vacuum. The crude product was taken up in CH₂Cl₂ and charged to a 40 (M) Biotage silica gel cartridge. Gradient elution 15-100% B over 2 L (A=CH₂Cl₂; B=ethyl acetate) gave Example J4, (S)-tert-butyl 2-(4-((1,3-dioxolan-2-yl)methyl)-5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate 2.22 g (40%). ¹H NMR (500 MHz, CDCl₃) δ 7.46 (s, 4H), 4.94-4.92 (m, 1H), 4.77 (t, J=4.9 Hz, 1H), 4.15-4.12 (m, 2H), 3.81-3.75 (m, 2H), 3.3-3.37 (m, 2H), 3.0-2.90 (m, 2H), 2.10-2.05 (m, 4H), 1.94-1.91 (m, 1H), 1.49 (s, 9H) 1.36-1.34 (m, 1H). RT=1.8 minutes (condition 1); HRMS: Anal. C₂₃H₃₀BrN₃O₄ Calcd. 492.1492; found: 492.1505 (M+H)⁺.

J4a
Derived from
example J2a

RT = 1.68 min, (Cond 1)
HRMS: Anal. Calcd. for
C₂₂H₂₉BrN₃O₄ 478.1336; found:
478.1356 (M + H)⁺.

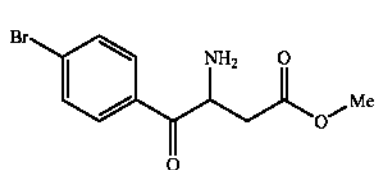
Synthetic Scheme 2



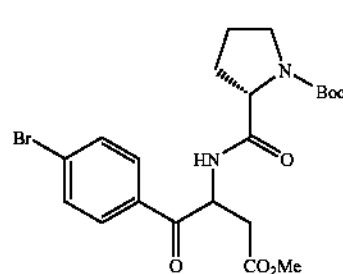


[1399] Benzyl bromide (9.98 g, 58.3 mmol) was added to a solution of 4-(4-bromophenyl)-4-oxobutanoic acid (15.0 g, 58.3 mmol) and K_2CO_3 (3.5 g, 58.3 mmol) in DMF (300 mL) and stirred for 18 hours. The reaction mixture was partitioned between water (200 mL) and ethyl acetate (500 mL). Sat'd $NaHCO_3$ soln (20 mL) was added and the aqueous layer extracted with ethyl acetate (2x) and the combined organic layers were washed with brine and dried and filtered. Concentration gave Example J5, benzyl 4-(4-bromophenyl)-4-oxobutanoate 16 g (79%) which was used without further purification. 1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, $J=8.6$ Hz, 2H), 7.61 (d, $J=8.5$ Hz, 2H), 7.35-7.34 (m, 5H), 5.14 (s, 2H), 3.27 (t, $J=6.7$ Hz, 2H), 2.81 (t, $J=6.7$ Hz, 2H). HRMS: Anal. $C_{17}H_{16}BrNO_3$ Calcd. 347.0277; found: 347.0283 ($M+H$) $^+$.

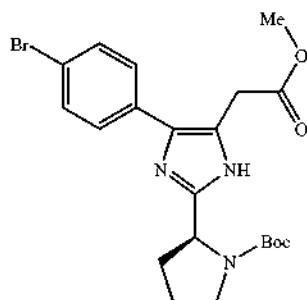
and the reaction mixture stirred 18 hours. The solvent was removed upon concentration and the residue taken up in ethyl acetate and wash with water, brine, dried Na_2SO_4 , and filtered. Concentration gave benzyl 3-azido-4-(4-bromophenyl)-4-oxobutanoate 17 g (95%) which was carried forward without further purification. Tin (II) chloride dehydrate (24.9 g, 131 mmol) was added to a solution of benzyl 3-azido-4-(4-bromophenyl)-4-oxobutanoate (17 g, 43.8 mmol) in CH_3OH (550 mL) and stirred for 14 hours at 65° C. The reaction was concentrated by rotary evaporation and dried under high vacuum for 18 hours to give a mixture of benzyl and Example J6, methyl 3-amino-4-(4-bromophenyl)-4-oxobutanoate, (transesterification had occurred) and carried forward with purification. RT=1.3 minutes (condition 1); LCMS: Anal. $C_{11}H_{12}BrNO_3$ Calcd. 286.0; found: 286.14 ($M+H$) $^+$.



[1400] Bromine (2.5 mL, 46.1 mmol) was added to a solution of Example J5, benzyl 4-(4-bromophenyl)-4-oxobutanoate (16 g, 46.1 mmol) in ether (200 mL) and 1,4-Dioxane (50 mL) and the solution was stirred for 6 hours before being concentrated by rotary evaporation and taken up in acetonitrile (450 mL). Sodium azide (3.0 g, 46.1 mmol) was added



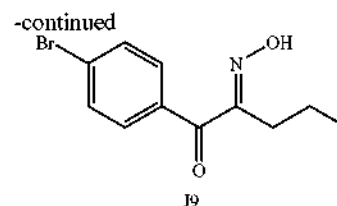
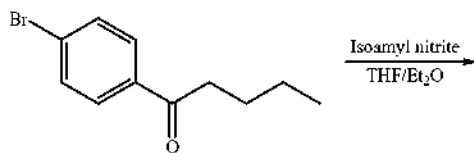
[1401] HATU (10.5 g, 27.6 mmol) was added to a solution of Example J6, methyl 3-amino-4-(4-bromophenyl)-4-oxobutanoate (10 g, 27.6 mmol), (S)-N-Boc-proline (7.13 g, 33.1 mmol), and Hunig's Base (45 mL, 276 mmol) in DMF (150 mL) and stirred for 18 hours at 24° C. The reaction was diluted with ethyl acetate (2 vol) and H₂O (¼ vol) and sat NaHCO₃ (½ vol). Filter through diatomaceous earth (Celite®) to remove tin salts. Extract aqueous layer (2×) with ethyl acetate, and concentrate combined organic to remove solvents (high vacuum on rotory evaporator). The residue was subject to a short silica gel chromatography to remove by-products, and the resultant crude product was charged (CH₂Cl₂) a 65 (M) Biotage silica gel cartridge. Gradient elution 15-70% B over 2 L (A=Hexanes; B=ethyl acetate) gave a less polar band of (2S)-tert-butyl 2-(4-(benzyloxy)-1-(4-bromophenyl)-1,4-dioxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate 1.35 g (8.7%) and more polar Example J7, (2S)-tert-butyl 2-(4-(methoxy)-1-(4-bromophenyl)-1,4-dioxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate 7.6 g (49%). RT=2.0 minutes (condition 1); LCMS: Anal. C₂₁H₂₇BrN₂O₆ Calcd. 383; found: 383 (M-Boc).



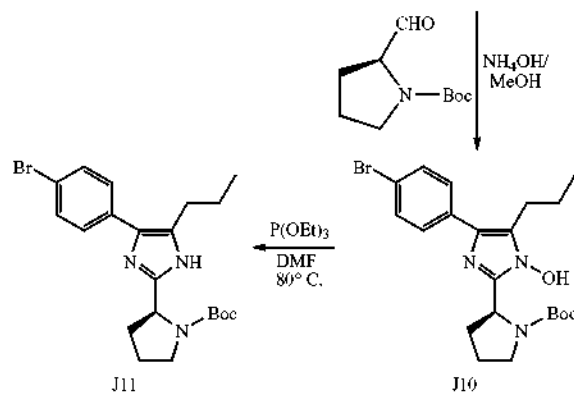
J8

[1402] Ammonium acetate (9.4 g, 157 mmol) was added to a solution of Example J7, (2S)-tert-butyl 2-(4-(methoxy)-1-(4-bromophenyl)-1,4-dioxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (7.6 g, 15.7 mmol) in xylene (80 mL) and stirred for 4 hours at 140° C. in a screw capped 150 mL pressure vessel. After being cooled, the reaction mixture was diluted with ethyl acetate and washed with sat NaHCO₃ and brine before being concentrated by rotory evaporation under high vacuum. The crude product was taken up in CH₂Cl₂ and charged to a 40 (M) Biotage silica gel cartridge. Gradient elution 15-100% B over 2 L (A=CH₂Cl₂; B=ethyl acetate) gave Example J8, (S)-tert-butyl 2-(4-(4-bromophenyl)-5-(2-methoxy-2-oxoethyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate 3.38 g (46%). ¹H NMR (500 MHz, DMSO-d₆) δ 7.54 (s, 4H), 4.83-4.73 (m, 1H), 3.81 (br. s, 1H), 3.62 (s, 3H), 3.53-3.51 (m, 1H), 3.38-3.31 (m, 2H), 2.25-2.15 (m, 1H), 1.99-1.83 (m, 3H), 1.41/1.16 (s, 9H). RT=1.6 minutes (Condition 1). LCMS: Anal. Calcd. for C₂₁H₂₆BrN₃O₄ 464.11; found: 464.40 (M+H)⁺.

Synthetic Scheme 3



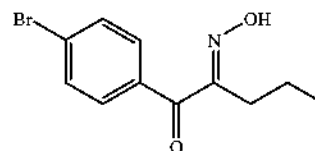
J9



J11

J10

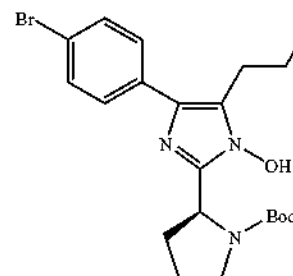
[1403] Reference: *J. Med. Chem.* (84), 27, 20. *Syn. Lett.* (2004) 2315.



J9

[1404] The conc. HCl (40 mL) was added dropwise to a solution of 1-(4-bromophenyl)pentan-1-one (4.68 g, 19.41 mmol) and sodium nitrite (4.02 g, 58.2 mmol) in THF (80 mL) at 0° C. and allowed to warm to room temperature and stirred 18 hours. The reaction mixture was diluted with diethyl ether and the organic phase washed with sat'd NaHCO₃ and brine. Concentration gave (Z)-1-(4-bromophenyl)-2-(hydroxyimino)pentan-1-one 3.1 g (33%) as an oil which was used without further purification. RT=2.1 min. (Condition 1) LCMS: Anal. Calcd. for C₁₁H₁₂BrN₁O₂ 270.01; found: 270.15 (M+H)⁺.

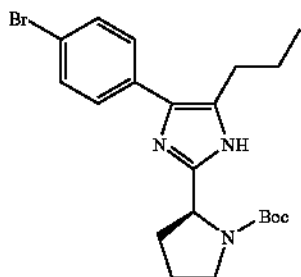
[1405] Reference: *Bioorg. Med. Chem. Lett* (2002) 1009.



J10

[1406] The 28% ammonium hydroxide (15 mL) was added to a solution of (Z)-1-(4-bromophenyl)-2-(hydroxyimino)pentan-1-one (1.5 g, 5.55 mmol) and (S)-N-Boc-proline (1.1 g, 5.55 mmol) in methanol (60 mL) and stirred for 18 hours at 24° C. The reaction mixture was partitioned between CH₂Cl₂ and water and the organic phase concentrated and applied (CH₂Cl₂) to a 40 (M) Biotage silica gel column. Gradient elution, 5-100%, over 1 L (A=Hexanes; B=ethyl acetate) gave (S)-tert-butyl 2-(4-(4-bromophenyl)hydroxy-5-propyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (863 mg, 34.5% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.54 (m, 4H), 5.0-4.88 (m, 1H), 3.53-3.41 (m, 1H), 3.41-3.36 (m, 1H), 2.72 (t, J=7.0 Hz, 2H), 2.24-2.03 (m, 2H), 1.96-1.91 (m, 1H), 1.89-1.81 (m, 1H), 1.60 (h, J=7.6 Hz, 2H), 1.39/1.17 (s, 9H). 0.92 (t, J=7.0 Hz, 3H). RT=1.9 min, (Condition 1) LCMS: Anal. Calcd. for C₂₁H₂₈BrN₃O₃ 450.13; found: 450.33 (M+H)⁺.

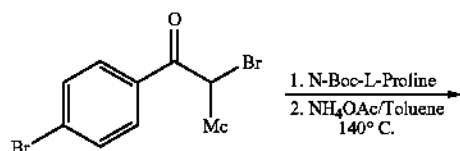
[1407] Reference: *Chem. Pharm. Bull* (1994) 42, 560.



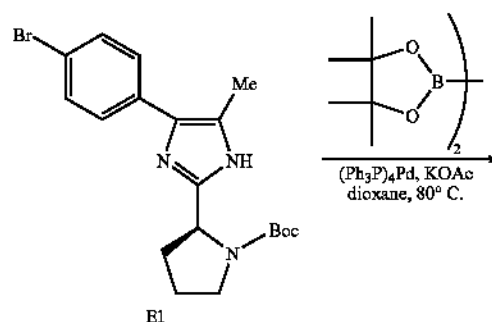
J11

[1408] The triethyl phosphite (0.9 mL, 5.33 mmol) was added to a solution of (S)-tert-butyl 2-(4-(4-bromophenyl)hydroxy-5-propyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (800 mg, 1.776 mmol) in DMF (2 mL) and stirred for 18 hours at 80° C. Add second 0.8 mL and the reaction was continued an additional 8 hours, cooled, and taken up in ethyl acetate (400 mL) and washed with water and brine. Apply in CH₂Cl₂ to a 25 (M) Biotage silica gel column. Gradient elution, 15-100%, over 750 mL (A=Hexanes; B=ethyl acetate) gave (S)-tert-butyl 2-(4-(4-bromophenyl)-5-propyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate 585 mg (76%). ¹H NMR (500 MHz, DMSO-d₆) δ 7.55-7.53 (m, 4H), 4.80-4.69 (m, 1H), 3.53-3.51 (m, 1H), 3.38-3.32 (m, 1H), 2.71 (t, J=7.0 Hz, 2H), 2.24-2.11 (m, 1H), 2.0-1.79 (m, 1H), 1.89-1.79 (m, 2H), 1.63-1.59 (m, 2H), 1.41/1.17 (s, 9H). 0.91 (t, J=7.6 Hz, 3H). RT=1.8 min, (Condition 1) LRMS: Anal. Calcd. for C₂₁H₂₈BrN₃O₂ 434.14; found: 434.0 (M+H)⁺.

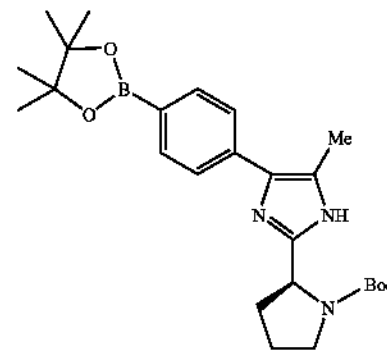
Synthetic Scheme 4



-continued



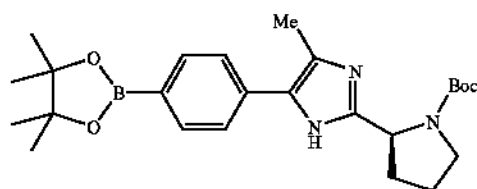
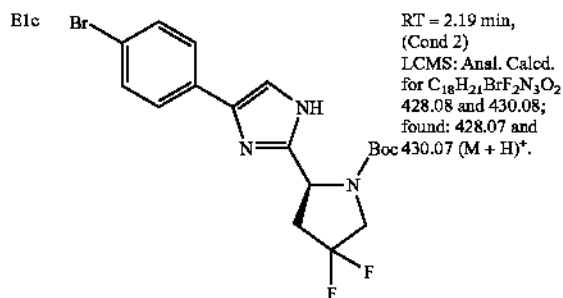
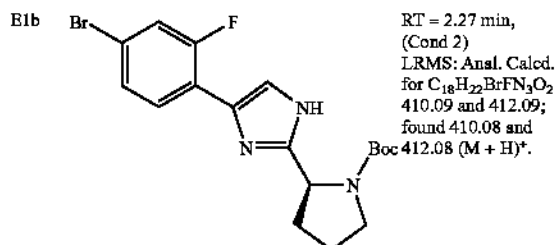
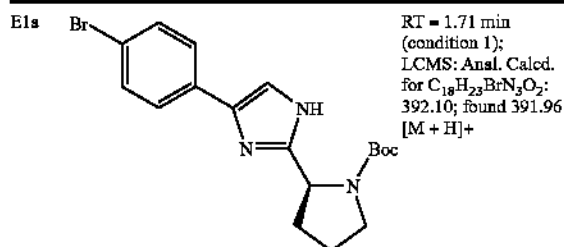
E1



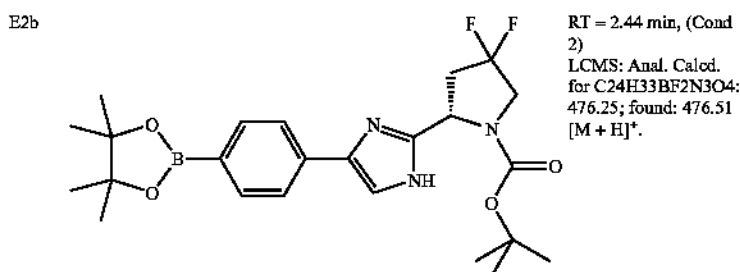
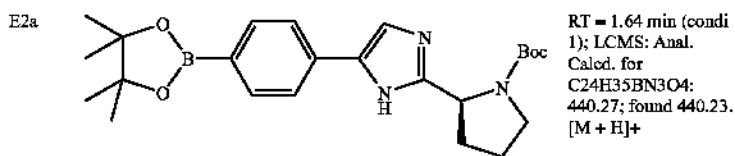
E2

[1409] To a mixture of 2,4'-dibromopropiophenone (4.96 g, 0.017 mol) and N-Boc-L-proline (4.09 g, 0.019 mol) in dry CH₃CN (75 mL) was added DIEA (3.30 mL, 0.019 mol) and the mixture was stirred at room temperature under Ar for 16 hours. The mixture was then concentrated under reduced pressure and the concentrate was partitioned with CH₂Cl₂-10% saturated NaHCO₃. The organic phase was washed (brine), dried (Na₂SO₄), filtered, and concentrated to give the proline ester (7.28 g, >100%) as a colorless gum which was used as such in the next step. LCMS: Anal. Calcd. for C₁₉H₂₄BrNO₅: 426; found: 426 (M+H)⁺.

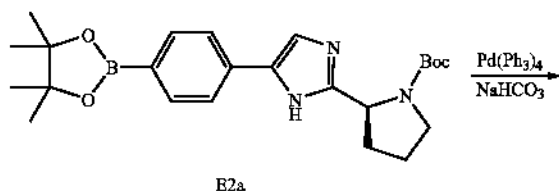
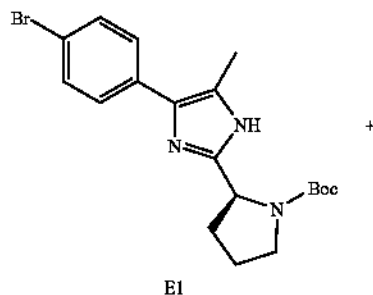
[1410] A mixture of the proline ester (0.435 g, 1.0 mmol) and ammonium acetate (0.308 g, 4.0 mmol) in toluene (5 mL) was heated at 140° C. (bath temperature) in a sealed tube for 5 hours. The cooled reaction mixture was evaporated and the residue was chromatographed (SiO₂/ethyl acetate-hexane, 3:2) to give Example E1 (0.320 g, 79%) as a nearly colorless foam. ¹H NMR (400 MHz, CDCl₃) δ 7.53 (s, 4H), 4.98 (m, 0.3H), 4.87 (m, 0.7H), 3.65 (m, 1H), 3.4-3.6 (m, 1H), 2.50 (s, 3H), 2.32 (m, 1H), 2.13 (m, 2H), 1.94 (m, 1H), 1.47 (s, 3H), 1.31 (s, 6H). LCMS: Anal. Calcd. for C₁₉H₂₄BrN₃O₂: 405, 407; found: 406, 408 (M+H)⁺.



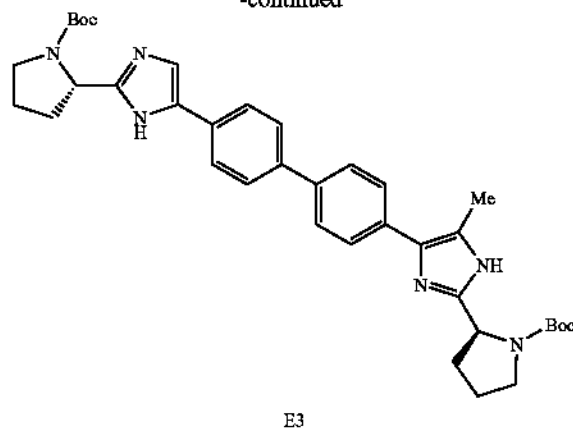
[1411] A mixture of Example E1, (S)-tert-butyl 2-(4-(4-bromophenyl)-5-methyl-1H-imidazol-2-yl)-pyrrolidine-1-carboxylate (1.568 g, 3.86 mmol), bis(pinacolato)diboron (2.058 g, 8.10 mmol) and potassium acetate (0.947 g, 9.65 mmol) in dioxane (25 mL) was purged with a stream of Ar bubbles for 10 min and then $(Ph_3P)_4Pd$ (0.223 g, 0.19 mmol) was added and purging with Ar was continued for another 10 min. The reaction vessel was then sealed and heated at 80° C. (bath temperature) for 18 hours. The cooled mixture was diluted with dichloromethane and then it was washed (H_2O , brine), dried (Na_2SO_4), filtered, and concentrated. The residue was triturated with ethyl acetate and the resulting solid was filtered, washed with a little ethyl acetate and dried in vacuo to give the title compound (quantitative) as a solid. It was used as such in the next step without further purification. 1H NMR (400 MHz, $DMSO-d_6$) δ 11.93 (br s, 0.3H), 11.71 (br s, 0.7H), 7.65 (br s, 4H), 4.79 (m, 0.4H), 4.69 (m, 0.6H), 3.52 (m, 1H), 3.36 (m, 2H), 2.38 (s, 3H), 1.78-2.26 (m, 4H), 1.41 (s, 4H), 1.30 (s, 10H), 1.17 (m, 6H). LCMS: Anal. Calcd. for $C_{25}H_{36}BN_3O_4$: 453; found: 454 $(M + H)^+$.



Synthetic Scheme 5

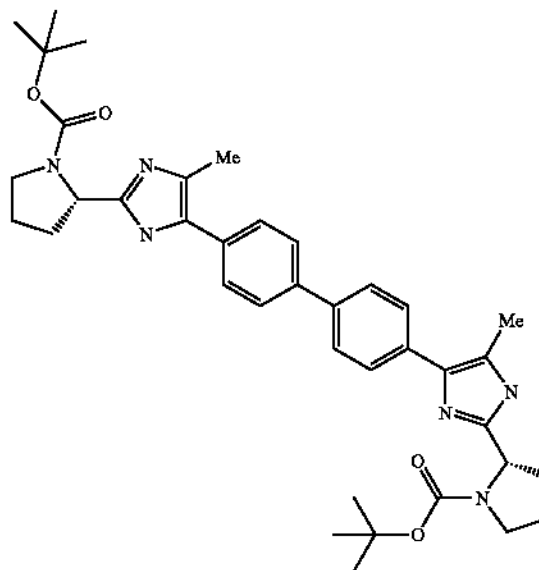


-continued



[1412] A mixture of Example E1, (S)-tert-butyl 2-(4-(4-bromophenyl)-5-methyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (0.682 g, 1.68 mmol), Example E2a, (S)-tert-butyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-ylpyrrolidine-1-carboxylate (0.764 g, 1.74 mmol) and NaHCO_3 (0.465 g, 5.53 mmol) in a mixture of DME (20 mL) and H_2O (5 mL) was purged with a stream of Ar bubbles for 10 min. To this mixture was added $(\text{Ph}_3\text{P})_4\text{Pd}$ (0.091 g, 0.08 mmol) and purging with Ar was continued for another 10 min. The reaction vessel was then sealed and heated at 80°C . (bath temperature) for 18 hours. The cooled mixture was concentrated under reduced pressure and the concentrate was diluted with ethyl acetate and washed with H_2O . The aqueous phase was back-extracted with ethyl acetate and the combined organic phase was washed (brine), dried (Na_2SO_4), filtered, and concentrated to give a gum. The residue was chromatographed (SiO_2 /ethyl acetate-hexane, 7:3) to give Example E3 (0.592 g, 59%) as a foam. ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.88 (m, 8H), 7.27 (s, 1H), 5.10 (t, $J=7.65$ Hz, 2H), 3.45 (m, 4H), 3.00 (m, 2H), 2.44 (s, 3H), 2.20 (br s, 4H), 1.99 (m, 2H), 1.53 (s, 18H). LCMS: Anal. Calcd. for $\text{C}_{37}\text{H}_{46}\text{N}_6\text{O}_4$: 638; found: 639 ($\text{M}+\text{H}$) $^+$.

E3a
Derived
from
example
E2 and E3

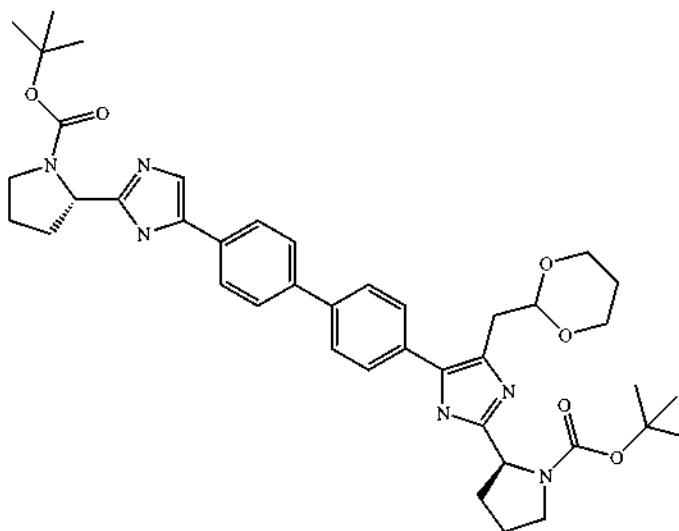


LCMS: Anal.
Calcd. for
 $\text{C}_{38}\text{H}_{48}\text{N}_6\text{O}_4$:
652; found:
653 ($\text{M}+\text{H}$) $^+$.

-continued

J12
Derived
from
example
E2a and J4

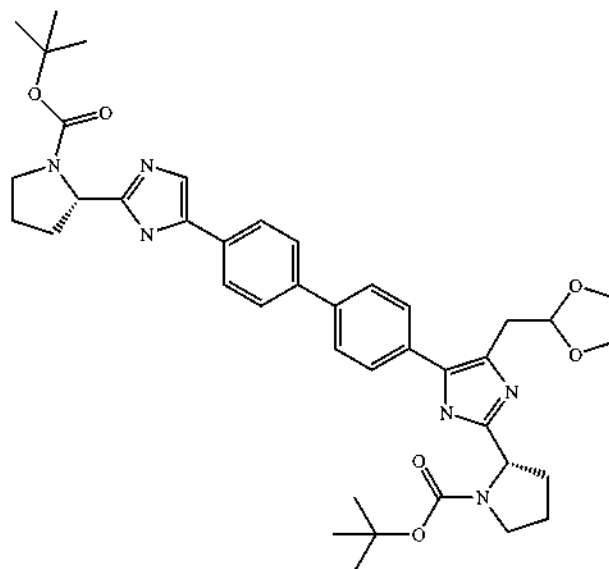
tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-4-(1,3-dioxan-2-ylmethyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate



RT = 1.65
min. (cond 3)
HRMS: Anal. Calcd.
for $C_{41}H_{53}N_6O_6$
725.4021; found:
725.4026 (M + H)⁺.

J12a
Derived
from
example
E2a and J4a

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-4-(1,3-dioxolan-2-ylmethyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate



RT = 1.62
min. (cond 1)
HRMS: Anal. Calcd.
for $C_{40}H_{51}N_6O_6$
711.3865; found:
711.3874 (M + H)⁺.

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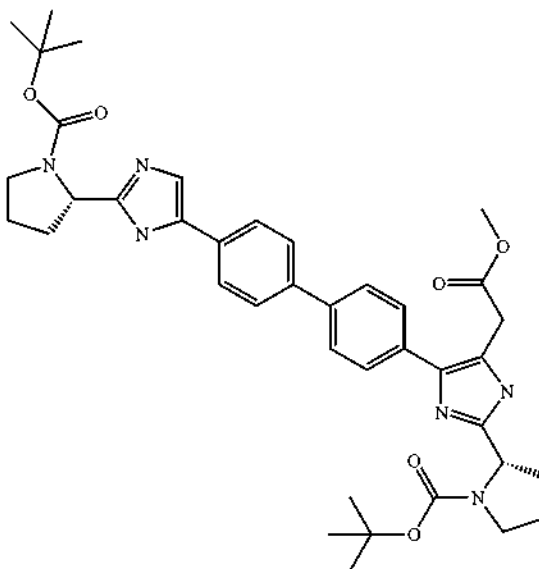
470

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-continued

J12b
Derived
from
example
E2a and J8

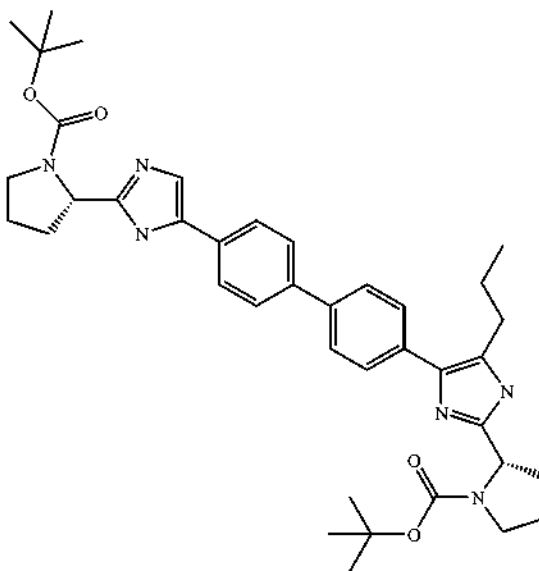
tert-butyl (2S)-2-(4-(4'-
(2-((2S)-1-(tert-
butoxycarbonyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-5-(2-
methoxy-2-oxoethyl)-
1H-imidazol-2-yl)-1-
pyrrolidinecarboxylate



RT = 1.72
min, (cond 1)
HRMS: Anal. Calcd.
for $C_{39}H_{48}N_6O_6$
697.3087; found:
697.3721 (M + H)⁺.

J12c
Derived
from
example
E2a and J11

tert-butyl (2S)-2-(4-(4'-
(2-((2S)-1-(tert-
butoxycarbonyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-5-propyl-
1H-imidazol-2-yl)-1-
pyrrolidinecarboxylate

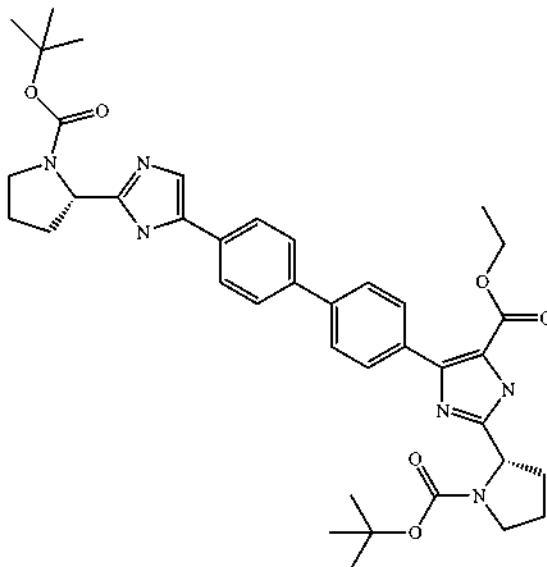


RT = 1.72
min, (cond 1)
LCMS: Anal. Calcd.
for $C_{39}H_{50}N_6O_4$
667.40; found:
667.30 (M + H)⁺.

-continued

J12d

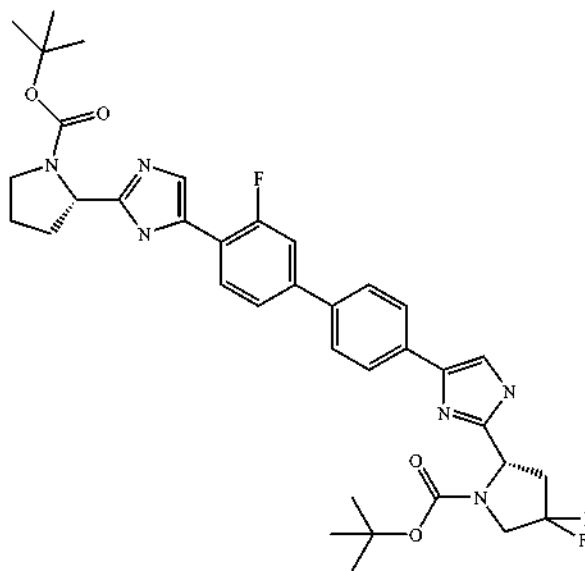
ethyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate



RT = 1.70
min. (95%)
(Cond 2);
LRMS: Anal. Calcd.
for C₃₈H₄₇N₆O₆
683.36; found:
683.42 (M + H)⁺

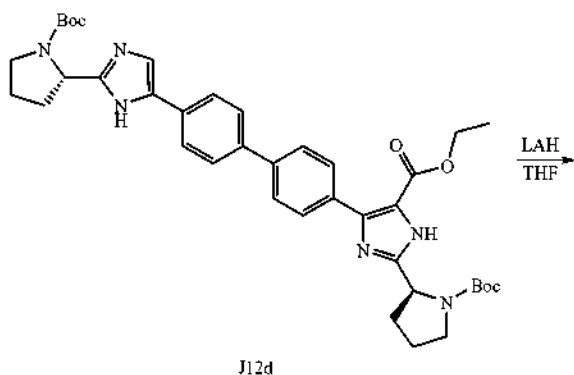
J12e
Derived
from
example
E2b and E1b

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-3'-fluoro-4-biphenyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinecarboxylate



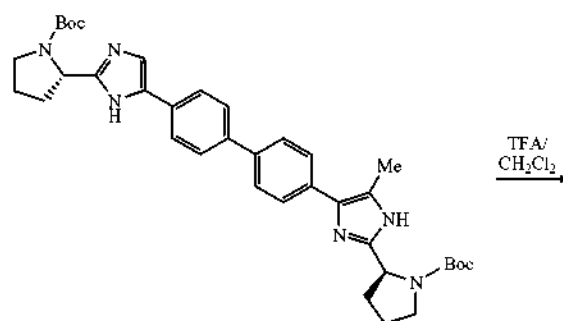
RT = 2.24
min. (cond 2)
LCMS: Anal. Calcd.
for C₃₆H₄₂F₃N₆O₄
679.32; found:
679.57 (M + H)⁺

Synthetic Scheme 6



J12f

Synthetic Scheme 7

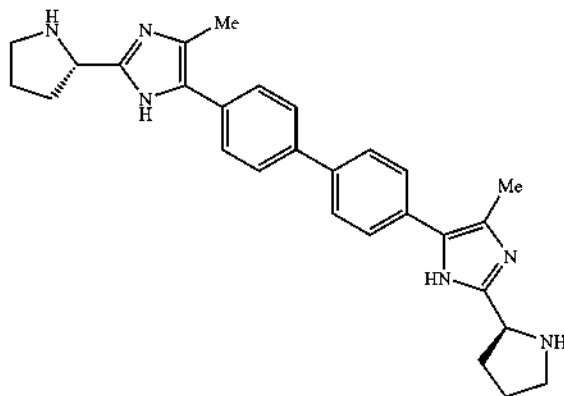


E4

[1413] The LAH (0.7 mL, 1M in THF) was added to a solution of Example J12d, (466 mg, 0.669 mmol) in THF (50 mL) and stirred at 0° C. for 1.5 hours before slowly allowing to warm to room temperature. After 3 hours the reaction was quenched with water (0.4 mL), 15% NaOH (0.4 mL) and water (0.4 mL) and the aluminum salts removed by filtration. The salts were rinsed with THF, the combined filtrates were concentrated, and the residue charged (CH₂Cl₂) to a 25 (S) Biotage silica gel cartridge and gradient eluted 15-100% over 1 L solvent (A=CH₂Cl₂; B=10% CH₃OH/ethyl acetate) to give Example J12f, tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-4-(hydroxymethyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate, 88 mg (20%) in addition to recovered J12d and over reduction. RT=1.7 minutes (Condition 1); LCMS Anal. Calcd. for C₃₇H₄₆N₆O₅ 665.36; found: 665.46 (M+H)⁺.

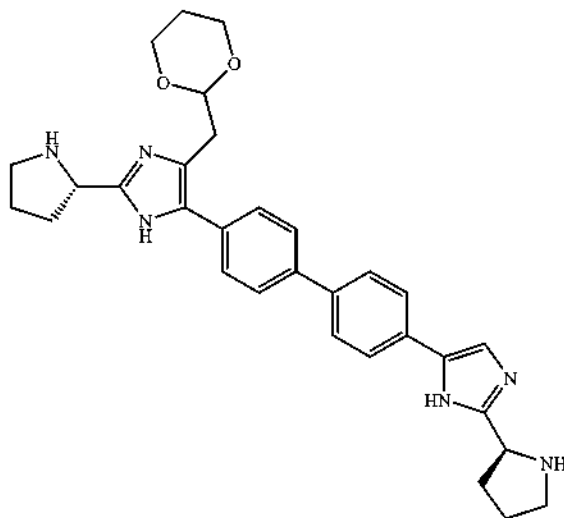
[1414] A solution of Example E3 (0.240 g, 0.376 mmol) in 5 mL of TFA-CH₂Cl₂ (4:1) was stirred at room temperature for 2 hours and then the volatiles were removed under reduced pressure. The resulting gum was taken up in a minimum volume of CH₃OH and adsorbed on an MCX LP cartridge (6 g, pre-conditioned with CH₃OH). The cartridge was washed with CH₃OH and then eluted with 2M NH₃ in CH₃OH. The product-containing fractions were combined and evaporated to give E4 (quantitative) as a gum which was used as such in the next step. LCMS: Anal. Calcd. for C₂₇H₃₀N₆ 438; found: 439 (M+H)⁺.

E4a



LCMS:
Anal.
Calcd. for
 $C_{28}H_{32}N_6$:
452; found:
453
(M + H)⁺.

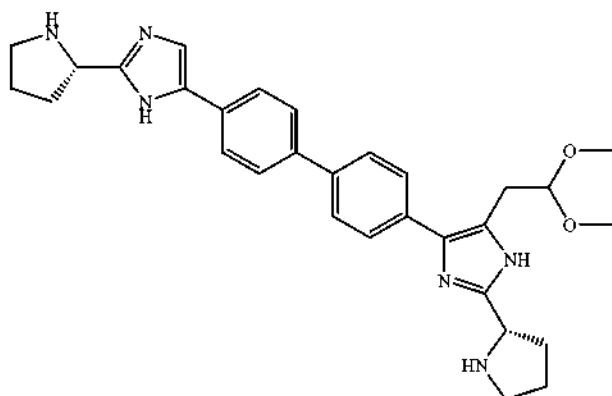
J13
Derived
from
example
J12



RT = 1.18
min, (cond
1)
LCMS:
Anal.
Calcd. for
 $C_{31}H_{36}N_6O_2$
525.29;
found:
525.31
(M + H)⁺.

Prepared
using
experi-
mental
conditions
from
example
152k-1.

J13a
Derived
from
example
J12a



RT = 1.14
min, (cond
1)
LCMS:
Anal.
Calcd. for
 $C_{30}H_{36}N_6O_2$
513.29;
found:
513.42
(M + H)⁺.

Prepared
using
experi-
mental
conditions
in
example
152k-1.

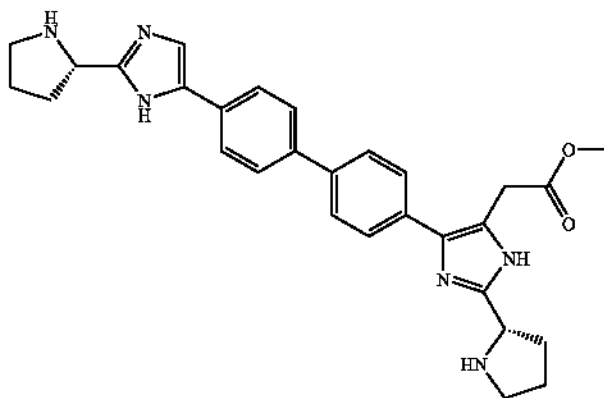
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-continued

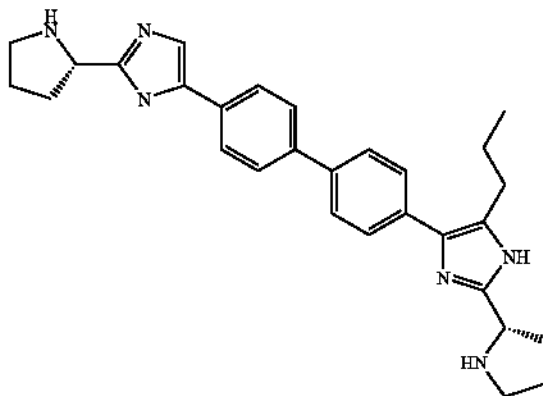
J13b
Derived
from
example
J12b



RT = 1.19
min, (cond
1)
LCMS:
Anal.
Calcd. for
 $C_{29}H_{32}N_6O_2$
497.26;
found:
497.48
(M + H)⁺.

Prepared
using
experi-
mental
conditions
as
outlined
in
example
152k-1.

J13c
Derived
from
example
J12c

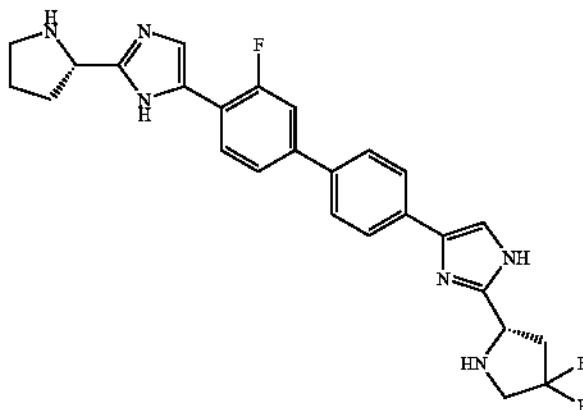


RT = 1.26
min, (cond
1)
LCMS:
Anal.
Calcd. for
 $C_{29}H_{30}N_6O_4$
467.28;
found:
467.55
(M + H)⁺.

Prepared
using
experi-
mental
conditions
from
example
152k-1.

J13e
Derived
from
example
J12e

2-((2S)-4,4-
difluoro-2-
pyrrolidinyl)-4-
(3'-fluoro-4'-
(2S)-2-
pyrrolidinyl)-
1H-imidazol-4-
yl)-4-
biphenyl)-1H-
imidazole

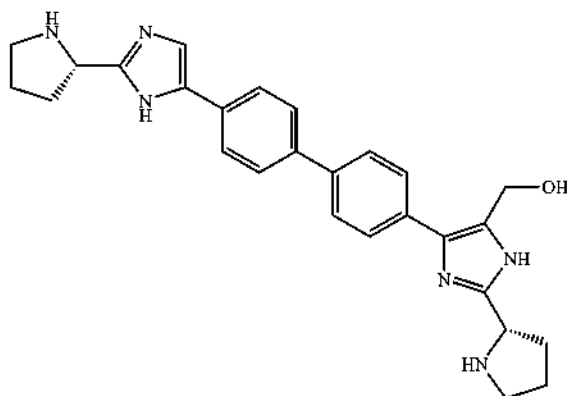


RT = 1.77
min,
(Cond 2)
LCMS:
Anal.
Calcd. for
 $C_{26}H_{26}F_3N_6$ 479.22;
found:
479.39
(M + H)⁺.

Prepared
using
experi-
mental
conditions
from
example
152k-1.

-continued

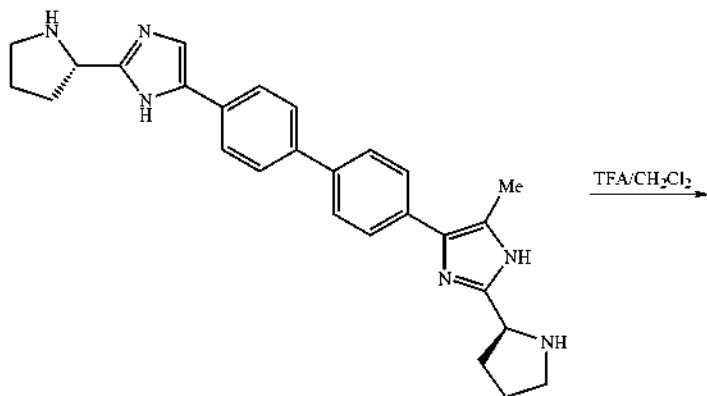
J13f
Derived
from
example
J12f



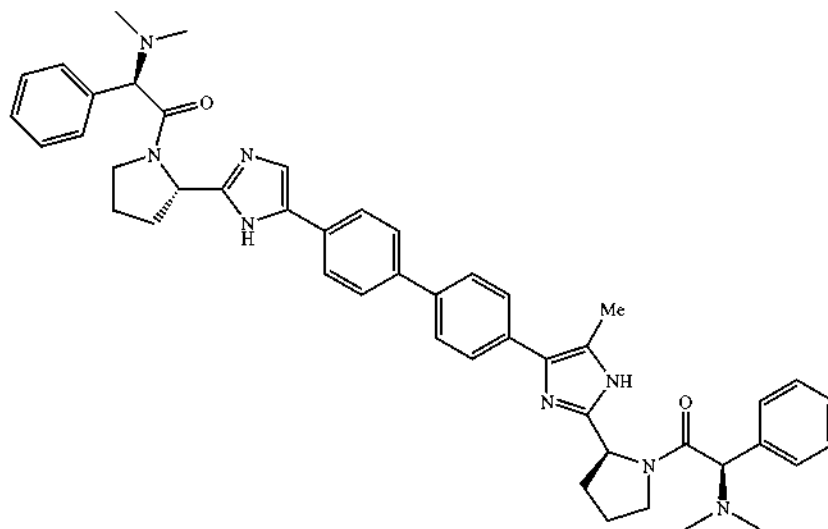
RT = 1.02
min, (cond
1)
LCMS:
Anal.
Calcd. for
 $C_{27}H_{30}N_6O$
455.25;
found:
455.47
($M + H$)⁺.

Prepared
using
experi-
mental
conditions
from
example
152k-1.

Synthetic Scheme 8



E4



E5

US 2009/0068140 A1

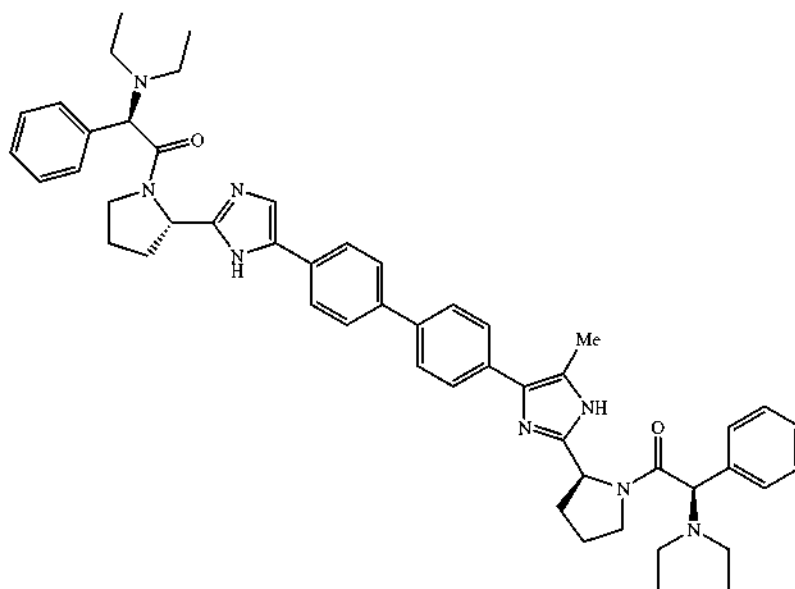
Mar. 12, 2009

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[1415] A solution of (R)-2-(dimethylamino)-2-phenylacetic acid hydrochloride (0.047 g, 0.220 mmol), HATU (0.084 g, 0.220 mmol) and DIEA (0.17 mL, 0.70 mmol) in dry DMF (1 mL) was stirred at room temperature for 5 min and then a solution of E4 (0.041 g, 0.094 mmol) in dry DMF (0.5 mL) was added. The mixture was stirred at room temperature for 18 hours and then it was quenched with AcOH (0.2 mL) and a few drops of TFA. This solution was submitted directly to preparative HPLC (C-18/CH₃CN—H₂O+0.1% TFA) to give the TFA salt of Example E5, (1R)-2-((2S)-2-(4-(4'-(2-((2S)-

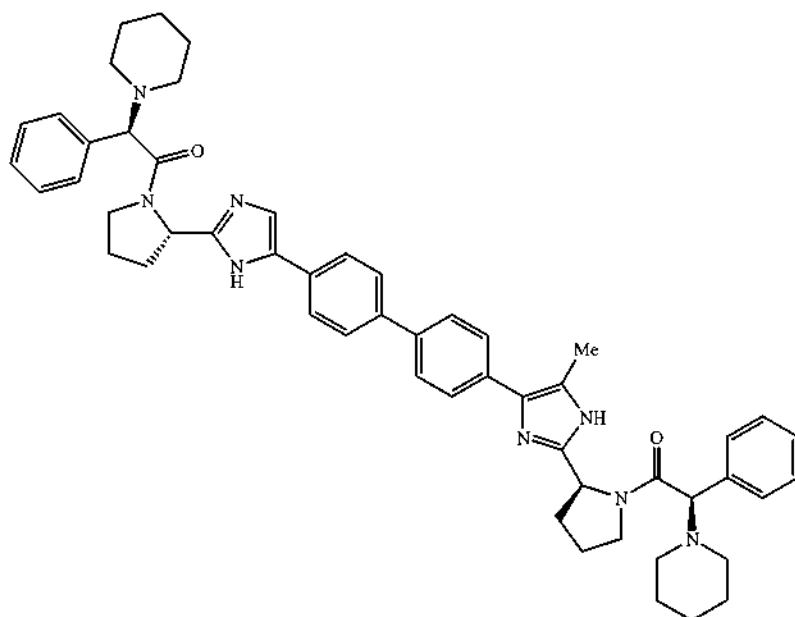
1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine (0.011 g, 10%) as a white solid. ¹HNMR (400 MHz, CH₃OH-d₄) δ 7.80-7.93 (m, 6H), 7.71-7.74 (m, 2H), 7.50-7.67 (m, 10H), 5.37-5.51 (m, 2H), 5.30 (m, 2H), 4.04 (br s, 3H), 3.00-3.13 (m, 4H), 2.81 (br s, 8H), 2.55 (s, 2H), 2.49 (s, 1H), 2.36 (m, 2H), 2.12-2.25 (m, 5H), 1.96 (br s, 2H). LCMS: Anal. Calcd. for C₄₇H₅₂N₈O₂: 760; found: 761 (M+H)⁺.

E5a (1R)-2-((2S)-2-(4-(4'-(2-((2S)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



LCMS:
Anal.
Calcd. for
C₅₁H₆₀N₈O₂:
816;
found: 817
(M + H)⁺.

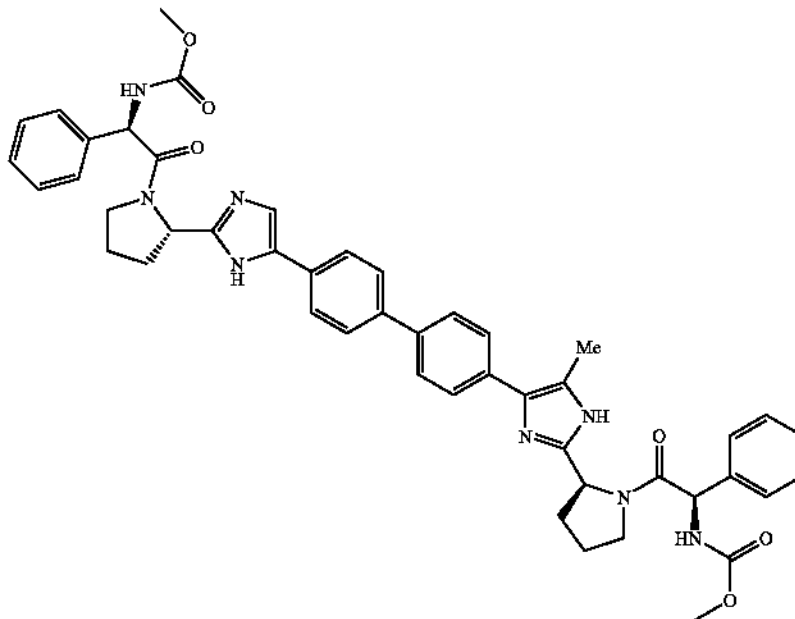
E5b 1-((1R)-2-((2S)-2-(4-(4'-(4-methyl-2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine



LCMS:
Anal.
Calcd. for
C₅₃H₆₀N₈O₂:
840;
found: 841
(M + H)⁺.

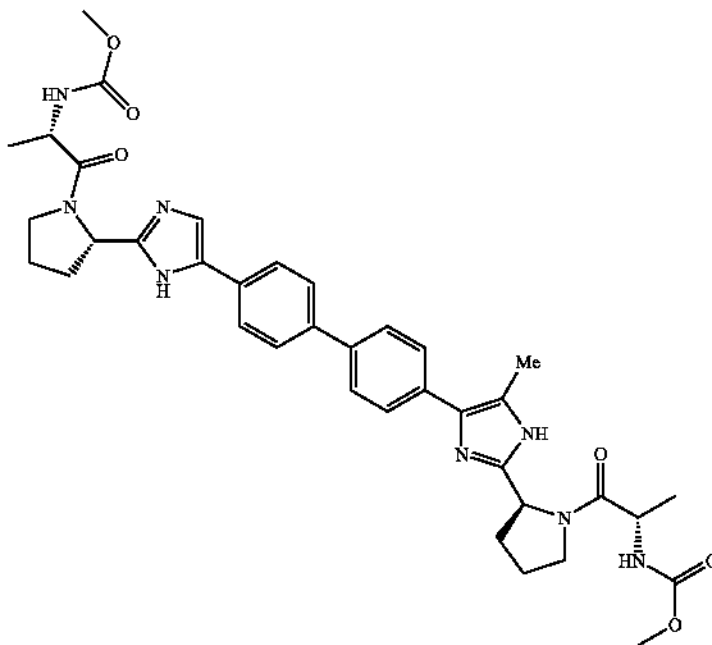
-continued

B5c methyl ((1R)-2-
Derived ((2S)-2-(4-(4'-(2-
from ((2S)-1-((2R)-2-
example (methoxycarbonyl)
E4 amino)-2-
phenylacetyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-5-
methyl-1H-
imidazol-2-yl)-1-
pyrrolidinyl)-2-
oxo-1-
phenylethyl)car-
bamate



LCMS:
Anal.
Calcd. for
 $C_{47}H_{48}N_8O_6$:
820;
found: 821
(M + H)⁺.

B5d methyl ((1S)-2-
Derived ((2S)-2-(4-(4'-(2-
from ((2S)-1-(N-
example (methoxycarbonyl)-
E4 L-alanyl)-2-
pyrrolidinyl)-4-
methyl-1H-
imidazol-5-yl)-4-
biphenyl)-1H-
imidazol-2-yl)-1-
pyrrolidinyl)-1-
methyl-2-
oxoethyl)carbamate

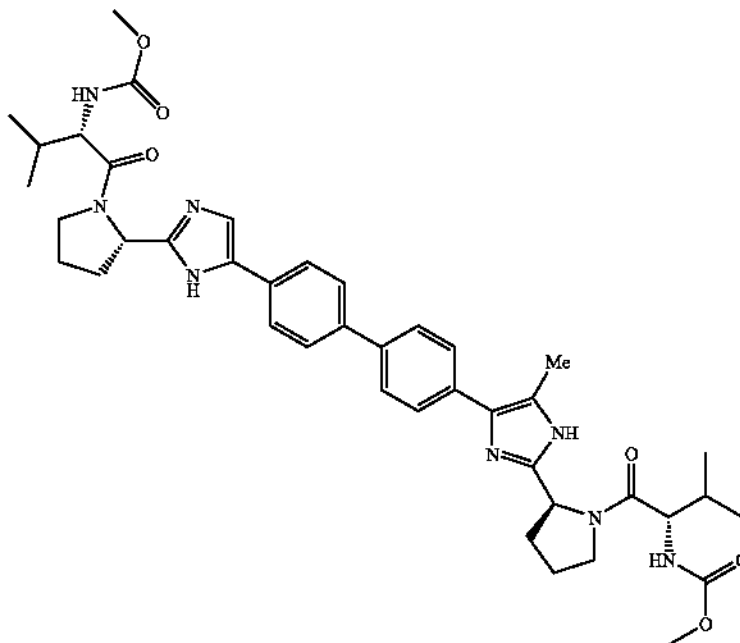


LCMS:
Anal.
Calcd. for
 $C_{37}H_{44}N_8O_6$:
696;
found: 697
(M + H)⁺.

-continued

B5e
Derived
from
example
E4

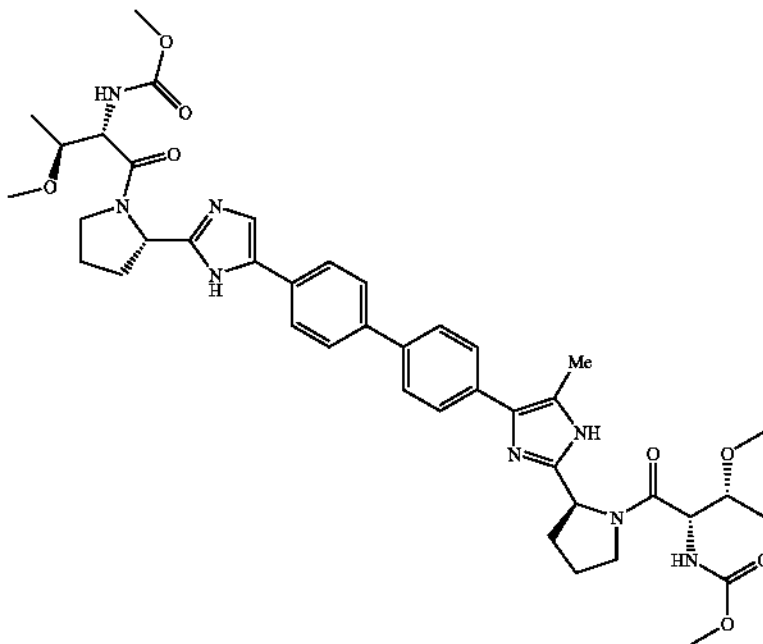
methyl ((1S)-1-
(((2S)-2-(4-(4'-2-
((2S)-1-((2S)-2-
(methoxycarbonyl)
amino)-3-
methylbutanoyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-5-
methyl-1H-
imidazol-2-yl)-1-
pyrrolidinyl)car-
bonyl)-2-methyl-
propyl)car-
bamate



LCMS:
Anal.
Calcd. for
 $C_{41}H_{52}N_8O_6$:
752;
found: 753
(M + H)⁺.

B5f
Derived
from
example
E4

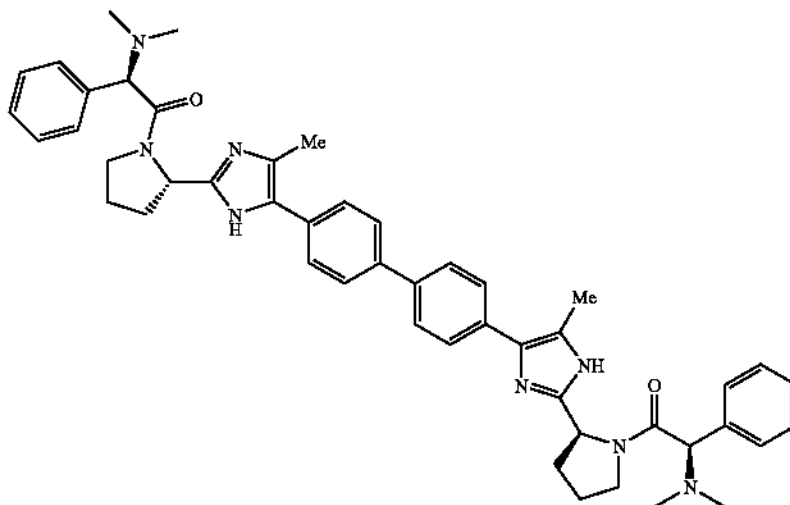
methyl ((1S,2R)-2-
methoxy-1-(((2S)-
2-(4-(4'-2-((2S)-1-
(N-
methoxycarbonyl)-
O-methyl-L-
threonyl)-2-
pyrrolidinyl)-4-
methyl-1H-
imidazol-5-yl)-4-
biphenyl)-1H-
imidazol-2-yl)-1-
pyrrolidinyl)car-
bonyl)propyl)car-
bamate



LCMS:
Anal.
Calcd. for
 $C_{41}H_{52}N_8O_9$:
784;
found: 785
(M + H)⁺.

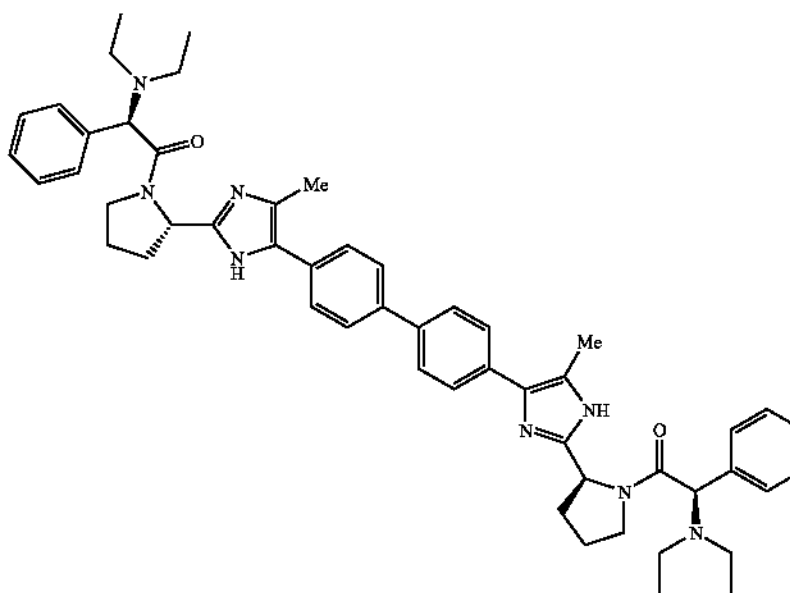
-continued

B5g
Derived
from
example
E4a
(1R,1'R)-2,2'-(4,4'-
biphenyldiylbis((4-
methyl-1H-
imidazole-5,2-
diyl)(2S)-2,1-
pyrrolidinediyl))bis
(N,N-dimethyl-2-
oxo-1-
phenylethanamine)



LCMS:
Anal.
Calcd. for
 $C_{48}H_{54}N_8O_2$:
774;
found: 775
(M + H)⁺.

E5h
Derived
from
example
E4a
(1R,1'R)-2,2'-(4,4'-
biphenyldiylbis((4-
methyl-1H-
imidazole-5,2-
diyl)(2S)-2,1-
pyrrolidinediyl))bis
(N,N-diethyl-2-
oxo-1-
phenylethanamine)

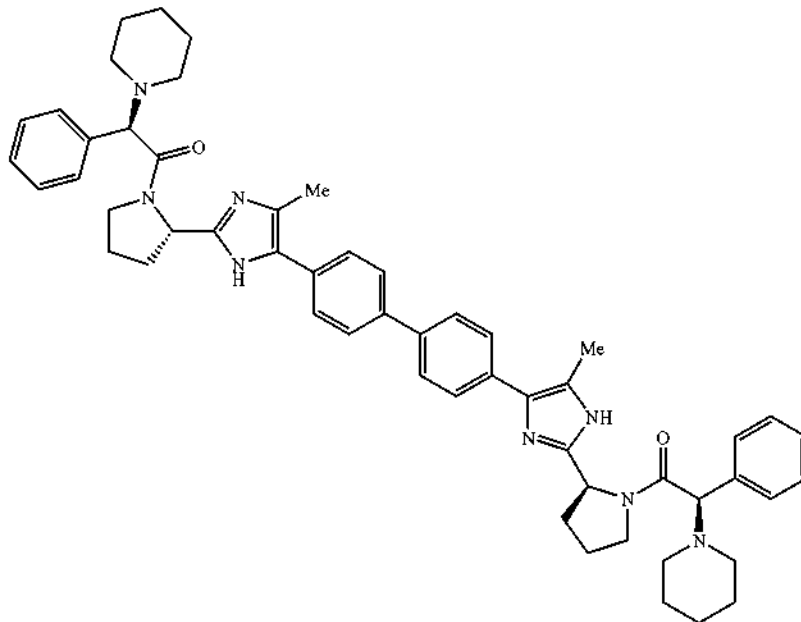


LCMS:
Anal.
Calcd. for
 $C_{52}H_{62}N_8O_2$:
830;
found: 831
(M + H)⁺.

-continued

E5i
Derived
from
example
E4a

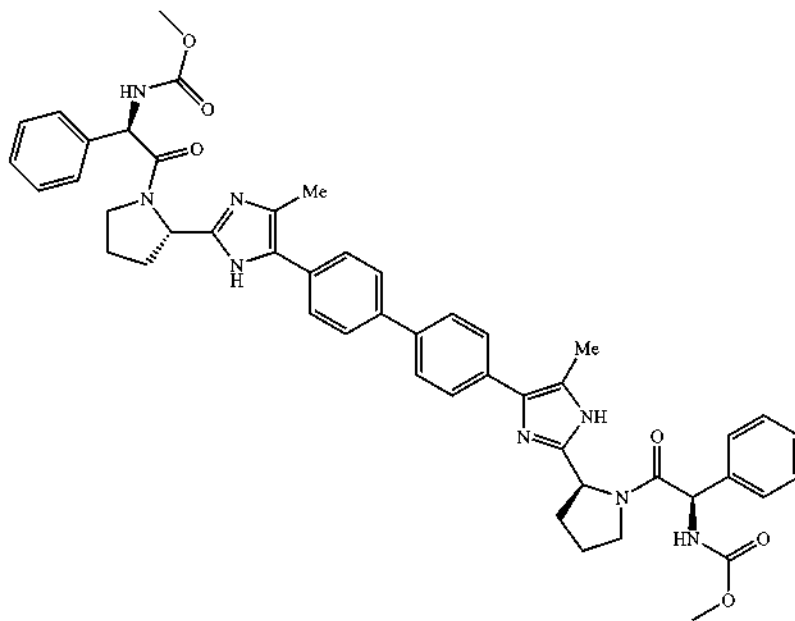
1,1'-(4,4'-
biphenyldiylbis((4-
methyl-1H-
imidazole-5,2-
diyl)(2S)-2,1-
pyrrolidine-
diyl((1R)-
2-oxo-1-phenyl-
2,1-
ethanediyl)))dipi-
peridine



LCMS:
Anal.
Calcd. for
C₅₄H₆₂N₈O₂:
854;
found: 855
(M + H)⁺.

E5j
Derived
from
example
E4a

dimethyl (4,4'-
biphenyldiylbis((4-
methyl-1H-
imidazole-5,2-
diyl)(2S)-2,1-
pyrrolidine-
diyl((1R)-
2-oxo-1-phenyl-
2,1-
ethanediyl)))bis-
carbamate



LCMS:
Anal.
Calcd. for
C₄₈H₅₀N₈O₆:
834;
found: 835
(M + H)⁺.

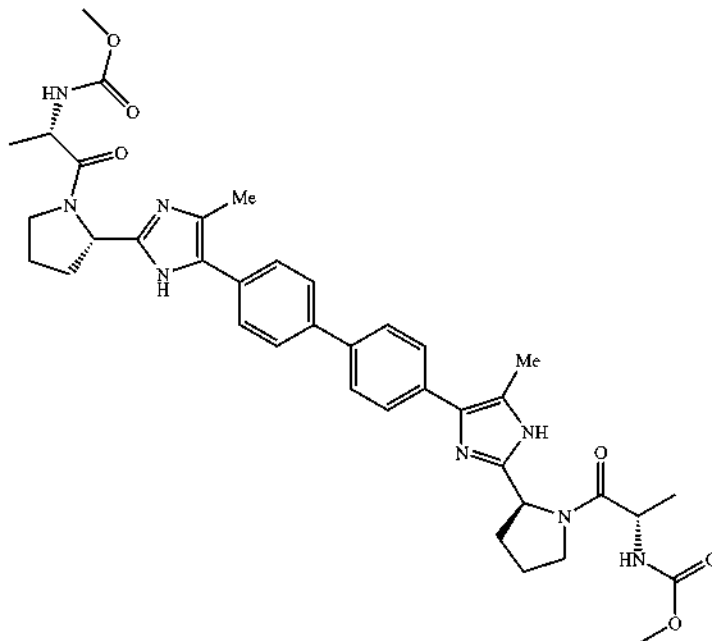
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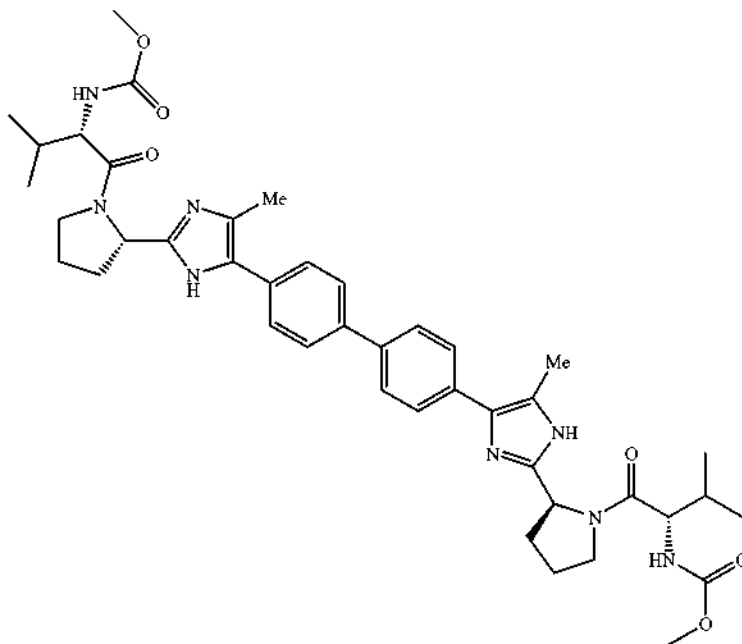
-continued

E5k methyl ((1S)-2-
Derived ((2S)-2-(4-(4'-(2-
from (2S)-1-(N-
example (methoxycarbonyl)-
E4a L-alanyl)-2-
pyrrolidinyl)-5-
methyl-1H-
imidazol-4-yl)-4-
biphenyl)-5-
methyl-1H-
imidazol-2-yl)-1-
pyrrolidinyl)-1-
methyl-2-
oxoethyl)carbamate



LCMS:
Anal.
Calcd. for
C38H46N8O6:
710;
found: 711
(M + H)⁺.

E5l methyl ((1S)-1-
Derived (((2S)-2-(4-(4'-(2-
from (2S)-1-((2S)-2-
example (methoxycarbonyl)
E4a amino)-3-
methylbutanoyl)-2-
pyrrolidinyl)-4-
methyl-1H-
imidazol-5-yl)-4-
biphenyl)-5-
methyl-1H-
imidazol-2-yl)-1-
pyrrolidinyl)car-
bonyl)-2-methyl-
propyl)carbamate



LCMS:
Anal.
Calcd. for
C42H54N8O6:
766;
found: 767
(M + H)⁺.

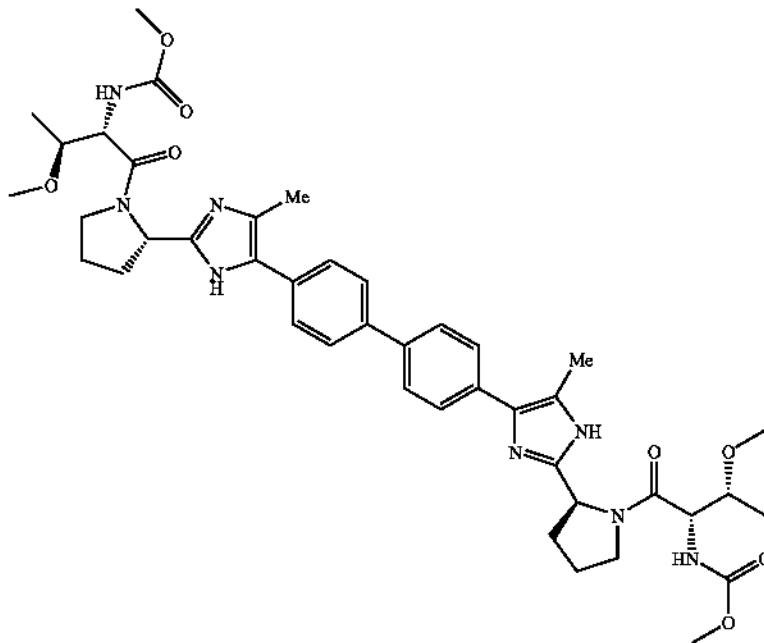
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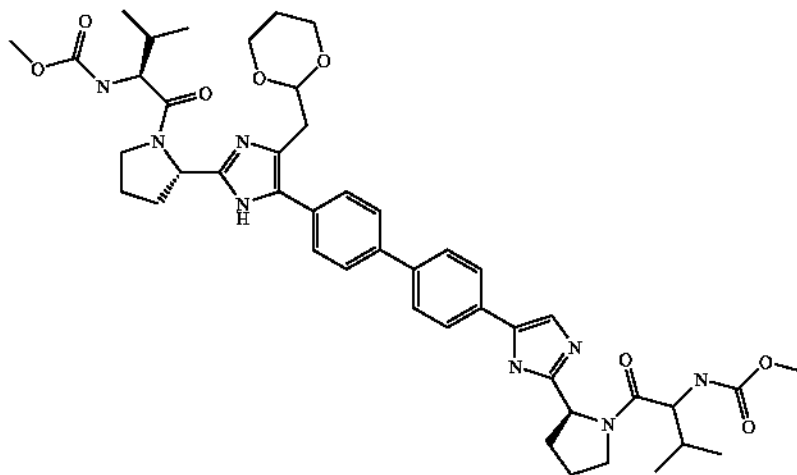
-continued

B5m methyl ((1S,2R)-2-methoxy-1-((2S)-2-(4-(4'-(2-((2S)-1-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-5-methyl-1H-imidazol-4-yl)-4-biphenyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate



LCMS:
Anal.
Calcd. for
C42H54N8O8:
798;
found: 799
(M + H)⁺.

J14 methyl ((1S)-1-(((2S)-2-(4-(1,3-dioxan-2-yl)methyl)-5-(4'-(2-((2S)-1-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methyl-propyl)carbamate



RT = 1.37
min, (Cond
1);
HRMS:
Anal.
Calcd. for
C45H58N8O8
839.4450;
found:
839.4456
(M + H)⁺.

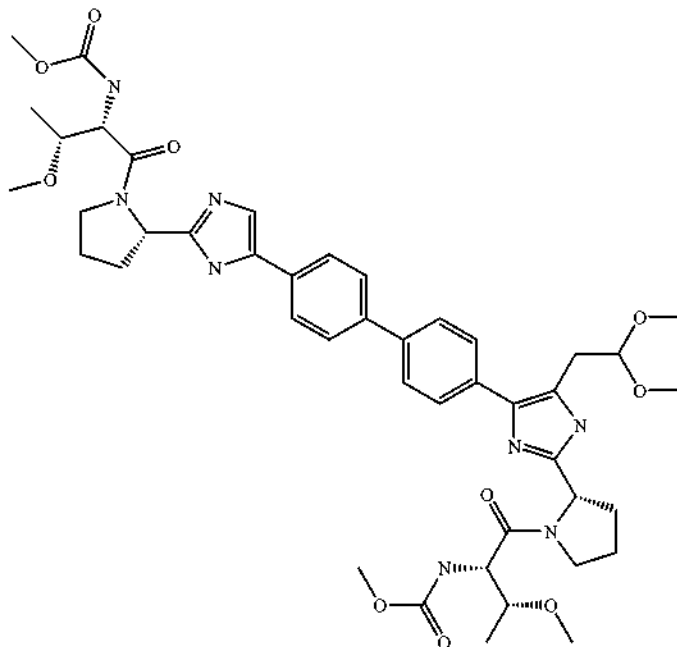
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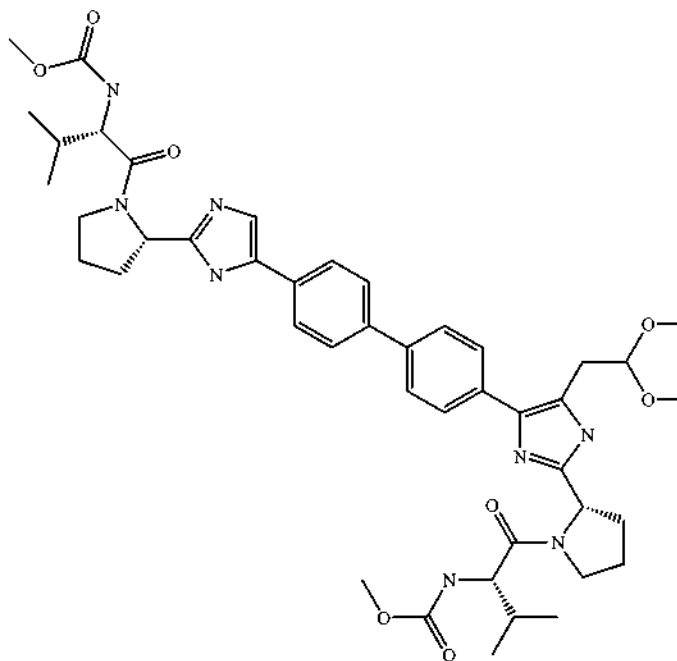
-continued

J14a methyl ((1S,2R)-1-
Derived from
example J13a (((2S)-2-(4-(2,2-
dimethoxyethyl)-5-
(4'-(2-((2S)-1-(N-
(methoxycarbonyl)-
O-methyl-L-
threonyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-1H-
imidazol-2-yl)-1-
pyrrolidinyl)car-
bonyl)-2-methoxy-
propyl)carbamate



RT = 1.44
min, (Cond
1);
HRMS:
Anal.
Calcd. for
 $C_{44}H_{58}N_8O_{10}$
859.4349;
found:
859.4352
(M + H)⁺.

J14a.1 methyl ((1S)-1-
Derived from
example J13a (((2S)-2-(4-(2,2-
dimethoxyethyl)-5-
(4'-(2-((2S)-1-
(2S)-2-
(methoxycarbonyl)
amino)-3-
methylbutanoyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-1H-
imidazol-2-yl)-1-
pyrrolidinyl)car-
bonyl)-2-methyl-
propyl)carbamate



RT = 1.44
min, (Cond
1);
HRMS:
Anal.
Calcd. for
 $C_{44}H_{58}N_8O_8$
827.4450;
found:
827.4449
(M + H)⁺.

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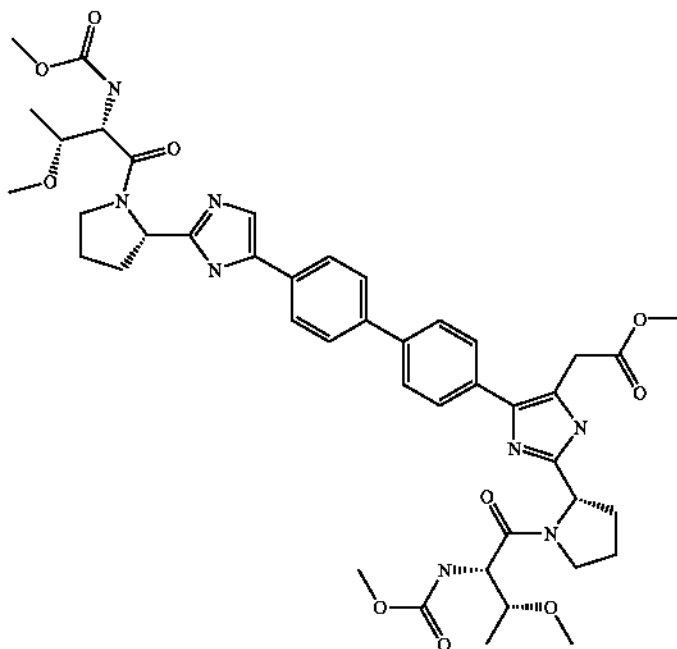
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-continued

J14b
Derived
from
example
J13b

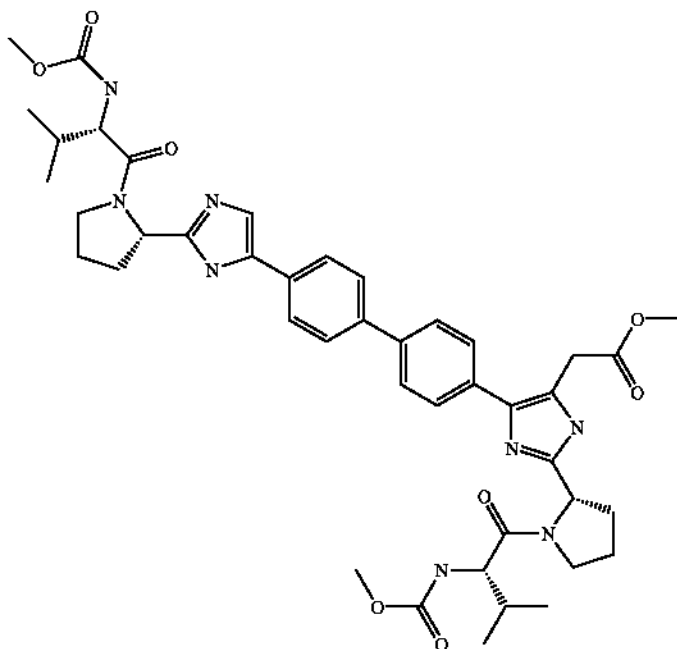
methyl (2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-5-yl)acetate



HRMS:
Anal.
Calcd. for
 $C_{43}H_{54}N_8O_{10}$
843.4036;
found:
843.4046
(M + H)⁺.

J14b.1
Derived
from
example
J13b

methyl (2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-5-yl)acetate



RT = 1.42
min, (Cond
1);
HRMS:
Anal.
Calcd. for
 $C_{43}H_{54}N_8O_8$
811.4137;
found:
811.4154
(M + H)⁺.

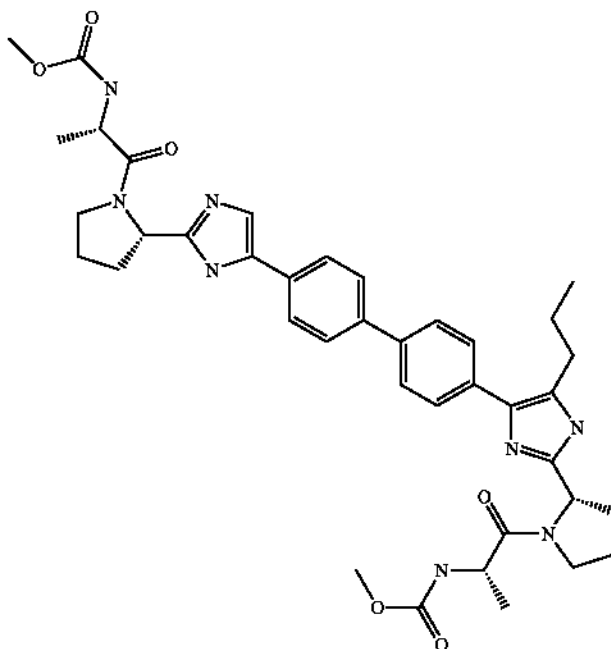
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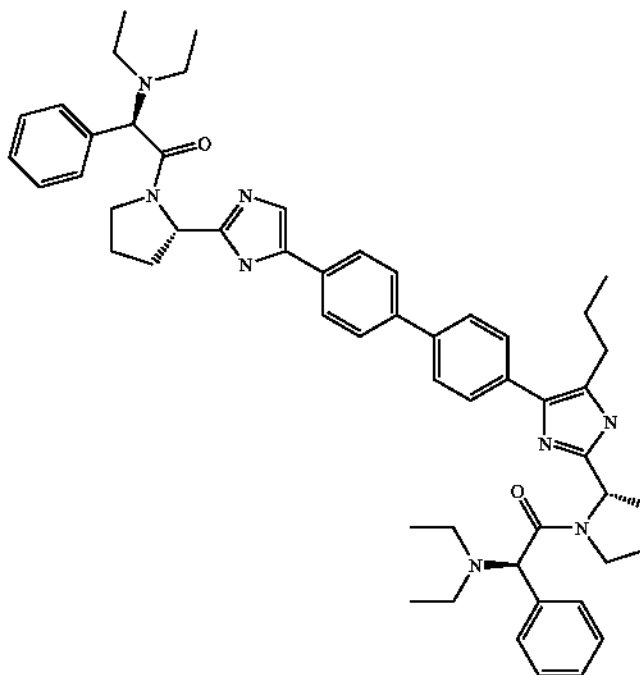
-continued

J14c methyl ((1S)-2-
Derived ((2S)-2-(4-(4'-(2-
from ((2S)-1-(N-
example (methoxycarbonyl)-
J13c L-alanyl)-2-
pyrrolidinyl)-4-
propyl-1H-
imidazol-5-yl)-4-
biphenyl)-1H-
imidazol-2-yl)-1-
pyrrolidinyl)-1-
methyl-2-
oxoethyl)carbamate



RT = 1.42
min, (Cond
1);
HRMS:
Anal.
Calcd. for
C₃₉H₄₉N₈O₆
725.3775;
found:
725.3758
(M + H)⁺.

J14c.1 (1R)-2-((2S)-2-(4-
Derived (4'-(2-((2S)-1-
from ((2R)-2-
example (diethylamino)-2-
J13c phenylacetyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-5-
propyl-1H-
imidazol-2-yl)-1-
pyrrolidinyl)-N,N-
diethyl-2-oxo-1-
phenylethanamine



RT = 1.39
min, (Cond
1);
HRMS:
Anal.
Calcd. for
C₅₃H₆₅N₈O₂
845.5225;
found:
845.5207
(M + H)⁺.

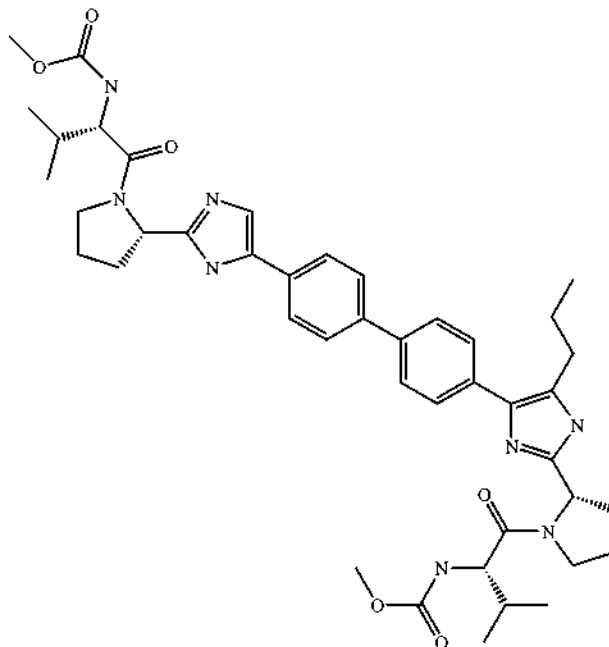
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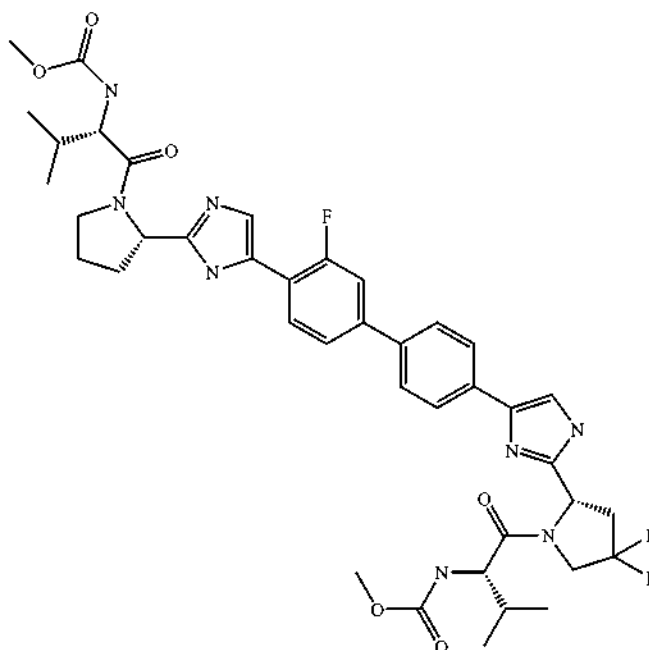
-continued

J14c.2 methyl ((1S)-1-
Derived from
example J13c (((2S)-2-(4-(4'-(2-
(2S)-1-((2S)-2-
(methoxycarbonyl)
amino)-3-
methylbutanoyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-5-
propyl-1H-
imidazol-2-yl)-1-
pyrrolidinyl)car-
bonyl)-2-methyl-
propyl)carbamate



RT = 1.59
min, (Cond
1);
HRMS:
Anal.
Calcd. for
 $C_{43}H_{57}N_9O_6$
781.4317;
found:
781.4377
(M + H)⁺.

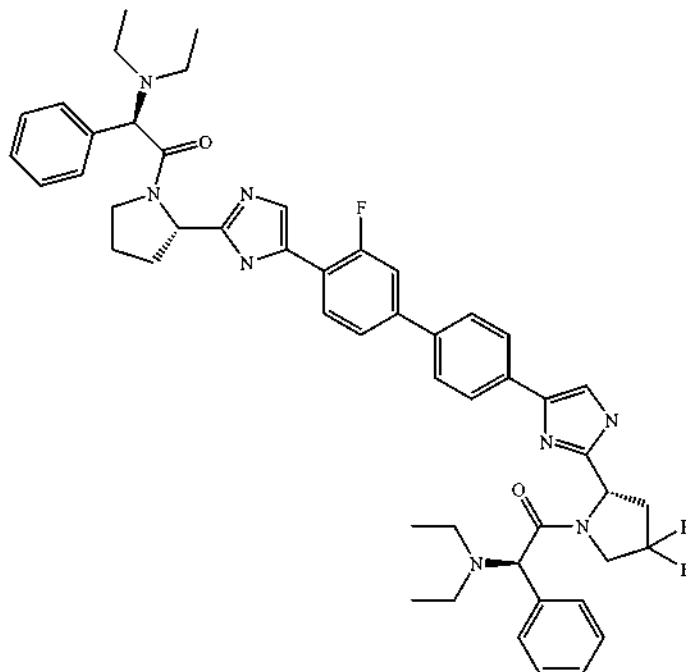
J14e methyl ((1S)-1-
Derived from
example J13e (((2S)-2-(4,4-difluoro-
2-(4-(3'-fluoro-4'-
(2-(2S)-1-((2S)-2-
(methoxycarbonyl)
amino)-3-
methylbutanoyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-5-
propyl-1H-
imidazol-2-yl)-1-
pyrrolidinyl)car-
bonyl)-2-methyl-
propyl)carbamate



RT = 1.99
min, (Cond
2)
HRMS:
Anal.
Calcd. for
 $C_{40}H_{48}F_3N_9O_6$
793.3643;
found:
793.3653
(M + H)⁺.

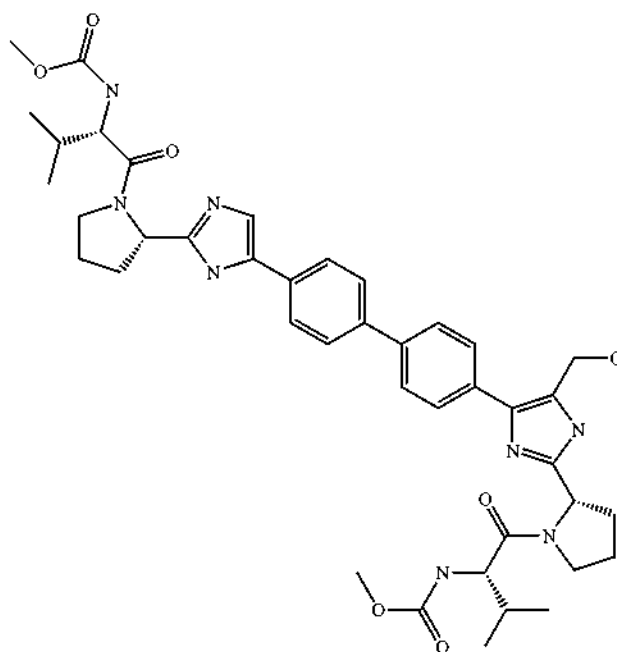
-continued

J14e.1 (1R)-2-((2S)-2-(4-
Derived from (4'-((2S)-1-
example (2R)-2-
J13e (diethylamino)-2-
phenylacetyl)-4,4-
difluoro-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-3-
fluoro-4-
biphenyl)-1H-
imidazol-2-yl)-1-
pyrrolidinyl)-N,N-
diethyl-2-oxo-1-
phenylethanamine



RT = 1.79
min, (Cond
2)
HRMS:
Anal.
Calcd. for
 $C_{50}H_{56}F_3N_8O_2$
857.4473;
found:
857.4478
(M + H)⁺.

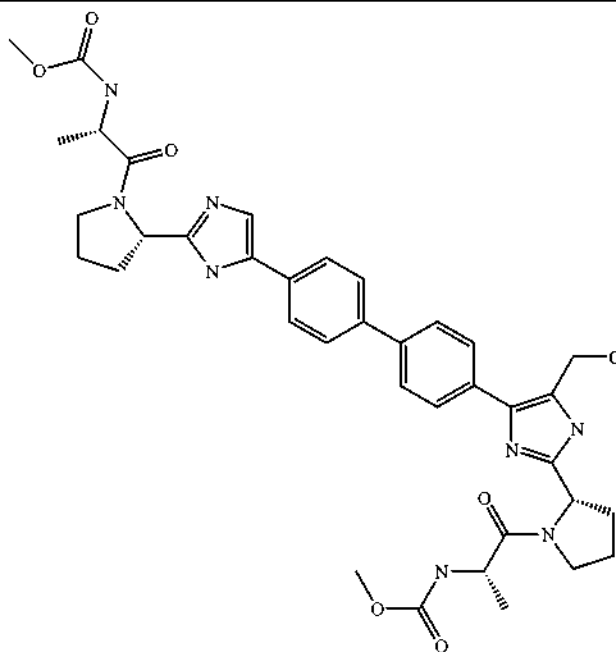
J14f methyl ((1S)-1-
Derived from (((2S)-2-(4-
from (hydroxymethyl)-5-
example (4'-((2S)-1-
J13f (2S)-2-
((methoxycarbonyl)
amino)-3-
methylbutanoyl)-2-
pyrrolidinyl)-1H-
imidazol-4-yl)-4-
biphenyl)-1H-
imidazol-2-yl)-1-
pyrrolidinyl)-car-
bonyl)-2-methyl-
propyl)carbamate



RT = 1.40
min,
(Cond 1);
HRMS:
Anal.
Calcd. for
 $C_{41}H_{53}N_8O_7$
769.4037;
found:
769.4020
(M + H)⁺.

-continued

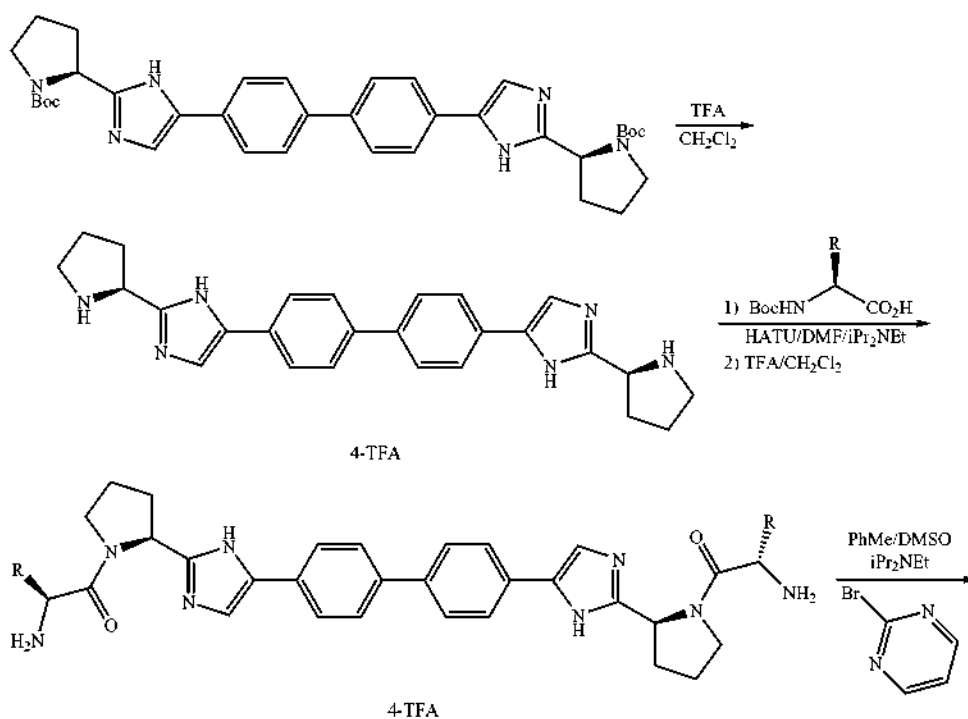
J14f.1 methyl ((1S)-2-
Derived ((2S)-2-(4-(4'-
from (hydroxymethyl)-2-
example ((2S)-1-(N-
J13f (methoxycarbonyl)-
L-alanyl)-2-
pyrrolidinyl)-1H-
imidazol-5-yl)-4-
biphenyl)-1H-
imidazol-2-yl)-1-
pyrrolidinyl)-1-
methyl-2-
oxoethyl)carbamate



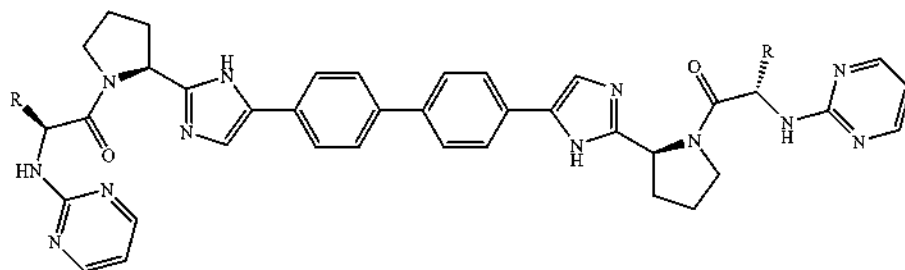
RT = 1.21
min.
(Cond 1);
HRMS:
Anal.
Calcd. for
 $C_{37}H_{45}N_8O_7$
713.3411;
found:
713.3391
(M + H)⁺.

Section PY
[1416]

Scheme 1



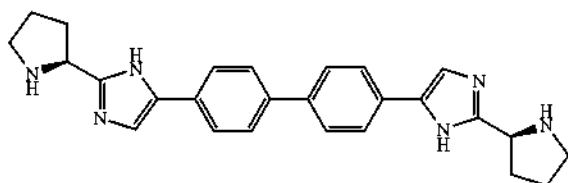
-continued



Example PY1

4,4'-bis(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)
biphenyl trifluoroacetic acid salt

[1417]



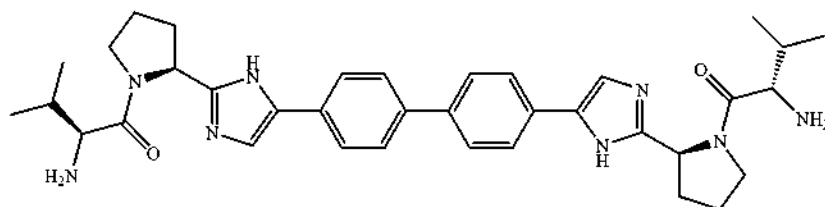
4-TFA

[1418] To a solution of (2S,2'S)-tert-butyl 2,2'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl)dipyrrolidine-1-carboxylate (2.61 g, 4.18 mmol) in CH_2Cl_2 (25 mL) was added TFA (12 mL) and the mixture was allowed to stir at room temperature. After allowing the reaction to stir for 2 hours it was concentrated to dryness in vacuo. The material was used without further purification in subsequent steps. LCMS: Anal. Calcd. for $\text{C}_{26}\text{H}_{28}\text{N}_6$: 424; found: 425 (M+H)⁺.

Example PY2

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(biphenyl-4,4'-diyl)
bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))
bis(2-amino-3-methylbutan-1-one)

[1419]



[1420] To a solution of 4,4'-bis(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl tetrakis(2,2,2-trifluoroacetate) (2.695 g, 3.06 mmol), (S)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid (1.60 g, 7.34 mmol) and DIEA (5.3 mL, 30.6 mmol) in DMF (15 mL) was added HATU (2.39 g, 6.27 mmol) and the mixture was allowed to stir at room temperature for 14 h. MeOH (5 mL) was added and the mixture was allowed to stir for 4 h. It was then poured into ca. 150 mL of cold water and allowed to stand for 20 min. The solid was filtered and dried under vacuum overnight and then purified by biotage (40+M, 0 to 25% MeOH in EtOAc) to give a yellow brown foam (1.76 g, 70%). ¹HNMR (300 MHz, DMSO-d₆) δ 12.11-12.17 (m, 1H), 11.76 (s, 1H), 7.73-7.94 (m, 4H), 7.62-7.70 (m, 4H), 7.49 (d, J=1.8 Hz, 1H), 6.76 (d, J=8.5 Hz, 1H), 5.06 (dd, J=2.7, 6.3 Hz, 2H), 4.00-4.07 (m, 2H), 3.77 (s, br, 3H), 2.07-2.15 (m, 4H), 1.88-2.00 (m, 6H), 1.37 (s, 18H), 0.88 (d, J=6.6 Hz, 6H), 0.82 (d, J=6.6 Hz, 6H). LCMS: Anal. Calcd. for $\text{C}_{46}\text{H}_{62}\text{N}_8\text{O}_6$: 822; found: 823 (M+H)⁺. The material was suspended in CH_2Cl_2 (15 mL) and TFA (6 mL) was added. After stirring for 2 h the solvents were removed in vacuo giving a yellow orange solid. The solid was partitioned between sat NaHCO_3 and EtOAc however the material was insoluble in EtOAc. Therefore the volatiles were removed in vacuo and the residue was loaded on to an SCX cation exchange cartridge and eluted with MeOH and then NH_3 in MeOH (2M). The appropriate fractions were concentrated in vacuo to give a yellow foam (1.24 g, 65%). LCMS: Anal. Calcd. for $\text{C}_{36}\text{H}_{46}\text{N}_8\text{O}_2$: 622; found: 623 (M+H)⁺. The material was used as is in subsequent steps.

[1421] The following were prepared similarly. Note that in some cases the TFA salt obtained from the Boc deprotection was carried forward directly.

Example	Structure	Analytical Data
Example PM3		LCMS: Anal. Calcd. for $C_{30}H_{30}N_8O_2$: 618; found: 619 (M + H) ⁺ .
Example PM4		LCMS: Anal. Calcd. for $C_{27}H_{28}N_8O_2$: 566; found: 567 (M + H) ⁺ .
Example PM5		LCMS: Anal. Calcd. for $C_{31}H_{32}N_8O_2$: 594; found: 595 (M + H) ⁺ .
Example PM6		LCMS: Anal. Calcd. for $C_{31}H_{32}N_8O_4$: 626; found: 627 (M + H) ⁺ .
Example PM7		LCMS: Anal. Calcd. for $C_{30}H_{30}N_8O_4$: 618; found: 619 (M + H) ⁺ .

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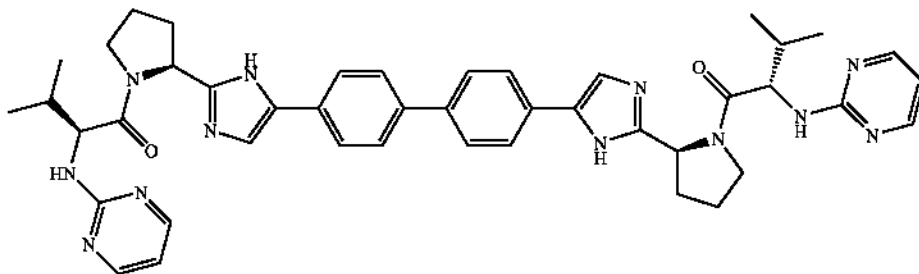
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Example PY8

(N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl
(2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-
butanediy)))di(2-pyrimidinamine)

[1422]



[1423] A mixture of (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(bi-phenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrroli-dine-2,1-diyl))bis(2-amino-3-methylbutan-1-one) (222 mg, 0.36 mmol), 2-bromopyrimidine (0.170 g, 1.07 mmol) and $i\text{Pr}_2\text{NEt}$ (0.25 mL, 1.432 mmol) in toluene (3 mL) and DMSO (0.5 mL) was heated at 90° C. overnight. LCMS indicated the reaction to be incomplete therefore heating was continued for a further 12 hours. The volatiles were removed in vacuo and the residue was diluted with MeOH and purified by prep HPLC ($\text{CH}_3\text{CN}-\text{H}_2\text{O}-\text{NH}_4\text{OAc}$). The appropriate fractions were concentrated in vacuo and subsequently re-purified by prep HPLC ($\text{CH}_3\text{CN}-\text{H}_2\text{O}-\text{TFA}$). The appropriate fractions were adsorbed onto an MCX cation exchange resin cartridge (Oasis) and the resin was washed with MeOH and eluted with 2M NH_3 in MeOH. The solvent was removed in

vacuo and the residue was lyophilized to give a colorless solid (17.2 mg, 6%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.15, 12.28 (s, 1H, rotamers, 1:1 ratio), 8.28 (d, $J=4.8$ Hz, 4H), 7.79 (app d, $J=8.1$ Hz, 4H), 7.62-7.70 (m, 4H), 7.49 (d, $J=1.5$ Hz, 2H), 6.85 (d, $J=8.4$ Hz, 2H), 6.60 (t, $J=4.8$ Hz, 2H), 5.05 (dd, $J=6.9$, 4.0 Hz, 2H), 4.50 (app t, unresolved dd, $J=8.5$, 8.0 Hz, 2H), 3.98-4.06 (m, 2H), 3.78-3.85 (m, 2H), 1.98-2.23 (m, 10H), 0.96 (d, $J=6.6$ Hz, 6H), 0.92 (d, $J=6.6$ Hz, 6H). LCMS: Anal. Calcd. for $\text{C}_{44}\text{H}_{50}\text{N}_{12}\text{O}_2$: 778; found: 779 ($\text{M}+\text{H}$) $^+$.

[1424] The following were prepared similarly:

[1425] Note that in some cases the TFA salt obtained from the Boc deprotection was carried forward directly and an appropriate amount of $i\text{Pr}_2\text{NEt}$ was added to the reaction mixture.

Com-
pound

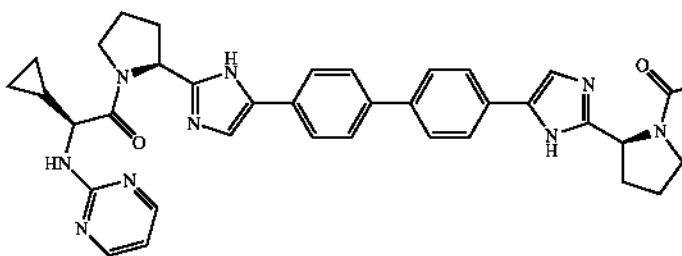
Name

Example

Structure

Analytical
Data

N,N'-(4,4'-
biphenyl-
diyl
bis(1H-
imidazole-
4,2-diyl
(2S)-
2,1-
pyrroli-
dinediyl
((1S)-1-
cyclo-
propyl-
2-oxo-2,1-
ethane-
diyl)))
di(2-
pyrimidin-
amine)

Example
PY9

LCMS:
Anal.
Calcd. for
 $\text{C}_{36}\text{H}_{42}\text{N}_8\text{O}_2$:
618;
found: 619
($\text{M}+\text{H}$) $^+$.

-continued

Compound Name	Example	Structure	Analytical Data
N,N'-(4,4'-biphenyl-diyl bis(1H-imidazole-4,2-diyl (2S)-2,1-pyrrolidinediyl ((2S)-1-oxo-1,2-propanediyl))) di(2-pyrimidine-amine)	Example PY10		LCMS: Anal. Calcd. for $C_{32}H_{38}N_8O_2$: 566; found: 567 (M + H) ⁺ .
N,N'-(4,4'-biphenyl-diyl bis(1H-imidazole-4,2-diyl (2S)-2,1-pyrrolidinediyl ((2S)-1-oxo-1,2-butane-diyl))) di(2-pyrimidin-amine)	Example PY11		LCMS: Anal. Calcd. for $C_{34}H_{42}N_8O_2$: 594; found: 595 (M + H) ⁺ .
N,N'-(4,4'-biphenyl-diyl bis(1H-imidazole-4,2-diyl (2S)-2,1-pyrrolidinediyl ((2S)-3-methoxy-1-oxo-1,2-propanediyl))) di(2-pyrimidin-amine)	Example PY12		LCMS: Anal. Calcd. for $C_{34}H_{42}N_8O_4$: 626; found: 627 (M + H) ⁺ .

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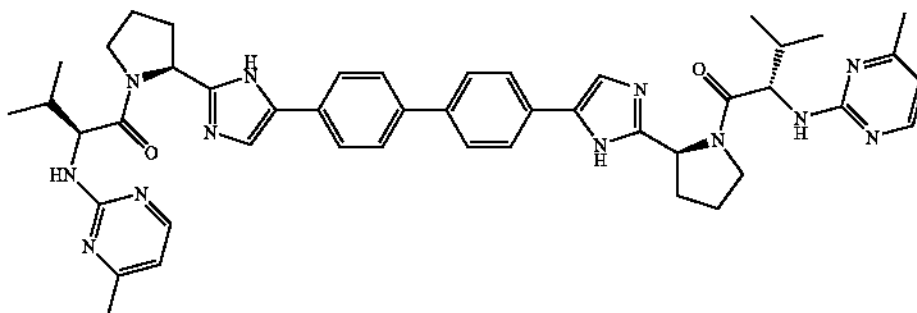
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-continued

Compound Name	Example	Structure	Analytical Data
N,N'-(4,4'-biphenyl-diyl bis(1H-imidazole-4,2-diyl (2S)-2,1-pyrrolidinediyl ((2S,3R)-3-methoxy-1-oxo-1,2-butanediyl))) di(2-pyrimidinamine)	Example PY13		LCMS: Anal. Calcd. for C ₃₆ H ₄₂ N ₈ O ₂ : 618; found: 619 (M + H) ⁺ .

Example PY14
Modified Method

[1426]



[1427] A mixture of (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-amino-3-methylbutan-1-one) (50 mg, 0.080 mmol), 2-chloro-4-methylpyrimidine (103 mg, 0.803 mmol), and DIPEA (0.140 mL, 0.803 mmol) in NMP (3 mL) was heated in a sealed tube for 4 h at 140° C. using a Microwave. The volatiles were removed in vacuo and the residue was diluted with MeOH and filtered through a Strata XC MCX cartridge. The cartridge was washed with methanol.

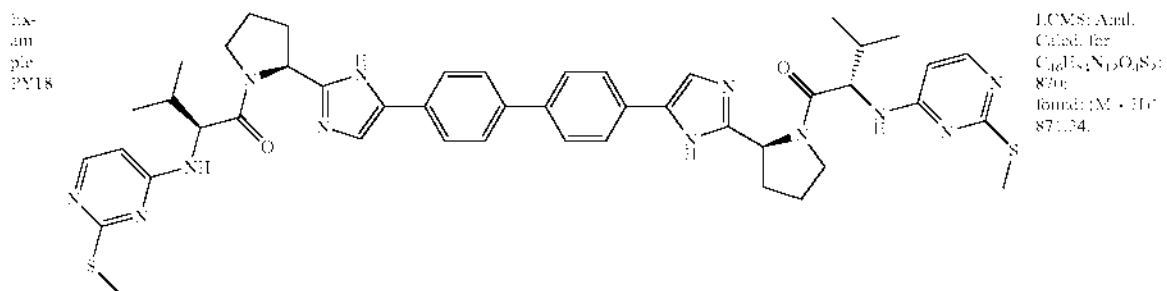
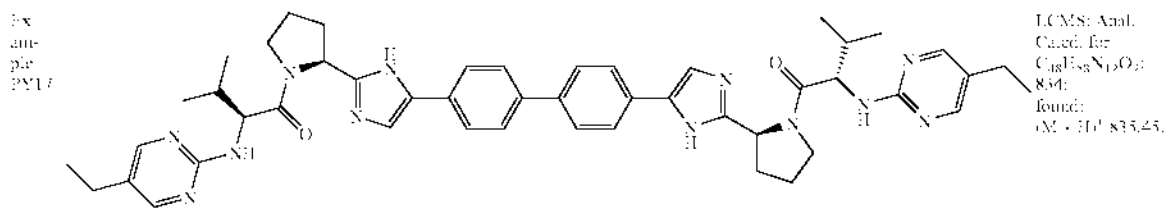
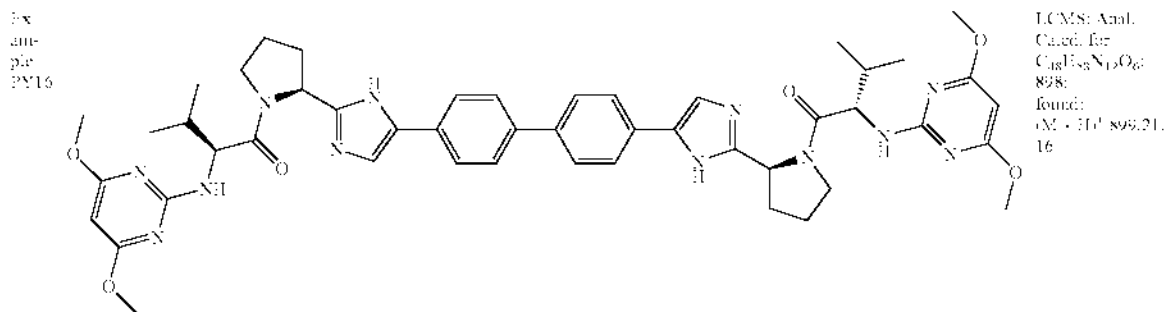
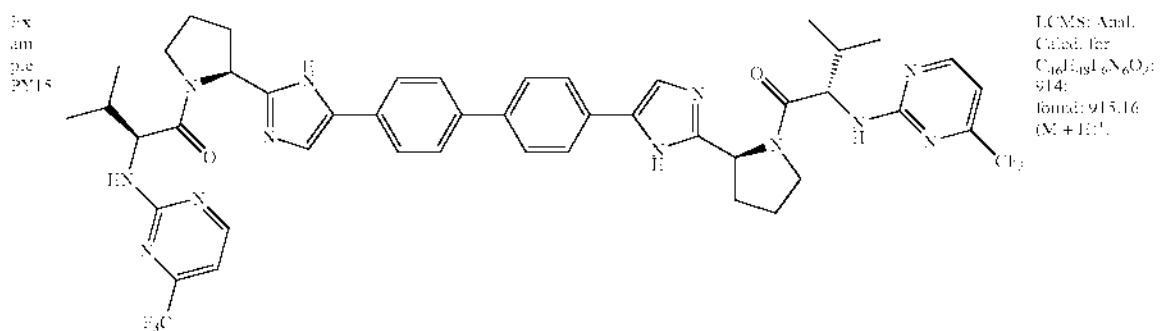
The compound was released from the cartridge by washing with a solution of 2M of Ammonia/Methanol. The filtrate was evaporated under reduced pressure to give an orange oil. The crude material was purified HPLC (CH₃CN—H₂O—NH₄OAc). The appropriate fractions were concentrated in vacuo and subsequently re-purified by prep HPLC (CH₃CN—H₂O—TFA). The appropriate fractions were concentrated in vacuo to give a Yellow solid (21.5 mg, 31.9%). LCMS: Anal. Calcd. for C₄₆H₅₄N₁₂O₂: 807; found: 807.5 (M+H)⁺.

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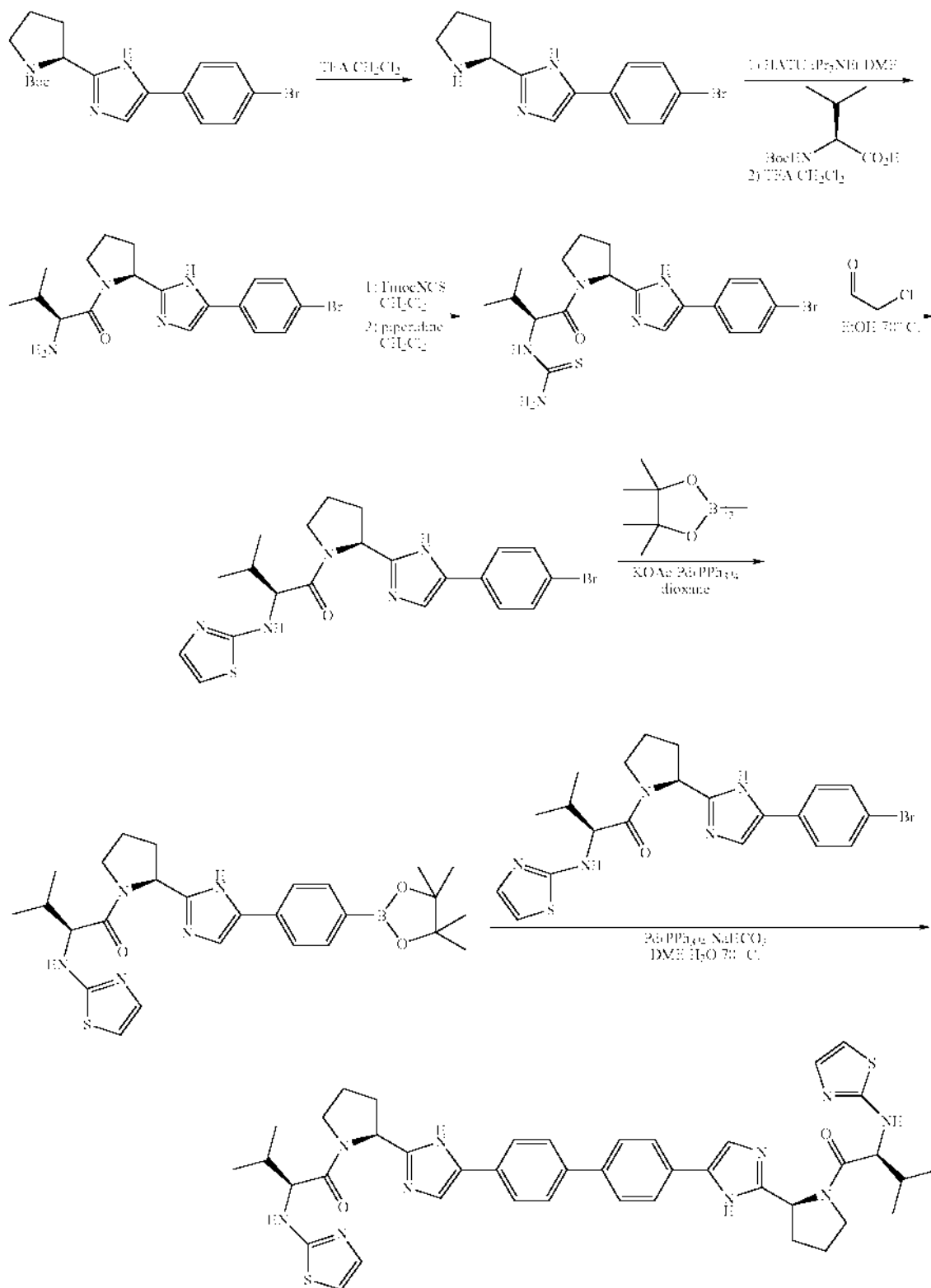
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Ex- am- ple	Structure	Analytical Data
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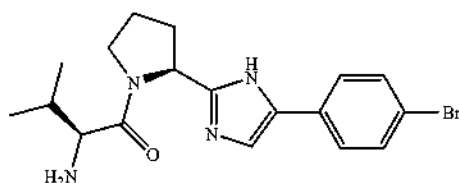
Scheme 2



Example PY19

(S)-2-amino-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methylbutan-1-one

[1428]

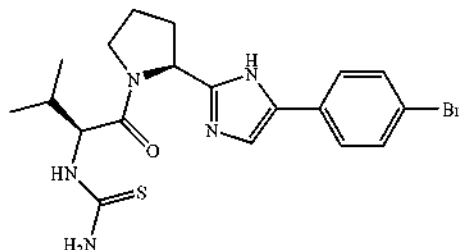


[1429] The title compound was prepared from (S)-tert-butyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate and (S)-2-amino-3-methylbutanoic acid by the procedures detailed in Examples 1 and 2. ¹HNMR (300 MHz, DMSO-d₆) δ 11.73 (s, 1H), 7.68 (d, J=5.9 Hz, 1H), 7.65 (d, J=5.9 Hz, 1H), 7.46-7.58 (m, 3H), 5.14, 5.05 (dd, J=7.0, 3.0 Hz, 1H, rotamers, 1:1 ratio), 3.66 (app t, J=6.5 Hz, 1H), 3.53-3.61 and 3.38-3.47 (m, 1H, rotamers, 1:1 ratio), 3.28 (s, 2H), 1.70-2.21 (m, 6H), 0.75-0.88 (m, 6H). LCMS: Anal. Calcd. for C₁₈H₂₃BrN₄O: 390, 392; found: 391, 393 (M+H)⁺.

Example PY20

1-((S)-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)thiourea

[1430]

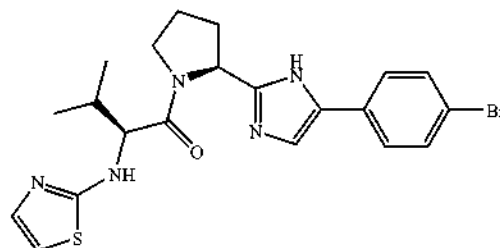


[1431] To a solution of (S)-2-amino-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methylbutan-1-one (1.530 g, 3.91 mmol) in CH₂Cl₂ (10 mL) was added O-(9H-fluoren-9-yl)methyl carbonisothiocyanatide (1.100 g, 3.91 mmol) as a solid in one portion. The mixture was allowed to stir at room temperature for 12 h. Piperidine (2 mL) was added to the mixture and it was allowed to stir at room temperature for 1 h. A further portion of piperidine (2 mL) was added and the solution allowed to stir 1 h. The solution was concentrated to dryness and the residue was purified by column chromatography (biotage, eluting with 5:4.5:0.5 hex:EtOAc:MeOH, and then 5% MeOH in EtOAc). The title compound as obtained as a light yellow glass (1.30 g, 74%). ¹HNMR (300 MHz, DMSO-d₆) δ 11.81 (s, H), 7.65 (d, J=8.8 Hz), 7.63-7.71 (m, overlap with previous peak, 2H total), 7.42-7.56 (m, 2H), 7.10-7.14 (m, 1H), 5.06 (dd, J=7.0, 3.0 Hz, 1H), 4.94 (app t, J=8.0 Hz, 1H), 4.72-4.76 and 4.56-4.62 (m, 1H, rotamers, 1:1 ratio), 3.77-3.90 (m, 1H), 2.07-2.14 (m, 2H), 1.90-1.98 (m, 3H), 0.93 (d, J=7.0 Hz, 3H), 0.84 (d, J=7.0 Hz, 3H). LCMS: Anal. Calcd. for C₁₉H₂₄BrN₅OS: 449, 451; found: 450, 452 (M+H)⁺.

Example PY21

(S)-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-2-(thiazol-2-ylamino)butan-1-one

[1432]



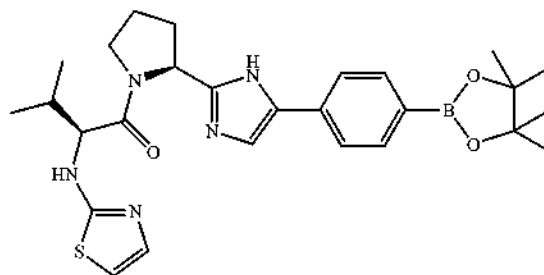
[1433] A solution of 1-((S)-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)thiourea (1.29 g, 2.86 mmol) was dissolved in EtOH (50 mL) and 2-chloroacetaldehyde (0.4 mL, 3.15 mmol) was added. The mixture was heated at 70° C. overnight. A further portion of 2-chloroacetaldehyde (0.4 mL, 3.15 mmol) was added and heating continued for a further 12 h. The solution was concentrated in vacuo and the residue was purified by column chromatography (biotage, eluting with 50% EtOAc in hexanes and then 10% MeOH in EtOAc). The desired product was isolated as a orange-brown foam (557.2 mg). LCMS (NH₄OAc) shows this to be of sufficient purity. Eluting further with 100% MeOH gave a second fraction (980.8 mg) which was shown to contain the product by TLC (5:4.5:0.5 hex:EtOAc:MeOH). This second fraction from the column was re-purified to give a light orange-brown foam (426.6 mg). The two fractions were combined to afford the title compound as a orange brown foam (983.8 mg, 72%).

[1434] ¹HNMR (300 MHz, CD₃OD) δ 7.57 (app d, J=8.0 Hz, 2H), 7.47 (app d, J=8.0 Hz, 2H), 7.32 (s, 1H), 6.98 (d, J=3.6 Hz, 1H), 6.55 (d, J=3.6 Hz, 1H), 5.32-5.35 and 5.10-5.15 (m, 1H, rotamers, 1:3 ratio), 4.08-4.15 (m, 1H), 3.82-3.90 (m, 1H), 3.03-3.15 (m, 1H), 2.03-2.33 (m, 4H), 1.06 and 0.99 (d, J=7.0 Hz, 3H, rotamers 1:3 ratio), 1.04 and 0.94 (d, J=7.0 Hz, 3H, rotamers 1:3 ratio). LCMS: Anal. Calcd. for C₂₁H₂₄BrN₅OS: 473, 475; found: 474, 476 (M+H)⁺.

Example PY22

(S)-3-methyl-1-((S)-2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-(thiazol-2-ylamino)butan-1-one

[1435]



[1436] A mixture of (S)-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-2-(thiazol-2-ylamino)butan-1-one (87.5 mg, 0.184 mmol), 4,4',4'',5,5',5''-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (141 mg, 0.553 mmol), potassium acetate (91 mg, 0.922 mmol) and Pd(Ph₃P)₄ (21.31 mg, 0.018 mmol) was suspended in dioxane and degassed by bubbling N₂ through the mixture. It was then heated at 85° C. After heating for 4 h the mixture was concentrated and purified by passing through a pad of silica gel eluting with 1:1 hex:EtOAc, and then EtOAc (neat) to give afforded the desired product as a light yellow film (101 mg). LCMS (CH₃CN—H₂O—NH₄OAc) showed that the product

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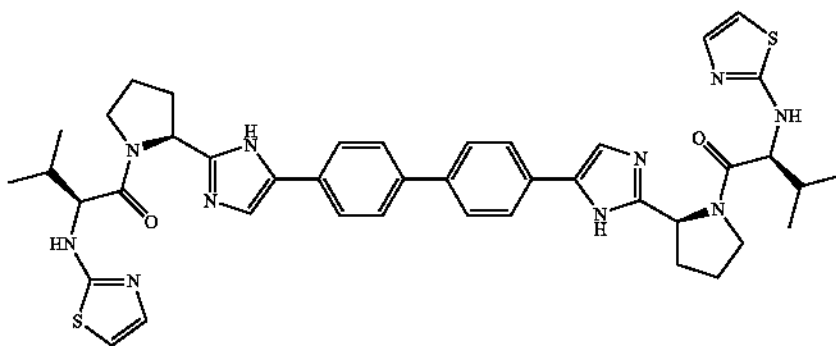
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was contaminated with ca. 10% PPh₃O. The material was used as is in subsequent steps. LCMS: Anal. Calcd. for C₂₇H₃₆BN₅O₃S: 521; found: 522 (M+H)⁺.

Example PY23

(N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl (2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))bis(1,3-thiazol-2-amine)

[1437]



[1438] A mixture of (S)-3-methyl-1-((S)-2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-(thiazol-2-ylamino)butan-1-one (275 mg, 0.527 mmol), (S)-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-2-(thiazol-2-ylamino)butan-1-one (250 mg, 0.527 mmol), NaHCO₃ (133 mg, 1.582 mmol) and Pd(Ph₃P)₄ (60.9 mg, 0.053 mmol) in DME (3 mL) and Water (1 mL) was degassed by passing a stream of N₂

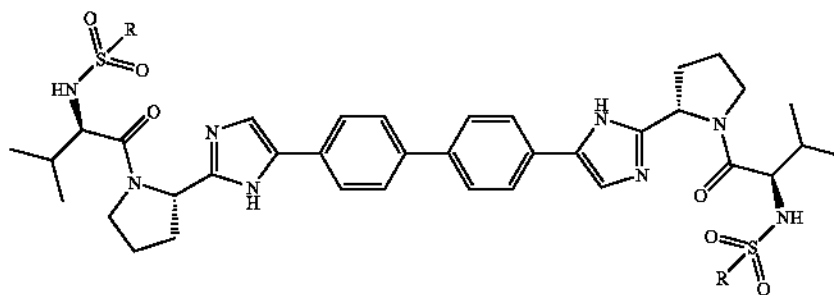
matography (biotage) eluting with 0 to 20% MeOH in EtOAc. Further purification by prep HPLC (CH₃CN—H₂O—NH₄OAc) followed by lyophilization afforded the title compound as a colorless solid (6.9 mg, 2%).

[1439] ¹HNMR (300 MHz, DMSO-d₆) δ 13.41 (s, 1H), 11.75 (s, 2H), 7.75-7.80 (m, 4H), 7.68-7.71 (m, 4H), 7.49 (s, 2H), 6.99 (d, J=3.7 Hz, 2H), 6.57 (d, J=3.7 Hz, 2H), 5.34-5.36 (m, 1H), 5.07 (app dd, J=3.7, 7.0 Hz, 2H), 4.42 (t, J=8.4 Hz, 2H), 3.98-4.05 (m, 2H), 3.79-3.85 (m, 2H), 3.44-3.56 (m,

1H), 1.97-2.21 (m, 8H), 1.01 and 0.95 (d, J=7.0 Hz, 6H, rotamers, 1:3 ratio), 0.99 and 0.92 (d, J=7.0 Hz, 6H, rotamers, 1:3 ratio). LCMS: Anal. Calcd. for C₄₂H₄₈N₁₀O₂S₂: 788; found: 789 (M+H)⁺.

Examples FY1-FY3

[1440]



through the mixture. The vessel was sealed and the reaction was heated at 80° C. overnight. The reaction mixture was diluted with H₂O and extracted with EtOAc containing ca. 5% MeOH (×3). The combined org layers were concentrated, dissolved in MeOH and loaded onto an MCX cartridge. The cartridge was washed with MeOH and then NH₃ in MeOH (2M). The appropriate fractions were concentrated in vacuo and the residue was purified by prep HPLC (CH₃CN—H₂O—NH₄OAc). The material was purified by column chro-

[1441] Examples FY1-FY3 were prepared according to the protocols described for the synthesis of Example F66 and by employing appropriate materials.

LC/MS Condition:

Column: Phenomenex 10u 3.0×50 mm

Start % B=0

Final % B=100

Gradient Time=3 min




[1442] Flow Rate=4 mL/Min

Wavelength=220

Solvent A=10% MeOH—90% H₂O—0.1% TFA

Solvent B=90% MeOH—10% H₂O—0.1% TFA

[1443]

Example	R	RT (LC-Cond. is noted above); % homogeneity index; MS data.
FY1		2.03 min; >95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₃₈ H ₅₁ N ₈ O ₆ S ₂ 779.34; found: 779.72
FY2		2.19 min; >95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₀ H ₅₃ N ₈ O ₆ S ₂ 807.37; found: 807.78
FY3		2.24 min; >95%; LC/MS: Anal. Calcd. for [M + H] ⁺ C ₄₂ H ₅₅ N ₈ O ₆ S ₂ 831.37; found: 832.02

Biological Activity

[1444] An HCV Replon assay was utilized in the present disclosure, and was prepared, conducted and validated as described in commonly owned PCT/US2006/022197 and in O'Boyle et. al. *Antimicrob Agents Chemother.* 2005 April; 49(4): 1346-53.

[1445] HCV 1b-377-neo replicon cells were used to test the currently described compound series as well as cells resistant to compound A due to a Y2065H mutation in NS5A (described in application PCT/US2006/022197). The compounds tested were determined to have more than 10-fold less inhibitory activity on cells resistant to compound A than wild-type cells indicating a related mechanism of action between the two compound series. Thus, the compounds of the present disclosure can be effective to inhibit the function of the HCV NS5A protein and are understood to be as effective in combinations as previously described in application PCT/US2006/022197 and commonly owned WO/04014852. Further, the compounds of the present disclosure can be effective against the HCV 1b genotype. It should also be understood that the compounds of the present disclosure can inhibit multiple genotypes of HCV. Table 2 shows the EC₅₀ values of representative compounds of the present disclosure against the HCV 1b genotype. In one embodiment compounds of the present disclosure are active against the 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. EC₅₀ ranges against HCV 1b are as follows: A=1-10 μM; B=100-999 nM; C=1-99 nM; and D=1-999 pM.

[1446] The compounds of the present disclosure may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A.

TABLE 2

Example	Range
1	D
24-4e	C
24-4f	B
24-4g	A
25-1	D
25-2	D
25-3	D
25-4	D
25-5	D
25-6	C
25-7	C
25-8	D
24-4h	D
120-9	D
120	D
120-5	C
120-6	C
120-7	D
120-8	C
103-3	D
103-4	D
103-1	D
103-2	D
103-5	D
103-6	C
103-8	D
103-7	D
151 isomer 1	C
151 isomer 2	B
152j-9	C
152j-10	C
152j-1	C
152j-2	D
153c-5	C
153c-6	C
153c-2	C
153c-1	C
152j-7	C
152j-8	D
153c-3	A
153c-4	A
152j-11	D
152j-12	D
152j-15	D
152j-28	D
152j-13	C
152j-14	C
152j-19	D
152j-16	D
152j-3	D
152j-20	C
152j-17	D
152j-18	D
152j-3	D
152j-5	D
152j-6	D
152i-2	D
152i-1	D
152j-24	D
152j-23	D
153c-7	C
152j-22	D
24-18-2	D
24-18-1	D
24-18-4	D
24-18-5	D
24-18-6	D
24-18-3	D
152j-21	D
152i-3	D
131.1-2	D
131.1-1	D
24-4a	D
120-1	D

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TABLE 2-continued

Example	Range
120-2	D
120-3	D
120-4	D
24-10	D
24-9	D
24-8	D
24-11	C
24-12	C
11	C
24-16	D
24-18	D
24-17	D
24-15	C
24-13	B
24-14	C
24-4b	C
24-4c	D
24-4d	D
148	C
149	D
150	C
24-5	D
24-6	D
24-7	D
24-1	D
24-2	D
24-3	D
28-1	D
28-2	D
28-3	D
28-4	D
28-5	D
84-1	D
84-2	D
84-3	D
84-4	D
84-7	C
84-10	C
84-12	D
84-14	C
84-15	C
84-17	D
84-18	C
84-19	C
84-20	C
84-24	D
84-26	D
84-27	D
84-28	D
84-32	D
84-33	D
84-34	C
84-35	D
84-36	D
84-38	D
84-39	D
84-40	D
84-44	D
84-46	D
84-47	D
84-48	D
84-49	D
84-50	D
84-51	D
84-52	D
84-53	D
84-54	D
84-55	D
84-56	D
84-57	D
84-58	D
84-59	D
84-60	D
84-61	D

TABLE 2-continued

Example	Range
84-62	D
84-63	D
84-64	D
84-65	C-D
84-66	C-D
84-67	D
84-68	C
84-69	D
84-70	C
84-71	C
84-72	C
84-73	C
84-74	D
84-75	C
84-76	D
84-77	D
84-78	D
84-79	D
84-80	D
84-81	D
84-82	D
84-83	D
84-84	D
84-85	D
84-86	D
84-87	D
94-1	D
94-2	C
94-3	D
94-6	C-D
94-9	D
94-10	D
94-12	C
94-13	D
94-17	D
94-19	D
94-20	C
94-24	D
94-25	D
94-26	D
94-27	C
94-30	D
94-32	C
94-33	C
94-34	C
94-36	D
94-37	C
94-38	D
94-42	D
94-44	D
94-45	D
94-46	D
94-47	D
94-48	D
94-49	D
94-50	D
94-51	D
94-52	D
94-53	D
94-54	D
94-55	D
94-56	D
107-1	D
107-2	D
107-3	D
107-4	D
107-5	D
107-6	D
107-7	D
107-8	D
107-9	D
107-10	D
107-11	D
107-12	D

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TABLE 2-continued

Example	Range
107-13	D
107-14	D
107-15	D
107-16	D
107-17	D
107-18	D
107-19	D
107-20	D
107-21	D
107-22	D
107-23	D
107-24	D
107-25	D
107-26	D
107-27	D
107-28	D
107-29	D
107-30	D
107-31	D
107-32	D
107-33	D
107-34	D
107-35	D
107-36	D
107-37	D
107-38	D
107-39	D
107-40	D
107-41	D
107-42	D
107-43	D
107-44	D
2	D
3	D
4	D
5	C
6	C
7	D
8	D
24-23	D
9	C
10	C
11	C
12	C
13	C
14	B
15	C
16	C
17	D
18	D
19	D
20	C
21	D
22	D
23	D
24	C
25	D
26	C
27	C
28	C
29	D
30	C
31	D
32	C
33	D
34	D
35	D
36	D
37	D
38	D
39	D
40	D
41	D
42	D

TABLE 2-continued

Example	Range
43	D
44	D
45	D
46	D
47	D
48	D
49	D
50	B
51	D
52	D
53	D
54	D
55	D
56	D
57	D
58	D
59	D
60	D
61	D
62	D
63	D
64	D
65	C
67	D
68	D
69	D
70	C
71	D
72	C
73	D
74	D
75	D
76	D
77	D
78	D
79	D
80	D
81	D
82	D
83	D
84	D
85	D
86	D
87	D
88	D
89	D
90	D
91	D
92	D
93	D
94	D
95	D
96	D
97	D
98	D
99	D
100	D
101	D
102	D
103	D
104	D
105	D
106	D
107	D
108	D
109	C
110	D
111	D
112	D
113	D
114	D
115	D
116	D
117	D

TABLE 2-continued

Example	Range
118	D
119	D
120	D
121	D
122	D
123	D
124	D
125	D
126	D
127	D
128	D
129	D
130	D
131	D
132	D
133	C
134	D
135	D
136	D
138	D
139	D
140	D
141	D
142	C
143	D
144	D
145	D
146	D
147	D
LS2	C
LS3	C
LS4	C
LS16	C
LS6	B
LS11	A
LS14	D
LS20	D
LS21	D
LS22	D
LS23	D
LS24	D
LS25	D
LS26	D
LS27 D'imer 1	D
LS27 D'imer 2	D
LS36	D
LS37	D
F5	D
F6	D
F7	D
F8	D
F14	D
F15	D
F16	D
F17	D
F20	B
F21	B
F22	B
F25	D
F26	C
F27	C
F28	C
F29	C
F30	C
F32	B
F33	B
F34	C
F35	B
F37	B
F38	D
F39	D
Diastereomer	
F41	D
F43	D

TABLE 2-continued

Example	Range
F48	D
F49	C
F51	D
F52	D
F53	D
F54	D
F55	D
F56	D
F57	D
F58	D
F60	D
F61	C
F62	C
F63	D
F64	C
F65	B
F66	C
F67	C
F69	B
F70	B
F71	D
cj-48	B
cj-49	C
cj-50	D
cj-51	D
cj-52	D
cj-53	D
cj-54	D
cj-55	D
cj-56	D
cj-57	D
cj-58	D
cj-59	D
cj-60	D
cj-61	D
cj-62	D
cj-63	D
cj-64	D
cj-65	D
cj-66	D
cj-67	D
cj-68	D
cj-69	D
cj-70	D
cj-71	D
cj-72	D
cj-73	D
cj-74	C
cj-75	D
cj-76	D
cj-77	D
cj-78	D
cj-79	D
cj-80	D
cj-81	D
cj-82	D
cj-83	D
cj-84	D
cj-85	D
cj-86	D
cj-87	D
cj-88	D
cj-89	D
cj-90	D
cj-91	D
cj-92	C
cj-93	D
cj-94	D
cj-95	D
cj-96	D
cj-97	D
cj-98	D
cj-99	D
cj-100	D

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TABLE 2-continued

Example	Range
ej-101	D
ej-102	D
ej-103	D
ej-104	D
ej-105	D
ej-106	D
ej-107	D
ej-108	D
ej-109	D
ej-110	D
ej-111	D
ej-112	D
ej-113	D
ej-114	D
ej-115	D
ej-116	D
ej-117	D
ej-118	D
ej-119	D
ej-120	D
ej-121	D
ej-122	D
ej-45	D
ej-41	D
ej-47	C
ej-43	D
ej-44	D
ej-40	D
ej-46	D
ej-42	D
ej-36	D
ej-37	D
ej-38	D
ej-39	D
ej-32	D
ej-33	D
ej-34	D
ej-35	C
ej-136	D
ej-137	C
ej-138	A
ej-139	C
ej-140	B
ej-141	A
ej-142	A
ej-143	A
ej-144	D
ej-145	C
ej-146	B
ej-147	C
ej-148	C
ej-149	C
ej-150	C
ej-151	C
ej-152	C
ej-153	D
ej-154	D
ej-155	C
ej-156	D
ej-126	D
ej-127	C
ej-128	D
ej-129	D
ej-130	D
ej-131	C
ej-132	B
ej-133	C
ej-134	C
ej-135	C
ej-125	C
ej-15c	D
ej-20c	D
ej-20b	D
ej-20a	D

TABLE 2-continued

Example	Range
ej-17	D
ej-16	D
ej-20d	D
ej-20	D
ej-15a	D
ej-15	D
ej-15d	D
ej-11n	C
ej-11o	C
ej-11p	D
ej-11m	C
ej-11h	D
ej-11i	D
ej-11j	D
ej-11k	D
ej-11e	A
ej-11f	C
ej-11g	C
ej-11d	D
ej-11b	D
ej-11	D
ej-11a	D
ej-11c	D
JG-3	D
JG-4	C
JG-5	D
JG-6	C
JG-7	D
JG-8	D
JG-9	D
JG-10	C
JG-12	D
JG-13	C
JG-14	D
JG-15	D
JG-16	D
JG-17	D
OL-1	D
OL-2	D
OL-3	C
OL-4	D
OL-5	D
OL-6	D
OL-7	D
OL-8	D
OL-9	D
OL-10	D
OL-11	D
OL-12	D
OL-13	D
OL-19	D
OL-20	C
OL-21	D
D73	D
D74	D
D75	D
D76	D
D77	D
J16	D
J17	D
J18	D
J19	D
J20	D
J21	D
J22	D
J23	D
J24	D
J25	D
J26	D
J27	D
J28	C
J29	D
J30	C
J31	D

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TABLE 2-continued

Example	Range
J37	D
J38	D
J39	D
J40	D
J41	D
J42	D
J42.a	D
J45	D
J46	D
J47	D
J48	D
J49	D
J50	D
J51	C
D33	D
D34	D
D35	D
D36	D
D37	D
D38	D
D39	D
D40	D
D41	D
D42	D
D43	D
D44	D
D45	D
D46	D
D47	D
D48	D
D49	D
D50	D
D51	D
D52	D
D53	D
D54	D
D55	D
D56	D
D57	D
D58	D
D59	D
D60	D
D61	D
D62	D
D63	D
D64	D
D65	D
D66	D
D67	D
D68	D
D69	D
D70	D
M1	>A
M2	C
M3	C
M4	B
M5	A
M6	A
M7	>A
M8	A
M9	B
M10	>A
M11	C
M12	C
M13	B
M14	B
M15	B
M16	A
M17	B
M18	A
M19	>A
M21	C
M22	A
M23	C

TABLE 2-continued

Example	Range
M24	C
M25	C
M26	B
M27	C
M28	A
M28-2	B
M29	>A
M30	C
M31	C
M32	B
M33	C
M34	C
M35	C
M36	C
M37	C
M38	C
M39	C
M40	C
M41	C
M42	C
M43	C
M44	B
M45	C
M46	C
M47	C
M48	C
M49	C
M50	C
M51	C
M52	C
M53	C
M54	C
M55	C
M56	C
M57	C
M58	C
M59	C
M60	C
M61	C
M62	C
M63	C
M64	C
M65	C
M66a	B
M66b	B
M66x	C
M67a	B
M67b	B
M68	B
M69	B
M70	C
M71	C
M72	C
M73	B
M74	C
M75	C
M76	C
M77	C
M78	C
M79	C
M80	C
M81	B
M82	C
M83	C
M84	C
M85	C
M86	C
M87	C
M88	C
M89	C
M90	A
M91	C
M91x	C
M91y	B

TABLE 2-continued

Example	Range
M92	A
M93	C
M94	C
M95	C
M96	B
M97	C
M98	C
M99	C
M100	C
M101	B
M102	C
M103	B
M104	B
M105	C
M106	C
M107	C
M108	C
M109	C
M110	C
M111	A
M112	C
M113	C
M114	>A
M115	>A
M116	>A
M117	>A
M118	>A
M119	B
M120	B
M121	B
M122	C
M123	A
M124	C
M125	C
M126	C
M127	C
M128	C
M129	A
M130	C
M131	D
M132	D
M133	D
M134	C
M135	D
M136	C
M137	D
M138	D
M139	D
M140	D
M140a-ii	C
M140a-i	C
M141	C
M142	C
M143	C
M144	D
M145	D
M146	D
M147	D
M148	D
M149	C
M150	D
M151	D
M152	D
M153	D
M154	D
M155	C
M156	C
M157	D
M158	C
M159	D
M160	C
M161	C
M162	C
E5	D

TABLE 2-continued

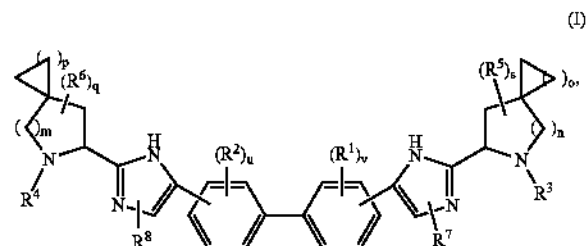
Example	Range
E5a	D
E5b	D
E5c	D
E5d	D
E5e	D
E5f	D
E5g	D
E5h	D
E5i	D
E5j	D
E5k	D
E5l	D
E5m	D
J14	D
J14a	D
J14a.1	D
J14b	D
J14b.1	D
J14c	D
J14c.1	D
J14c.2	D
J14e	D
J14e.1	D
J14f	D
J14f.1	C

[1447] It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

[1448] The compounds of the present disclosure may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A. Compounds of the present disclosure may inhibit multiple genotypes of HCV.

What is claimed is:

1. A compound of Formula (I)



or a pharmaceutically acceptable salt thereof, wherein

m and n are independently 0, 1, or 2;

o and p are independently 1, 2, or 3;

q and s are independently 0, 1, 2, 3, or 4;

u and v are independently 0, 1, 2, or 3;

each R¹ and R² is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbo-

nyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $\text{—NR}^a\text{R}^b$, $(\text{NR}^a\text{R}^b)\text{alkyl}$, and $(\text{NR}^a\text{R}^b)\text{carbonyl}$; R^3 and R^4 are each independently selected from hydrogen and $\text{R}^9\text{—C(O)—}$, and $\text{R}^9\text{—C(S)—}$;

each R^5 and R^6 is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $\text{—NR}^a\text{R}^b$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

R^7 and R^8 are each independently selected from hydrogen, alkoxy, carbonyl, alkyl, arylalkoxy, carboxy, haloalkyl, $(\text{NR}^a\text{R}^b)\text{carbonyl}$, and trialkylsilylalkoxyalkyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxy, carbonyl, alkoxy, carbonylalkyl, alkyl, alkoxy, carbonylalkyl, aryl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclalkenyl, heterocyclalkoxy, heterocyclalkyl, heterocyclalkoxyalkyl, hydroxyalkyl, $\text{—NR}^a\text{R}^d$, $\text{R}^c\text{R}^d\text{alkenyl}$, $(\text{NR}^a\text{R}^d)\text{alkyl}$, and $(\text{NR}^a\text{R}^d)\text{carbonyl}$.

2. A compound selected from

methyl ((1S)-2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(N-(methoxycarbonyl)-L-alanyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-1-methyl-2-oxoethyl)carbamate; dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate;

methyl (2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

methyl ((1R)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-acetyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(5-(3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

N-((1S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-acetamido-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)acetamide;

tert-butyl ((1S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl-

yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

(2S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-amino-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-3-methyl-1-oxo-2-butanamine;

N-((1S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((cyclopropylcarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)cyclopropanecarbamate;

tert-butyl ((1R)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((tert-butoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

N-((1R)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-acetamido-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)acetamide;

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))di(2-pyrimidinamine);

methyl ((1S)-1-((6S)-6-(4-(4'-(2-((6S)-5-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl (2-((6S)-6-(4-(4'-(2-((6S)-5-((methoxycarbonyl)amino)acetyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((6S)-6-(4-(4'-(2-((6S)-5-(N-(methoxycarbonyl)-L-alanyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)-1-methyl-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(6S)-5-azaspiro[2.4]heptane-6,5-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate;

methyl ((1R)-1-((6S)-6-(4-(4'-(2-((6S)-5-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(6S)-5-azaspiro[2.4]heptane-6,5-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

methyl ((1R)-1-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((2S)-1-oxo-1,2-butanediyl)))biscarbamate;

methyl 2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(((methoxycarbonyl)amino)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl 2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((methoxycarbonyl)amino)-2-methylpropanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(N-(methoxycarbonyl)-L-alanyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

4,4'-(4,4'-biphenyldiyl)bis(2-((2S,5S)-5-methyl-1-(3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazole);

4,4'-(4,4'-biphenyldiyl)bis(2-((2S,5S)-5-methyl-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazole);

(2R,2'R)-1,1'-(4,4'-biphenyldiyl)bis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)))bis(3-methyl-1-oxo-2-butanol);

(2S,2'S)-1,1'-(4,4'-biphenyldiyl)bis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)))bis(3-methyl-1-oxo-2-butanol);

2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-4-(4'-(2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole;

tert-butyl 2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-4-(1,3-dioxan-2-ylmethyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl 2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-4-(1,3-dioxolan-2-ylmethyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl 2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-5-(2-methoxy-2-oxoethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl 2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-5-propyl-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

ethyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazole-4-carboxylate;

tert-butyl 2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-3'-fluoro-4-biphenyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinecarboxylate;

2-((2S)-4,4-difluoro-2-pyrrolidinyl)-4-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazole;

(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-(2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

1-((1R)-2-((2S)-2-(4-(4'-(4-methyl-2-((2S)-1-(2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

methyl ((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-(2R)-2-(methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-methyl-1H-imidazol-

5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-methyl-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

(1R,1'R)-2,2'-(4,4'-biphenyldiyl)bis((4-methyl-1H-imidazole-5,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

(1R,1'R)-2,2'-(4,4'-biphenyldiyl)bis((4-methyl-1H-imidazole-5,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

1,1'-(4,4'-biphenyldiyl)bis((4-methyl-1H-imidazole-5,2-diyl)(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy))dipiperidine;

dimethyl 4,4'-biphenyldiylbis((4-methyl-1H-imidazole-5,2-diyl)(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediy))biscarbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-5-methyl-1H-imidazol-4-yl)-4-biphenyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4-methyl-1H-imidazol-5-yl)-4-biphenyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-5-methyl-1H-imidazol-4-yl)-4-biphenyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(1,3-dioxan-2-ylmethyl)-5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(4-(2,2-dimethoxyethyl)-5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(2,2-dimethoxyethyl)-5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl 2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-5-yl)acetate;

methyl 2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-5-yl)acetate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-propyl-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-5-propyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-5-propyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-4,4-difluoro-2-(4-(3'-fluoro-4'-(2-((2S)-1-((2S)-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4,4-difluoro-2-pyrrolidinyl)-1H-imidazol-4-yl)-3-fluoro-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2S)-2-(4-(hydroxymethyl)-5-(4'-(2-((2S)-1-((2S)-2-(methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(4-(hydroxymethyl)-2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))di(2-pyrimidinamine);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))di(2-pyrimidinamine);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-1-oxo-1,2-propanediyl)))di(2-pyrimidinamine);

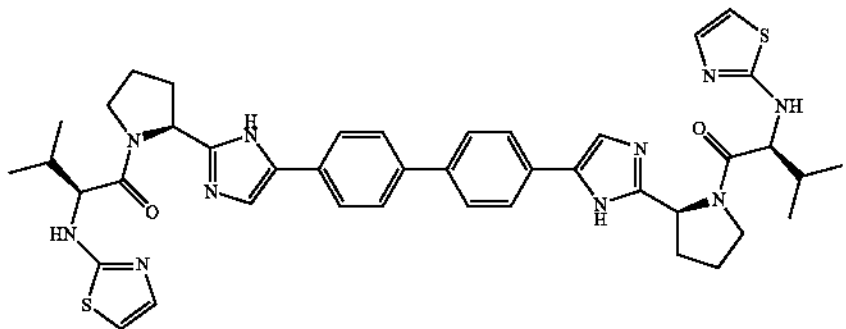
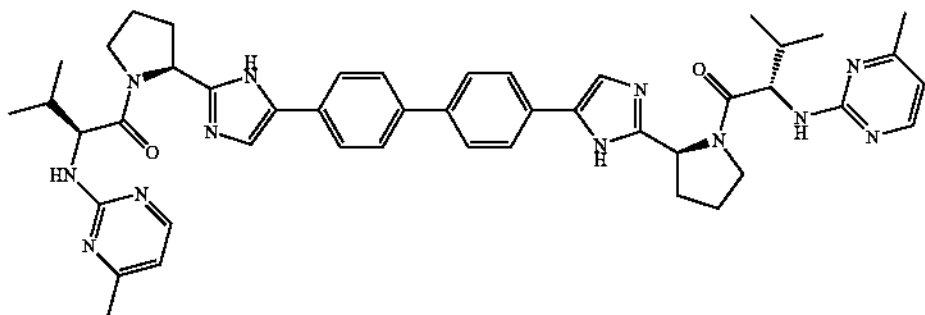
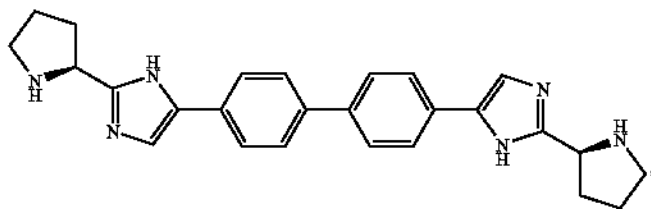
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-1-oxo-1,2-butanediyl)))di(2-pyrimidinamine);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methoxy-1-oxo-1,2-propanediyl)))di(2-pyrimidinamine); and

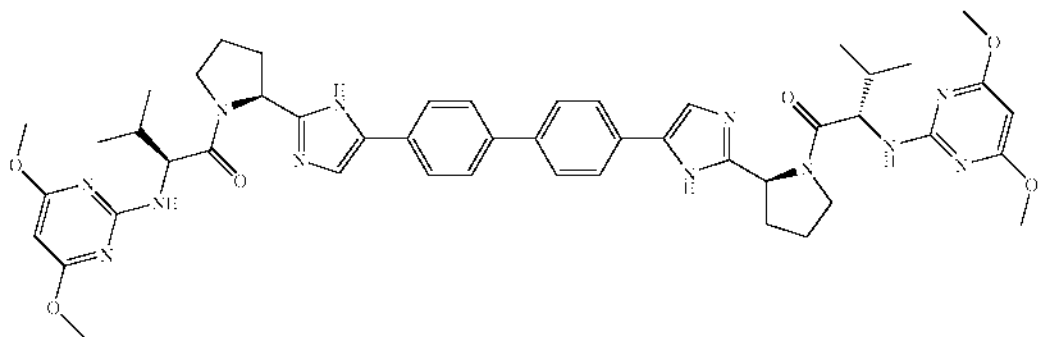
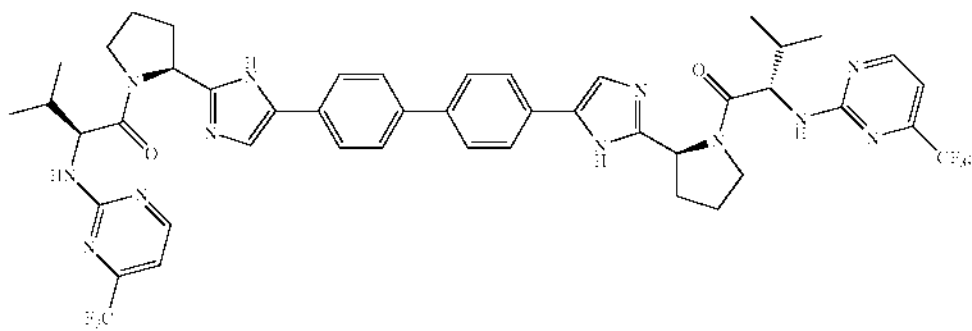
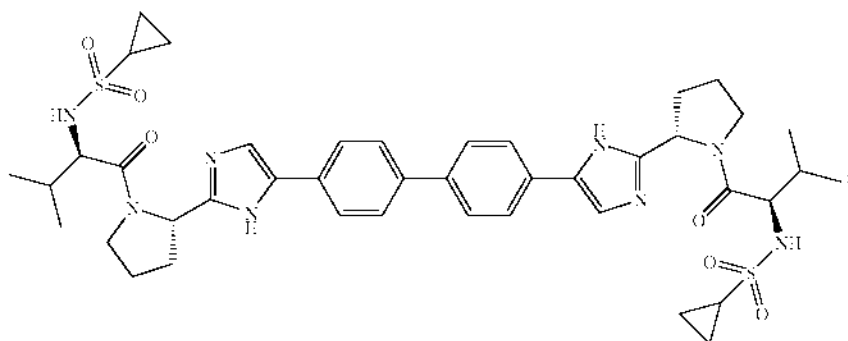
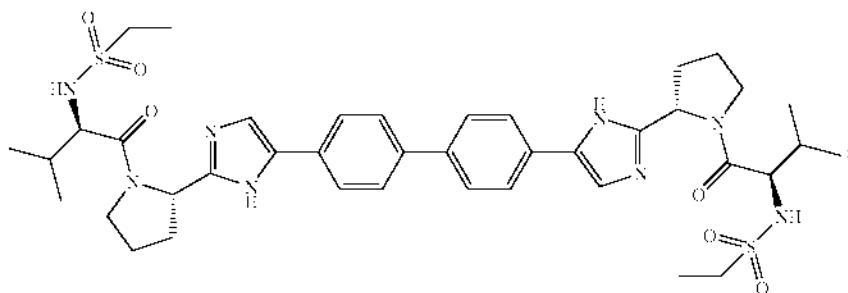
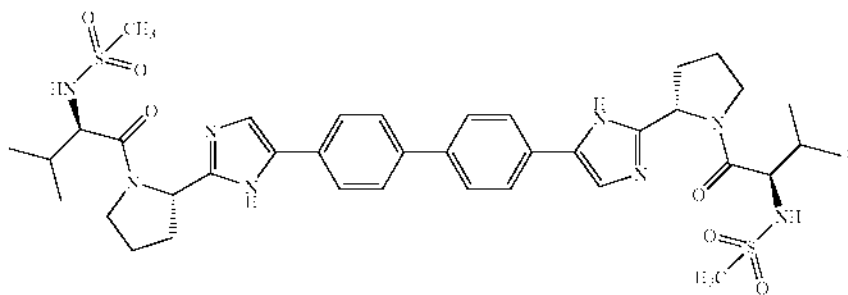
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S,3R)-3-methoxy-1-oxo-1,2-butanediyl)))di(2-pyrimidinamine);

or a pharmaceutically acceptable salt thereof.

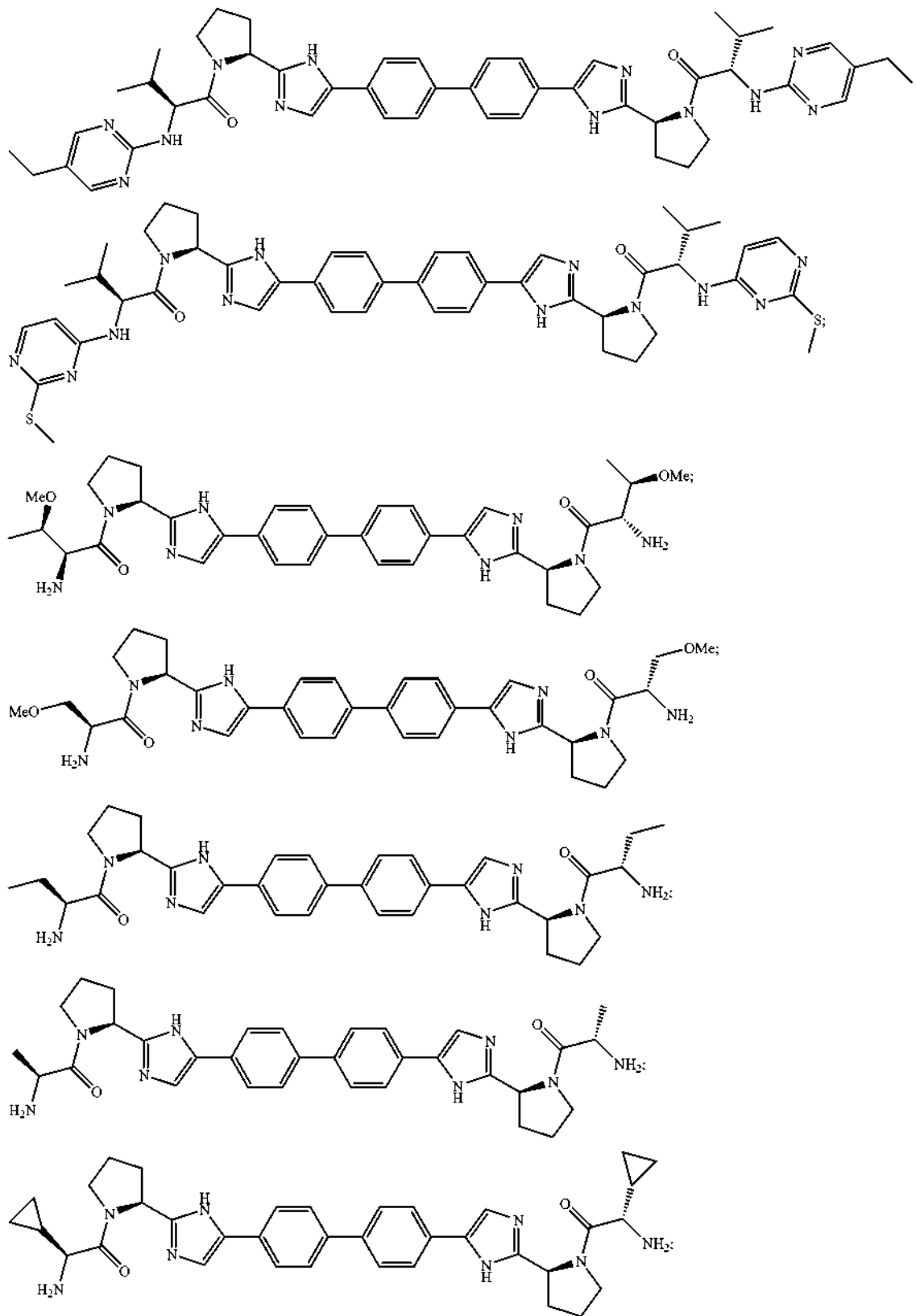
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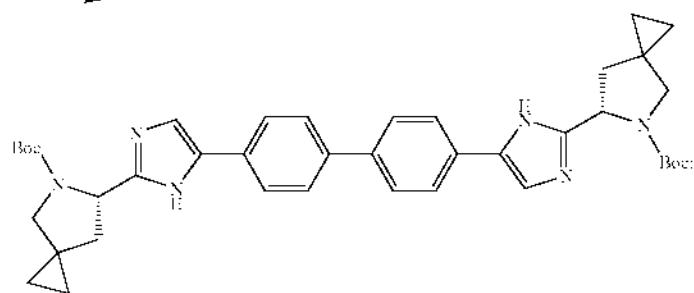
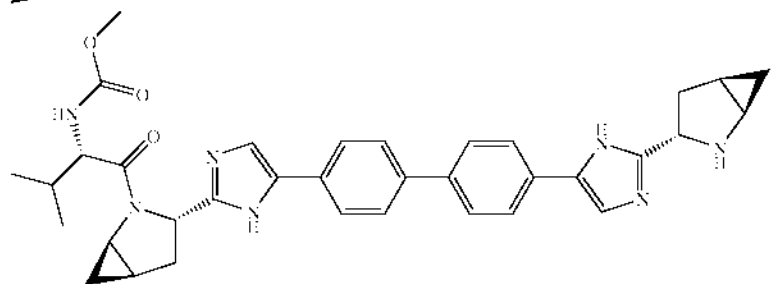
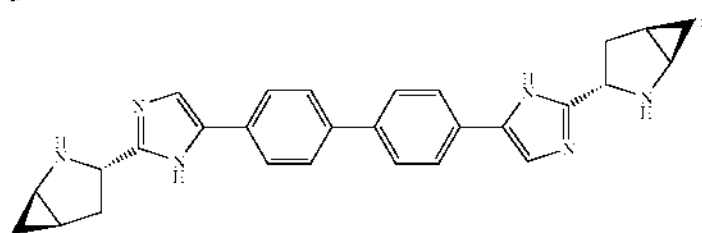
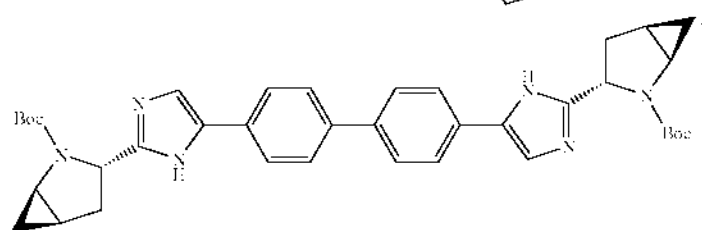
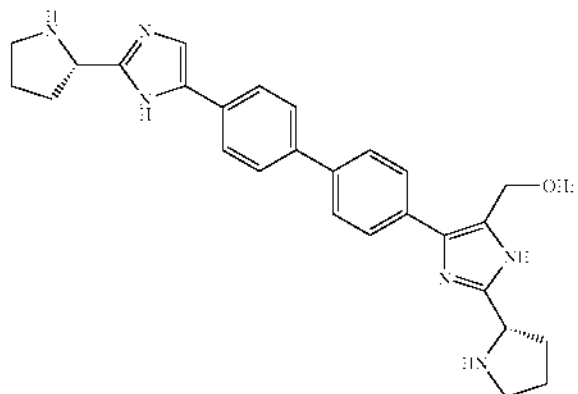
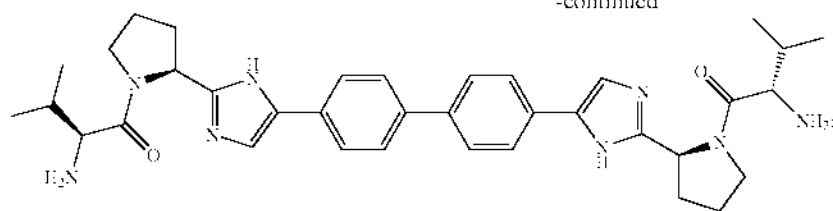
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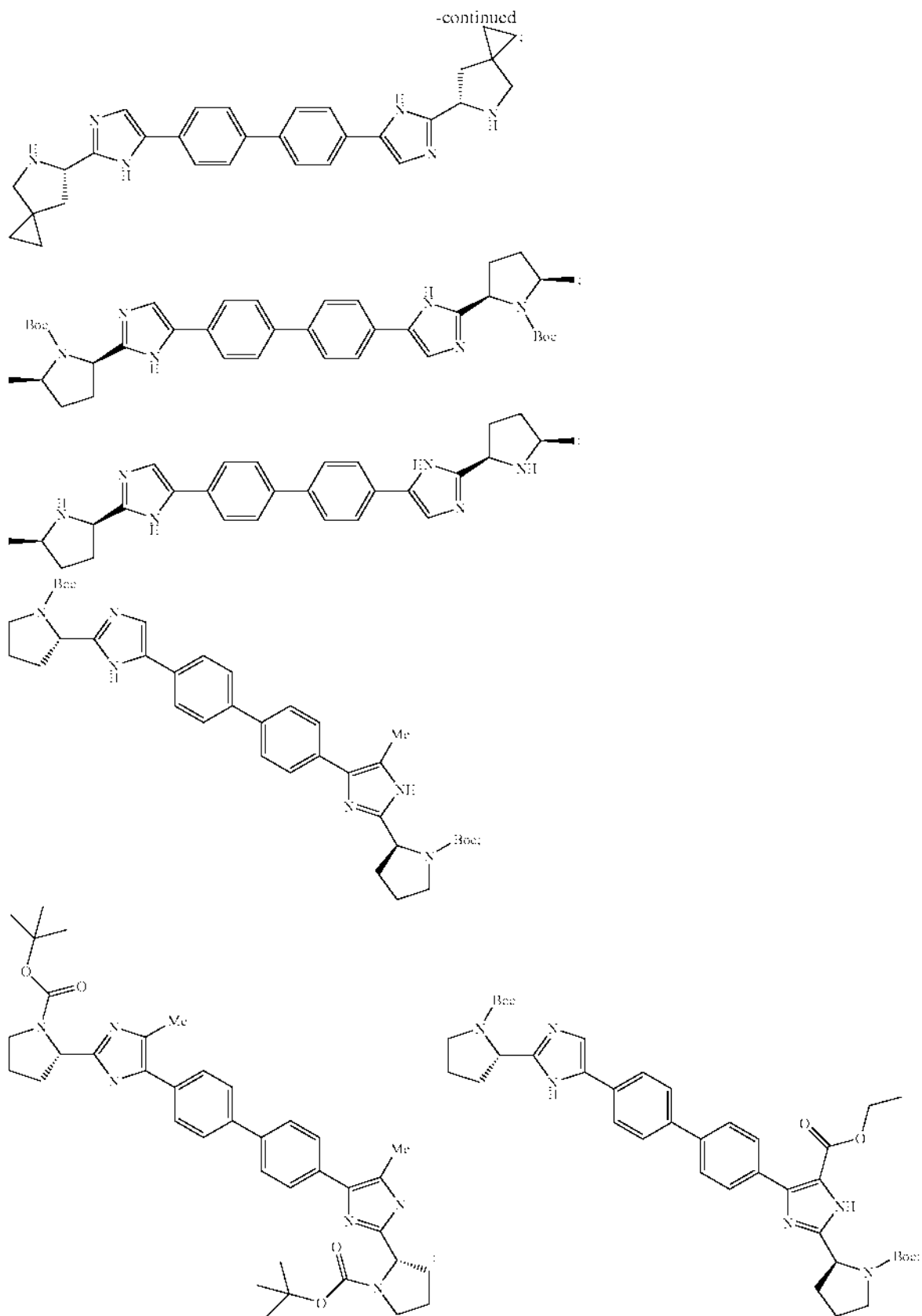


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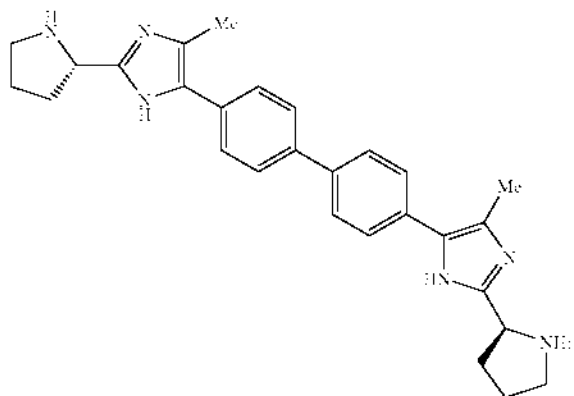
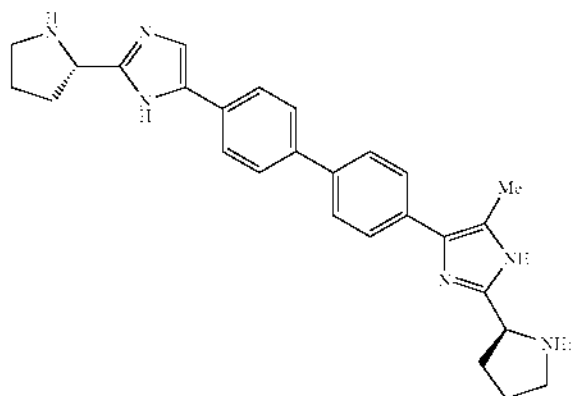
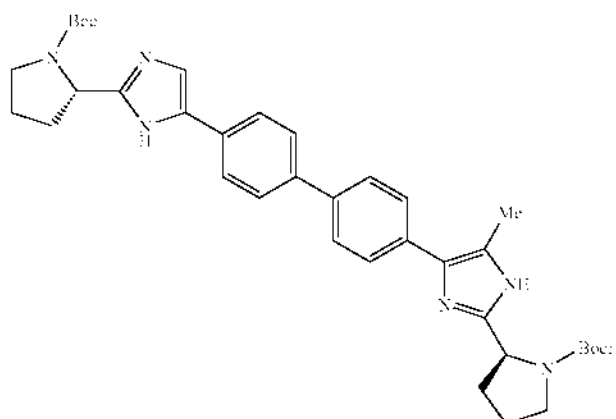
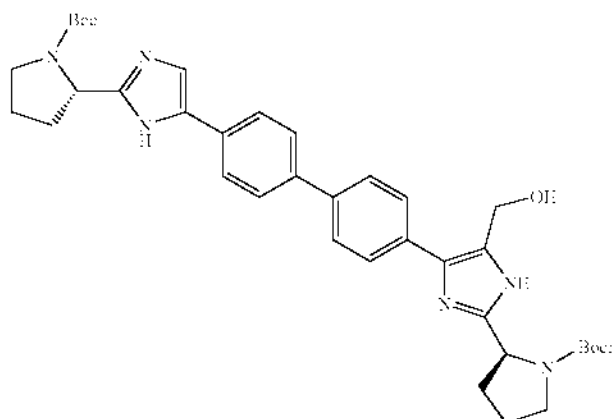


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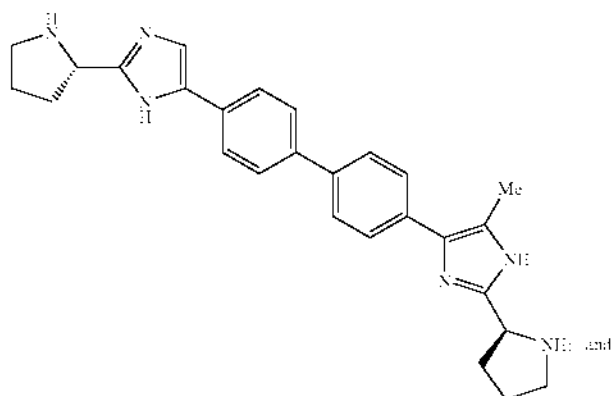
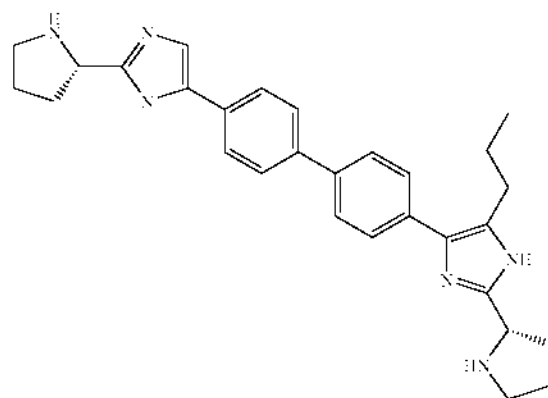
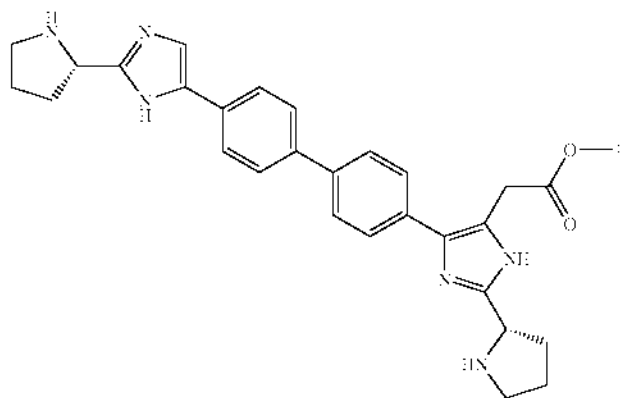
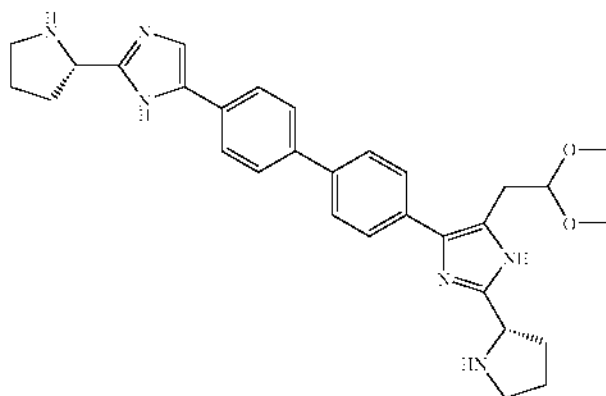
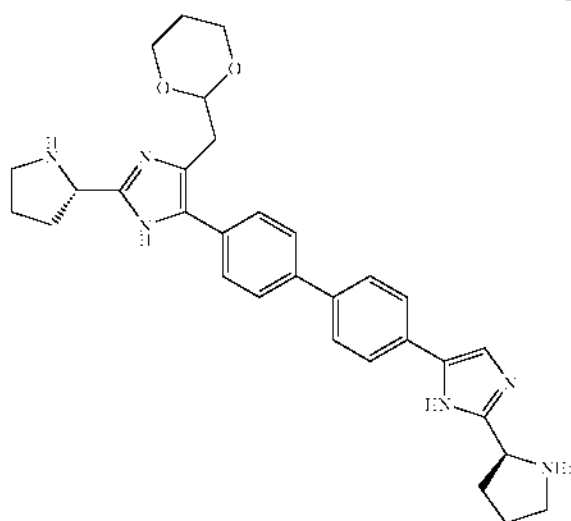




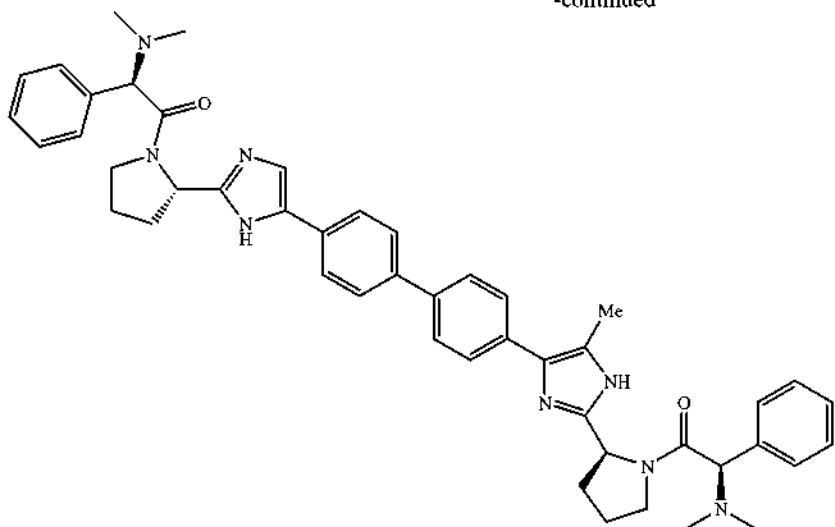
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or a pharmaceutically acceptable salt thereof.

4. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

5. The composition of claim 4 further comprising one or two additional compounds having anti-HCV activity.

6. The composition of claim 5 wherein at least one of the additional compounds is an interferon or a ribavirin.

7. The composition of claim 6 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

8. The composition of claim 5 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

9. The composition of claim 5 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

10. A composition comprising a compound of claim 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

11. The composition of claim 10 further comprising one or two additional compounds having anti-HCV activity.

12. The composition of claim 11 wherein at least one of the additional compounds is an interferon or a ribavirin.

13. The composition of claim 12 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

14. The composition of claim 11 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA,

anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

15. The composition of claim 11 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

16. A composition comprising a compound of claim 3, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. The composition of claim 16 further comprising one or two additional compounds having anti-HCV activity.

18. The composition of claim 17 wherein at least one of the additional compounds is an interferon or a ribavirin.

19. The composition of claim 18 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

20. The composition of claim 17 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

21. The composition of claim 17 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

22. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

23. The method of claim 22 further comprising administering one or two additional compounds having anti-HCV

activity prior to, after or simultaneously with the compound of claim 1, or a pharmaceutically acceptable salt thereof.

24. The method of claim 23 wherein at least one of the additional compounds is an interferon or a ribavirin.

25. The method of claim 24 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

26. The method of claim 23 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

27. The method of claim 23 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

28. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 2, or a pharmaceutically acceptable salt thereof.

29. The method of claim 28 further comprising administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of claim 2, or a pharmaceutically acceptable salt thereof.

30. The method of claim 29 wherein at least one of the additional compounds is an interferon or a ribavirin.

31. The method of claim 30 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

32. The method of claim 29 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the devel-

opment of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

33. The method of claim 29 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

34. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 3, or a pharmaceutically acceptable salt thereof.

35. The method of claim 34 further comprising administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of claim 3, or a pharmaceutically acceptable salt thereof.

36. The method of claim 35 wherein at least one of the additional compounds is an interferon or a ribavirin.

37. The method of claim 36 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

38. The method of claim 35 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

39. The method of claim 35 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

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(54) Title: BRIDGED BICYCLIC SERINE PROTEASE INHIBITORS

(57) Abstract: The present invention relates to peptidomimetic compounds which inhibit serine protease activity, particularly the activity of hepatitis c virus NS3-NS4A protease. As such, they act by interfering with the life cycle of the hepatitis c virus and are also useful as antiviral agents. The compounds of this invention have a bridged bicyclic moiety at the P2 position. The invention further relates to compositions comprising these compounds either for ex vivo use or for administration to a patient suffering from HCV infection. The invention also relates to methods of treating an HCV infection in a patient by administering a composition comprising a compound of this invention.

WO 03/006490 A1

BRIDGED BICYCLIC SERINE PROTEASE INHIBITORS

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TECHNICAL FIELD OF THE INVENTION

The present invention relates to peptidomimetic compounds which inhibit serine protease activity, particularly the activity of hepatitis C virus NS3-NS4A protease. As such, they act by interfering with the life cycle of the hepatitis C virus and are also useful as
10 antiviral agents. The compounds of this invention are characterized by a bridged bicyclic moiety at the P2 position. The invention further relates to compositions comprising these compounds either for ex vivo use or for
15 administration to a patient suffering from HCV infection. The invention also relates to methods of treating an HCV infection in a patient by administering a composition comprising a compound of this invention.

BACKGROUND OF THE INVENTION

20

Infection by hepatitis C virus ("HCV") is a compelling human medical problem. HCV is recognized as the causative agent for most cases of non-A, non-B hepatitis, with an estimated human seroprevalence of 3% globally [A. Alberti et al., "Natural History of
25 Hepatitis C," J. Hepatology, 31., (Suppl. 1), pp. 17-24 (1999)]. Nearly four million individuals may be infected in the United States alone [M..J. Alter et al., "The Epidemiology of Viral Hepatitis in the United States, Gastroenterol. Clin. North Am., 23, pp. 437-455 (1994);
30 M. J. Alter "Hepatitis C Virus Infection in the United States," J. Hepatology, 31., (Suppl. 1), pp. 88-91 (1999)].

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Upon first exposure to HCV only about 20% of infected individuals develop acute clinical hepatitis while others appear to resolve the infection spontaneously. In almost 70% of instances, however, the virus establishes a chronic infection that persists for decades [S. Iwarson, "The Natural Course of Chronic Hepatitis," FEMS Microbiology Reviews, 14, pp. 201-204 (1994); D. Lavanchy, "Global Surveillance and Control of Hepatitis C," J. Viral Hepatitis, 6, pp. 35-47 (1999)]. This usually results in recurrent and progressively worsening liver inflammation, which often leads to more severe disease states such as cirrhosis and hepatocellular carcinoma [M.C. Kew, "Hepatitis C and Hepatocellular Carcinoma", FEMS Microbiology Reviews, 14, pp. 211-220 (1994); I. Saito et. al., "Hepatitis C Virus Infection is Associated with the Development of Hepatocellular Carcinoma," Proc. Natl. Acad. Sci. USA, 87, pp. 6547-6549 (1990)]. Unfortunately, there are no broadly effective treatments for the debilitating progression of chronic HCV.

The HCV genome encodes a polyprotein of 3010-3033 amino acids [Q.-L. Choo, et. al., "Genetic Organization and Diversity of the Hepatitis C Virus." Proc. Natl. Acad. Sci. USA, 88, pp. 2451-2455 (1991); N. Kato et al., "Molecular Cloning of the Human Hepatitis C Virus Genome From Japanese Patients with Non-A, Non-B Hepatitis," Proc. Natl. Acad. Sci. USA, 87, pp. 9524-9528 (1990); A. Takamizawa et. al., "Structure and Organization of the Hepatitis C Virus Genome Isolated From Human Carriers," J. Virol., 65, pp. 1105-1113 (1991)]. The HCV nonstructural (NS) proteins are presumed to provide the essential catalytic machinery for

- 3 -

viral replication. The NS proteins are derived by proteolytic cleavage of the polyprotein [R. Bartenschlager et. al., "Nonstructural Protein 3 of the Hepatitis C Virus Encodes a Serine-Type Proteinase Required for Cleavage at the NS3/4 and NS4/5 Junctions," J. Virol., 67, pp. 3835-3844 (1993); A. Grakoui et. al., "Characterization of the Hepatitis C Virus-Encoded Serine Proteinase: Determination of Proteinase-Dependent Polyprotein Cleavage Sites," J. Virol., 67, pp. 2832-2843 (1993); A. Grakoui et. al., "Expression and Identification of Hepatitis C Virus Polyprotein Cleavage Products," J. Virol., 67, pp. 1385-1395 (1993); L. Tomei et. al., "NS3 is a serine protease required for processing of hepatitis C virus polyprotein", J. Virol., 67, pp. 4017-4026 (1993)].

The HCV NS protein 3 (NS3) contains a serine protease activity that helps process the majority of the viral enzymes, and is thus considered essential for viral replication and infectivity. It is known that mutations in the yellow fever virus NS3 protease decreases viral infectivity [Chambers, T.J. et. al., "Evidence that the N-terminal Domain of Nonstructural Protein NS3 From Yellow Fever Virus is a Serine Protease Responsible for Site-Specific Cleavages in the Viral Polyprotein", Proc. Natl. Acad. Sci. USA, 87, pp. 8898-8902 (1990)]. The first 181 amino acids of NS3 (residues 1027-1207 of the viral polyprotein) have been shown to contain the serine protease domain of NS3 that processes all four downstream sites of the HCV polyprotein [C. Lin et al., "Hepatitis C Virus NS3 Serine Proteinase: *Trans*-Cleavage Requirements and Processing Kinetics", J. Virol., 68, pp. 8147-8157 (1994)].

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The HCV NS3 serine protease and its associated cofactor, NS4A, helps process all of the viral enzymes, and is thus considered essential for viral replication. This processing appears to be analogous to that carried
5 out by the human immunodeficiency virus aspartyl protease, which is also involved in viral enzyme processing HIV protease inhibitors, which inhibit viral protein processing are potent antiviral agents in man, indicating that interrupting this stage of the viral life
10 cycle results in therapeutically active agents. Consequently it is an attractive target for drug discovery.

Several potential HCV protease inhibitors have been described in the prior art [PCT publication Nos. WO
15 00/09558, WO 00/09543, WO 99/64442, WO 99/07733, WO 99/07734, WO 99/50230, WO 98/46630, WO 98/17679 and WO 97/43310, United States Patent 5,990,276, M. Llinas-Brunet et al., Bioorg. Med. Chem. Lett., 8, pp. 1713-18 (1998); W. Han et al., Bioorg. Med. Chem. Lett., 10, 711-
20 13 (2000); R. Dunsdon et al., Bioorg. Med. Chem. Lett., 10, pp. 1571-79 (2000); M. Llinas-Brunet et al., Bioorg. Med. Chem. Lett., 10, pp. 2267-70 (2000); and S. LaPlante et al., Bioorg. Med. Chem. Lett., 10, pp. 2271-74 (2000)]. Unfortunately, there are no serine protease
25 inhibitors available currently as anti-HCV agents.

Furthermore, the current understanding of HCV has not led to any other satisfactory anti-HCV agents or treatments. The only established therapy for HCV disease is interferon treatment. However, interferons have
30 significant side effects [M. A. Wlaker et al., "Hepatitis C Virus: An Overview of Current Approaches and Progress," DDT, 4, pp. 518-29 (1999); D. Moradpour et

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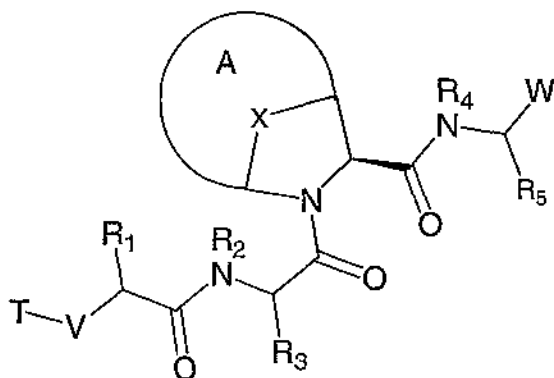
al., "Current and Evolving Therapies for Hepatitis C,"
Eur. J. Gastroenterol. Hepatol., 11, pp. 1199-1202
(1999); H. L. A. Janssen et al. "Suicide Associated with
Alfa-Interferon Therapy for Chronic Viral Hepatitis," J.
5 Hepatol., 21, pp. 241-243 (1994); P.F. Renault et al.,
"Side Effects of Alpha Interferon," Seminars in Liver
Disease, 9, pp. 273-277. (1989)] and induce long term
remission in only a fraction (~ 25%) of cases [O.
Weiland, "Interferon Therapy in Chronic Hepatitis C Virus
10 Infection" , FEMS Microbiol. Rev., 14, pp. 279-288
(1994)]. Moreover, the prospects for effective anti-HCV
vaccines remain uncertain.

Thus, there is a need for more effective anti-
HCV therapies. Such inhibitors would have therapeutic
15 potential as protease inhibitors, particularly as serine
protease inhibitors, and more particularly as HCV NS3
protease inhibitors. Specifically, such compounds may be
useful as antiviral agents, particularly as anti-HCV
agents.

20

SUMMARY OF THE INVENTION

The present invention solves the problem set
forth above by providing a compound of formula I:



25

(I)

- 6 -

wherein:

A, together with X and the atoms to which X is bound, is a 4- to 7-membered aromatic or non-aromatic ring having up to 4 heteroatoms independently selected from N, NH, O, SO, or SO₂; wherein said ring is optionally fused to a (C6-C10)aryl, (C5-C10)heteroaryl, (C3-C10)cycloalkyl or (C3-C10)heterocyclyl; wherein A has up to 3 substituents selected independently from J;

X is -[CH₂]_o-, -[CJ'J']_o-, -[CH₂]_m-O-, -[CH₂]_m-S(O)₂-,
 10 -[CH₂]_m-SO-, -[CH₂]_m-S-, -[CR₂₀R₂₀]_m-NR₂₁-, or -[CR₂₀R₂₀]_m-NJ''-, wherein:

R₂₁ is hydrogen or -C(O)-O-R₂₂;

o is 1 or 2;

R₂₂ is -(C1-C6)alkyl, -(C2-C6)alkenyl, or
 15 -(C2-C6)alkynyl;

m is 0 or 1;

J is halogen, -OR', -NO₂, -CF₃, -OCF₃, -R', oxo, -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂;

20 J' is halogen, -OR', -NO₂, -CF₃, -OCF₃, -R', -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂;

J'' is -OR', -CF₃, -OCF₃, -R', oxo, -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR',
 25 -SO₂R', -C(O)R', -COOR', or -CON(R')₂, wherein each R' is independently:

hydrogen,

-(C1-C12) aliphatic,

-(C3-C10)cycloalkyl or -cycloalkenyl,

30 -(C1-C12)aliphatic-[(C3-C10)cycloalkyl or -cycloalkenyl],

-(C6-C10)aryl,

- 7 -

- (C1-C12) aliphatic- (C6-C10) aryl,
- (C3-C10) heterocyclyl,
- (C1-C12) aliphatic- (C6-C10) heterocyclyl,
- (C5-C10) -heteroaryl, or
- (C1-C12) -aliphatic- (C5-C10) heteroaryl;

R₁ and R₃ are independently:

- (C1-C12) aliphatic,
- (C3-C10) -cycloalkyl or -cycloalkenyl,
- (C1-C12) -aliphatic- [(C3-C10) -cycloalkyl or

- cycloalkenyl],
- (C6-C10) -aryl,
- (C1-C12) aliphatic- (C6-C10) aryl,
- (C3-C10) -heterocyclyl,
- (C1-C12) aliphatic- (C6-C10) heterocyclyl,
- (C5-C10) heteroaryl, or
- (C1-C12) aliphatic- (C5-C10) heteroaryl,

wherein each of R₁ and R₃ is independently and optionally substituted with up to 3 substituents independently selected from J;

wherein up to 3 aliphatic carbon atoms in R₁ and R₃ may be replaced by a heteroatom selected from O, NH, S, SO, and SO₂ in a chemically stable arrangement;

R₂ and R₄ are independently

- hydrogen,
- (C1-C12) aliphatic,
- (C1-C12) aliphatic- (C3-C10) cycloalkyl, or
- (C1-C12) aliphatic- (C6-C10) aryl,

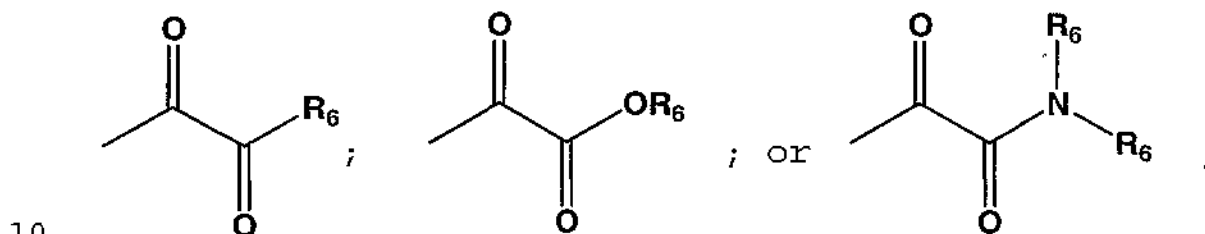
wherein each of R₂ and R₄ is independently and optionally substituted with up to 3 substituents independently selected from J;

- 8 -

wherein up to two aliphatic carbon atoms in R_2 and R_4 may be replaced by a heteroatom selected from O, NH, S, SO, and SO_2 ;

R_5 is -(C1-C12)aliphatic, wherein any hydrogen is
 5 optionally replaced with halogen, and wherein any hydrogen or halogen atom bound to any terminal carbon atom of R_5 is optionally substituted with sulfhydryl or hydroxy;

W is: $-C(O)OH$;



wherein each R_6 is independently:

- hydrogen,
 - (C1-C12)aliphatic,
 - (C6-C10)aryl,
 - 15 -(C6-C10)aryl-(C1-C12)aliphatic,
 - (C3-C10)-cycloalkyl or -cycloalkenyl,
 - (C1-C12)-aliphatic-[(C3-C10)-cycloalkyl or -cycloalkenyl],
 - (C3-C10)heterocyclyl,
 - 20 -(C3-C10)heterocyclyl-(C1-C12)aliphatic,
 - (C5-C10)heteroaryl, or
 - (C1-C12)aliphatic-(C5-C10)heteroaryl, or
- two R_6 groups, which are bound to the same nitrogen atom, form together with that nitrogen atom, a
- 25 -(C3-C10)heterocyclic ring;

wherein R_6 is optionally substituted with up to 3 J substituents or with a suitable electron withdrawing group;

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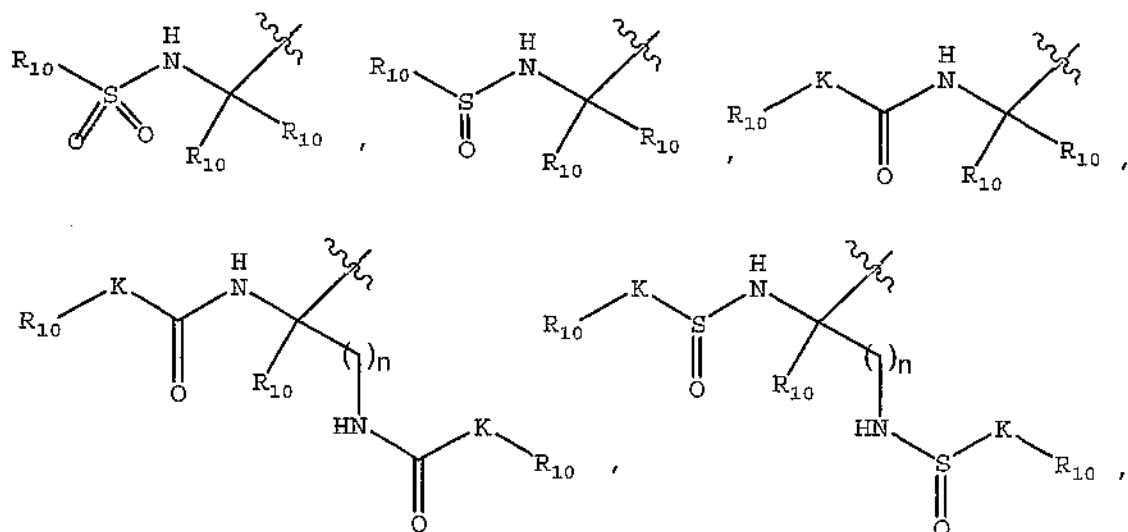
V is $-C(O)N(R_8)-$, $-S(O)N(R_8)-$, $-S(O)_2N(R_8)-$, a bond,
 $-CH(R_8)-$, $-N(R_8)-$, $-O-$, $-O-CH(R_8)-$, $-S-$, $-S-CH(R_8)-$, $-C(O)-$,
 $-C(O)-O-$, $-C(O)-S-$, $-C(O)-CH(R_8)-$, $-S(O)-$, $-S(O)-CH(R_8)-$,
 $-S(O)-N(R_8)-CH(R_8)-$, $-S(O)_2-$, $-S(O)_2-CH(R_8)-$, or $-S(O)_2-N(R_8)-$
 5 $CH(R_8)-$;

wherein R_8 is hydrogen or $-(C1-C12)$ aliphatic;

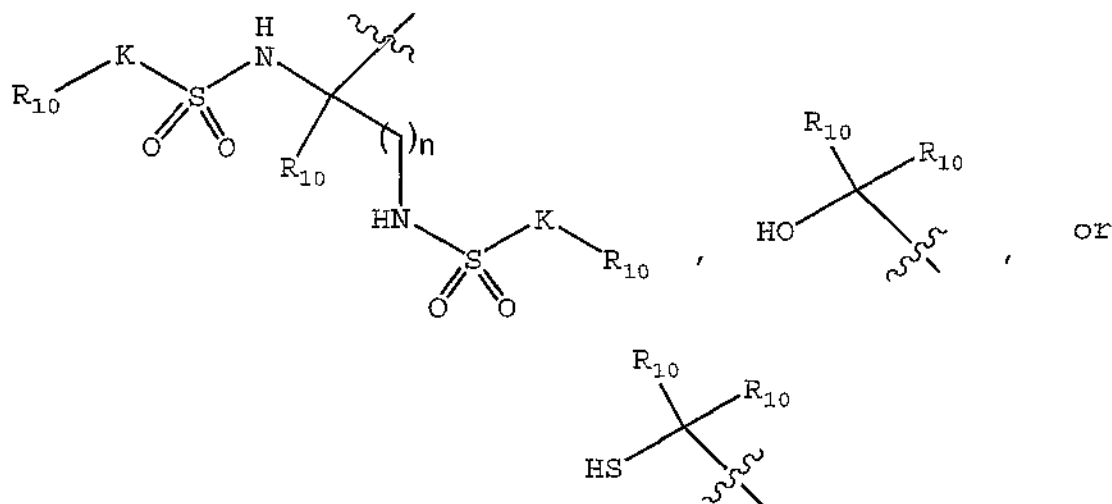
T is:

$-(C6-C10)$ aryl,
 $-(C1-C12)$ aliphatic- $(C6-C10)$ aryl,
 10 $-(C3-C10)$ -cycloalkyl or $-(C3-C10)$ -cycloalkenyl,
 $-(C1-C12)$ aliphatic- $[(C3-C10)$ -cycloalkyl or
 $-(C3-C10)$ -cycloalkenyl],
 $-(C3-C10)$ heterocyclyl,
 $-(C1-C12)$ aliphatic- $(C3-C10)$ heterocyclyl,
 15 $-(C5-C10)$ heteroaryl, or
 $-(C1-C12)$ aliphatic- $(C5-C10)$ heteroaryl; or

T is:



- 10 -



wherein:

R_{10} is:

- 5 hydrogen,
- (C1-C12) aliphatic,
- (C6-C10) aryl,
- (C1-C12) aliphatic- (C6-C10) aryl,
- (C3-C10)-cycloalkyl or -cycloalkenyl,
- 10 - (C1-C12) aliphatic- [(C3-C10)-cycloalkyl or
- cycloalkenyl],
- (C3-C10) heterocyclyl,
- (C1-C12) aliphatic- (C3-C10) heterocyclyl,
- (C5-C10) heteroaryl, or
- 15 - (C1-C12) aliphatic- (C5-C10) heteroaryl,

wherein each T is optionally substituted with up to 3 J substituents;

K is a bond, - (C1-C12) aliphatic, -O-, -S-, -NR₉-, -C(O)-, or -C(O)-NR₉-, wherein R₉ is hydrogen or - (C1-C12) aliphatic;

n is 1-3; and

each R₂₀ is independently hydrogen, - (C1-C6) aliphatic or -O- (C1-C6) aliphatic; or each R₂₀ is taken together

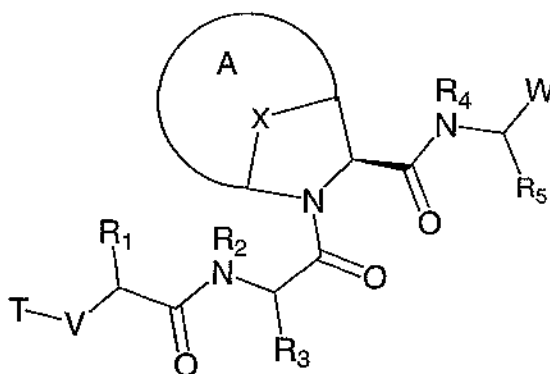
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with the carbon atoms to which they are bound to form a (C3-C6)cycloalkyl.

The invention also relates to compositions that comprise the above compound and the use thereof. Such compositions may be useful to pre-treat invasive devices to be inserted into a patient, to treat biologicals, such as blood, prior to administration to a patient, and for direct administration to a patient. In each case the composition will be used to inhibit HCV replication and to lessen the risk of or the severity of HCV infection.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound of



formula (I):

(I)

wherein:

A, together with X and the atoms to which X is bound, is a 4- to 7-membered aromatic or non-aromatic ring having up to 4 heteroatoms independently selected from N, NH, O, SO, or SO₂; wherein said ring is optionally fused to a (C6-C10)aryl, (C5-C10)heteroaryl, (C3-C10)cycloalkyl or (C3-C10)heterocyclyl; wherein A has up to 3 substituents selected independently from J;

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X is $-\text{[CH}_2\text{]}_o-$, $-\text{[CJ}'\text{J}']_o-$, $-\text{[CH}_2\text{]}_m\text{-O-}$, $-\text{[CH}_2\text{]}_m\text{-S(O)}_2-$,
 $-\text{[CH}_2\text{]}_m\text{-SO-}$, $-\text{[CH}_2\text{]}_m\text{-S-}$, $-\text{[CR}_{20}\text{R}_{20}]_m\text{-NR}_{21}-$, or $-\text{[CR}_{20}\text{R}_{20}]_m\text{-}$
 $\text{NJ}''-$, wherein:

R_{21} is hydrogen or $-\text{C(O)-O-R}_{22}$;

5 o is 1 or 2;

R_{22} is $-(\text{C1-C6})\text{alkyl}$, $-(\text{C2-C6})\text{alkenyl}$, or
 $-(\text{C2-C6})\text{alkynyl}$;

m is 0 or 1;

J is halogen, $-\text{OR}'$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{R}'$, oxo,
 10 $-\text{OR}'$, $-\text{O-benzyl}$, $-\text{O-phenyl}$, 1,2-methylenedioxy, $-\text{N(R}')(2)$,
 $-\text{SR}'$, $-\text{SOR}'$, $-\text{SO}_2\text{R}'$, $-\text{C(O)R}'$, $-\text{COOR}'$, or $-\text{CON(R}')(2)$;

J' is halogen, $-\text{OR}'$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{R}'$, $-\text{OR}'$,
 $-\text{O-benzyl}$, $-\text{O-phenyl}$, 1,2-methylenedioxy, $-\text{N(R}')(2)$, $-\text{SR}'$,
 $-\text{SOR}'$, $-\text{SO}_2\text{R}'$, $-\text{C(O)R}'$, $-\text{COOR}'$, or $-\text{CON(R}')(2)$;

15 J'' is $-\text{OR}'$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{R}'$, oxo, $-\text{OR}'$, $-\text{O-benzyl}$,
 $-\text{O-phenyl}$, 1,2-methylenedioxy, $-\text{N(R}')(2)$, $-\text{SR}'$, $-\text{SOR}'$,
 $-\text{SO}_2\text{R}'$, $-\text{C(O)R}'$, $-\text{COOR}'$, or $-\text{CON(R}')(2)$, wherein each R' is
independently:

hydrogen,

20 $-(\text{C1-C12})\text{ aliphatic}$,
 $-(\text{C3-C10})\text{ cycloalkyl}$ or $-\text{cycloalkenyl}$,
 $-(\text{C1-C12})\text{ aliphatic-}[(\text{C3-C10})\text{ cycloalkyl}$ or
 $-\text{cycloalkenyl}]$,

$-(\text{C6-C10})\text{ aryl}$,

25 $-(\text{C1-C12})\text{ aliphatic-}(\text{C6-C10})\text{ aryl}$,
 $-(\text{C3-C10})\text{ heterocyclyl}$,
 $-(\text{C1-C12})\text{ aliphatic-}(\text{C6-C10})\text{ heterocyclyl}$,
 $-(\text{C5-C10})\text{-heteroaryl}$, or
 $-(\text{C1-C12})\text{-aliphatic-}(\text{C5-C10})\text{ heteroaryl}$;

30 R_1 and R_3 are independently:

$-(\text{C1-C12})\text{ aliphatic}$,

$-(\text{C3-C10})\text{-cycloalkyl}$ or $-\text{cycloalkenyl}$,

- 13 -

-(C1-C12)-aliphatic-[(C3-C10)-cycloalkyl or
-cycloalkenyl],

-(C6-C10)-aryl,

(C1-C12)aliphatic-(C6-C10)aryl,

5 -(C3-C10)-heterocyclyl,

-(C1-C12)aliphatic-(C6-C10)heterocyclyl,

-(C5-C10)heteroaryl, or

-(C1-C12)aliphatic-(C5-C10)heteroaryl,

10 wherein each of R₁ and R₃ is independently and
optionally substituted with up to 3 substituents
independently selected from J;

15 wherein up to 3 aliphatic carbon atoms in R₁ and
R₃ may be replaced by a heteroatom selected from O,
NH, S, SO, and SO₂ in a chemically stable
arrangement;

R₂ and R₄ are independently

hydrogen,

-(C1-C12)aliphatic,

-(C1-C12)aliphatic-(C3-C10)cycloalkyl, or

20 -(C1-C12)aliphatic-(C6-C10)aryl,

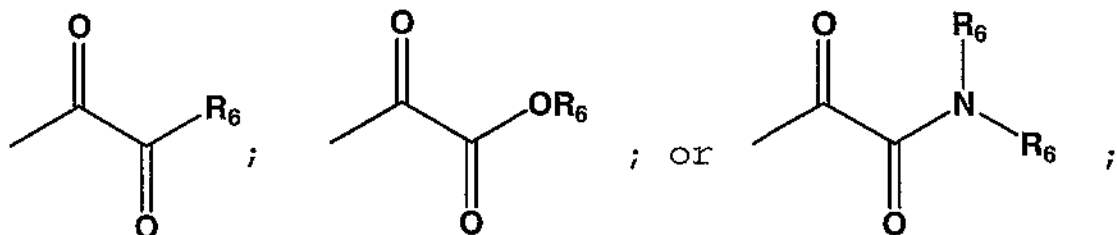
wherein each of R₂ and R₄ is independently and
optionally substituted with up to 3 substituents
independently selected from J;

25 wherein up to two aliphatic carbon atoms in R₂
and R₄ may be replaced by a heteroatom selected from
O, NH, S, SO, and SO₂;

30 R₅ is -(C1-C12)aliphatic, wherein any hydrogen is
optionally replaced with halogen, and wherein any
hydrogen or halogen atom bound to any terminal carbon
atom of R₅ is optionally substituted with sulfhydryl or
hydroxy;

W is: -C(O)OH;

- 14 -



wherein each R_6 is independently:

hydrogen,

-(C1-C12)aliphatic,

5 -(C6-C10)aryl,

-(C6-C10)aryl-(C1-C12)aliphatic,

-(C3-C10)-cycloalkyl or -cycloalkenyl,

-(C1-C12)-aliphatic-[(C3-C10)-cycloalkyl or
-cycloalkenyl],

10 -(C3-C10)heterocyclyl,

-(C3-C10)heterocyclyl-(C1-C12)aliphatic,

-(C5-C10)heteroaryl, or

-(C1-C12)aliphatic-(C5-C10)heteroaryl, or

15 two R_6 groups, which are bound to the same nitrogen
atom, form together with that nitrogen atom, a

-(C3-C10)heterocyclic ring;

wherein R_6 is optionally substituted with up to 3 J
substituents or with a suitable electron withdrawing
group;

20 V is -C(O)N(R_8)-, -S(O)N(R_8)-, -S(O)₂N(R_8)-, a bond,
-CH(R_8)-, -N(R_8)-, -O-, -O-CH(R_8)-, -S-, -S-CH(R_8), -C(O)-,
-C(O)-O-, -C(O)-S-, -C(O)-CH(R_8)-, -S(O)-, -S(O)-CH(R_8),
-S(O)-N(R_8)-CH(R_8), -S(O)₂-, -S-(O)₂-CH(R_8)-, or -S(O)₂-N(R_8)-
CH(R_8);

25 wherein R_8 is hydrogen or -(C1-C12)aliphatic;

T is:

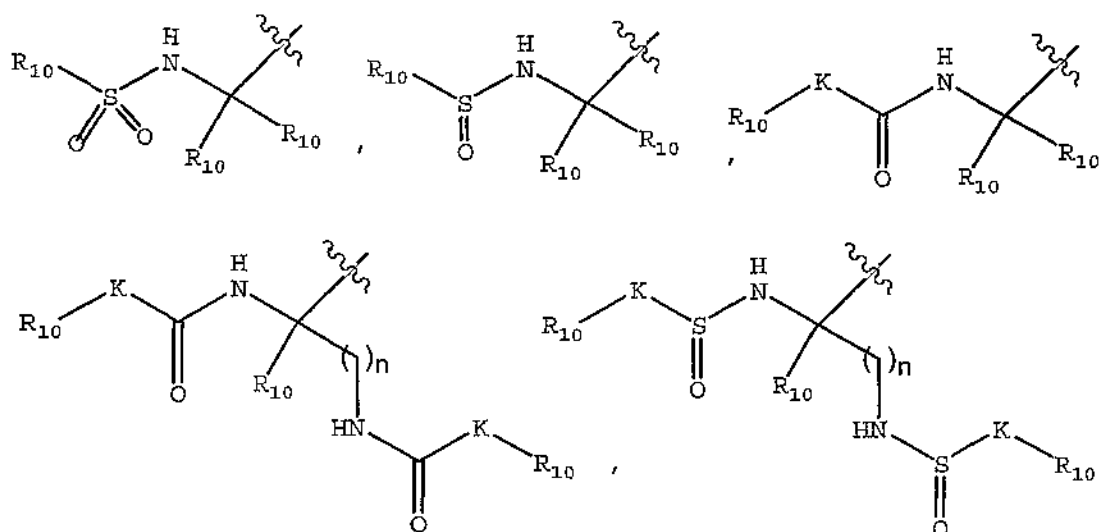
-(C6-C10)aryl,

-(C1-C12)aliphatic-(C6-C10)aryl,

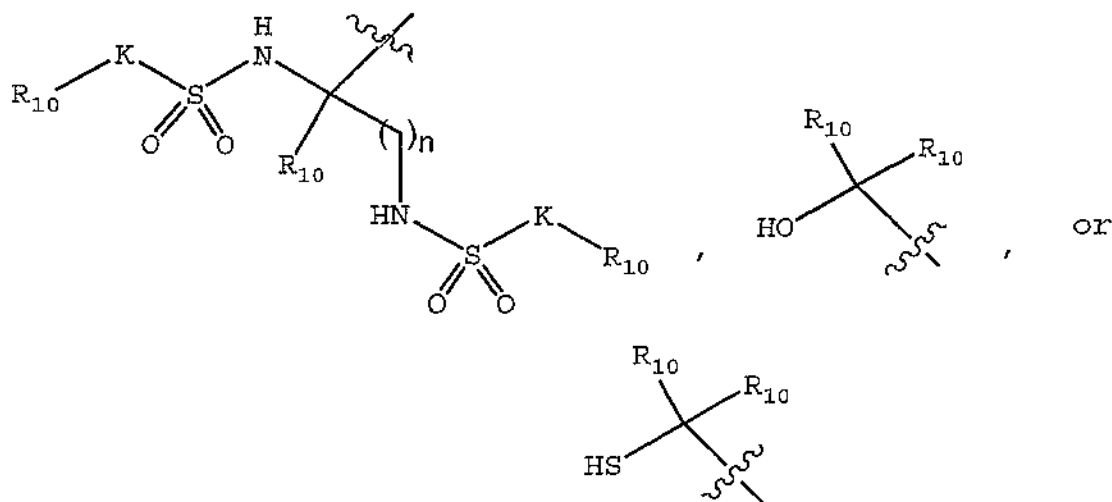
- 15 -

- (C3-C10)-cycloalkyl or -cycloalkenyl,
- (C1-C12)aliphatic-[(C3-C10)-cycloalkyl or
- cycloalkenyl],
- (C3-C10)heterocyclyl,
- 5 - (C1-C12)aliphatic-(C3-C10)heterocyclyl,
- (C5-C10)heteroaryl, or
- (C1-C12)aliphatic-(C5-C10)heteroaryl; or

T is:



10



wherein:

R₁₀ is:

- 16 -

hydrogen,
 - (C1-C12) aliphatic,
 - (C6-C10) aryl,
 - (C1-C12) aliphatic- (C6-C10) aryl,
 5 - (C3-C10)-cycloalkyl or -cycloalkenyl,
 - (C1-C12) aliphatic- [(C3-C10)-cycloalkyl or
 -cycloalkenyl],
 - (C3-C10) heterocyclyl,
 - (C1-C12) aliphatic- (C3-C10) heterocyclyl,
 10 - (C5-C10) heteroaryl, or
 - (C1-C12) aliphatic- (C5-C10) heteroaryl,

wherein each T is optionally substituted with up to
 3 J substituents;

K is a bond, - (C1-C12) aliphatic, -O-, -S-, -NR₉-,
 15 -C(O)-, or -C(O)-NR₉-, wherein R₉ is hydrogen or - (C1-
 C12) aliphatic;

n is 1-3; and

each R₂₀ is independently hydrogen, - (C1-C6) aliphatic
 or -O- ((C1-C6) aliphatic); or each R₂₀ is taken together
 20 with the carbon atoms to which they are bound to form a
 (C3-C6) cycloalkyl.

DEFINITIONS

The term "aryl" as used herein means a
 monocyclic or bicyclic carbocyclic aromatic ring system.
 25 Phenyl is an example of a monocyclic aromatic ring
 system. Bicyclic aromatic ring systems include systems
 wherein both rings are aromatic, e.g., naphthyl, and
 systems wherein only one of the two rings is aromatic,
 e.g., tetralin.

30 The bond "---" refers to an optionally present
 bond.

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The term "heterocyclyl" as used herein means a monocyclic or bicyclic non-aromatic ring system having up to 4, and preferably 1 to 3, heteroatom or heteroatom groups in each ring selected from O, N, NH, S, SO, or SO₂ in a chemically stable arrangement. In a bicyclic non-aromatic ring system embodiment of "heterocyclyl" one or both rings may contain said heteroatom or heteroatom groups.

Heterocyclic rings include 3-1H-benzimidazol-2-one, 3-(1-alkyl)-benzimidazol-2-one, 2-tetrahydrofuran-3-yl, 2-tetrahydrofuran-3-yl, 2-tetrahydrothiophen-3-yl, 3-tetrahydrothiophen-2-yl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidin-2-yl, 2-pyrrolidin-3-yl, 1-pyrrolidin-3-yl, 1-tetrahydropiperazin-2-yl, 2-tetrahydropiperazin-3-yl, 3-tetrahydropiperazin-1-yl, 1-piperidin-2-yl, 2-piperidin-3-yl, 3-piperidin-1-yl, 1-pyrazolin-3-yl, 4-pyrazolin-5-yl, 1-piperidin-2-yl, 2-piperidin-3-yl, 3-piperidin-4-yl, 2-thiazolidin-3-yl, 3-thiazolidin-4-yl, 1-imidazolidin-2-yl, 4-imidazolidin-5-yl, 1-imidazolidin-2-yl, indol-3-yl, tetrahydroquinolin-3-yl, tetrahydroisoquinolin-3-yl, benzothiolane, and benzodithiane.

The term "heteroaryl" as used herein means a monocyclic or bicyclic aromatic ring system having up to 4, and preferably 1 to 3, heteroatom or heteroatom groups in each ring selected from O, N, NH or S in a chemically stable arrangement. In such a bicyclic aromatic ring system embodiment of "heteroaryl":

- one or both rings may be aromatic; and

- 18 -

- one or both rings may contain said heteroatom or heteroatom groups.

Heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, benzimidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (e.g., 5-tetrazolyl), triazolyl (e.g., 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl), pyrazolyl (e.g., 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, purinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

Each of the above aryl, heterocyclyl or heteroaryl above may contain up to 3 substituents independently selected from halogen, -OR', -NO₂, -CF₃, -OCF₃, -R', oxo, -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -C(O)R', -COOR' or -CON(R')₂, wherein R' is independently selected from H, (C1-C6)-alkyl, (C2-C6)-alkenyl or alkynyl.

The term "aliphatic" as used herein means a straight chained or branched alkyl, alkenyl or alkynyl. It is understood that alkenyl or alkynyl embodiments need at least two carbon atoms in the aliphatic chain.

The term "cycloalkyl or cycloalkenyl" refers to a monocyclic or fused or bridged bicyclic carbocyclic

- 19 -

ring system that is not aromatic. Cycloalkenyl rings have one or more units of unsaturation. Preferred cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, nornbornyl, adamantyl and decalin-yl.

The phrase "chemically stable arrangement" as used herein refers to a compound structure that renders the compound sufficiently stable to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive condition, for at least a week.

According to a preferred embodiment, ring A together with X and the atoms to which X is bound, has up to 3 heteroatoms independently selected from N, NH, O, SO, and SO₂.

According to a preferred embodiment, ring A together with X and the atoms to which X is bound, is a 3-6 membered carbocyclic non-aromatic or aromatic ring. More preferably, ring A, together with X and the atoms to which X is bound, is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or phenyl. Even more preferably, ring A, together with X and the atoms to which X is bound, is cyclohexyl or cyclopentyl. Most preferably, ring A, together with X and the atoms to which X is bound, is cyclohexyl.

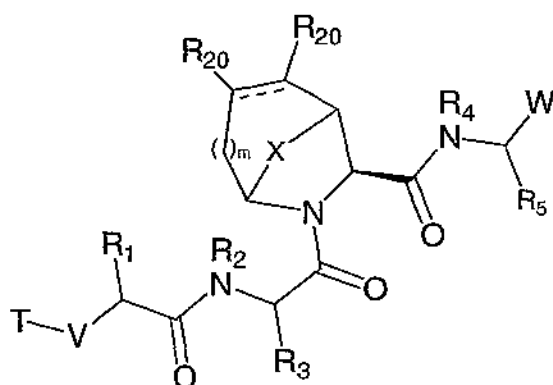
According to another preferred embodiment, ring A, together with X and the atoms to which X is bound, is a 3-6 membered heterocyclic ring. More preferably, ring A together with X and the atoms to which X is bound, is a 5-6 membered heterocyclic ring.

- 20 -

According to another preferred embodiment, ring A together with X and the atoms to which X is bound, is a 5-6 membered heteroaryl ring.

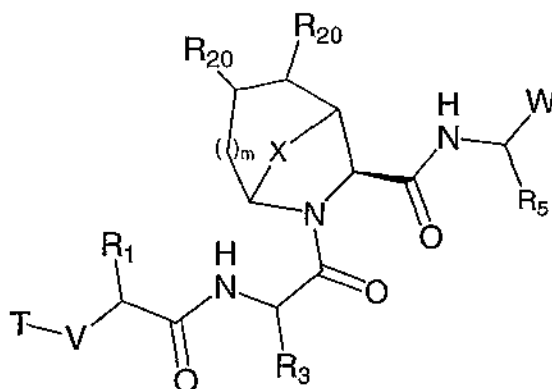
According to yet another preferred embodiment,
 5 ring A, together with X and the atoms to which X is bound, is fused to a (C6-C10)aryl, (C5-C10)heteroaryl, (C3-C10)cycloalkyl or (C3-C10)-heterocyclyl.
 Preferably, ring A together with X and the atoms to which X is bound, is fused to cyclohexyl, cyclopentyl, phenyl
 10 or pyridyl.

According to a preferred embodiment, compounds of the present invention have formula (IA):



wherein T, V, R₁, R₂, R₃, R₄, R₅, R₂₀, X, W, and m
 15 are as defined herein.

According to another preferred embodiment, compounds of the present invention have formula (IB):



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wherein T, V, R₁, R₃, R₅, R₂₀, X, W and m are as defined herein.

According to a preferred embodiment, V is -NH-.

According to another preferred embodiment, V is
5 -C(O)-.

According to another preferred embodiment, R₅ is C2-C3 alkyl substituted with 1-3 chlorine or fluorine.

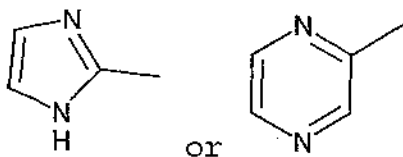
According to yet another preferred embodiment T or R⁶ is a heterocyclyl or heteroaryl, optionally having
10 up to 3 substituents as defined above.

According to yet another preferred embodiment, T is a -(C5-C10)heteroaryl.

According to yet another preferred embodiment, T is selected from 3-1H-benzimidazol-2-one, 3-(1-alkyl)-
15 benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, pyrazolinyl, 1,3-dihydro-imidazol-2-one, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 5-
20 tetrazolyl, pyrazolyl, pyrazinyl or 1,3,5-triazinyl.

Even more preferably, T or R⁷ is 3-1H-benzimidazol-2-one, 3-(1-alkyl)-benzimidazol-2-one,)²-pyrazolinyl, 1,3-dihydro-imidazol-2-one, 2-imidazolyl, 2-pyrrolyl, 2-pyrimidinyl, 5-pyrimidinyl, 5-tetrazolyl or
25 pyrazinyl.

Most preferred is when T or R⁷ is selected from:



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Preferred substituents on T or R⁷ in the above embodiments are halogen, -CF₃, -OCF₃, oxo, -COOR' or -CON(R')₂, wherein R' is as defined above.

In another preferred embodiment of the present invention, R¹ is -CH₂-CH(CH₃)-CH₃, -C(CH₃)₃, -CH(CH₃)₂,
5 -CH(CH₃)-CH₂-CH₃ or cyclohexyl. Most preferably R¹ is cyclohexyl.

According to another preferred embodiment, R₃ is selected from -C(CH₃)₂, -CH(CH₃)₂, -CH(CH₃)-CH₂-CH₃ or
10 cyclohexyl. More preferably, R₃ is selected from -C(CH₃)₃, or -CH(CH₃)₂.

According to yet another preferred embodiment, each R₂ is independently selected from -CH₃ or hydrogen. Even more preferred is when R₂ is hydrogen.

15 According to another preferred embodiment, R₅ is -CH₂CH₂CH₃, -CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂F, -CH₂CH₂CHF₂, or -CH₂CH₂CF₃. More preferred is when R₅ is -CH₂CH₂CH₂CH₃ or -CH₂CH₂CHF₂. Most preferably R₅ is -CH₂CH₂CH₂CH₃.

According to another preferred embodiment, R₅ is
20 -CH₂CH₃, -CH₂CH₂CH₃, -CH₂CH₂F, -CH₂CHF₂, or -CH₂CF₃. More preferred is when R₅ is -CH₂CH₂CH₃, or -CH₂CHF₂. Most preferably R₅ is -CH₂CH₂CH₃.

According to a preferred embodiment, W is -C(O)-C(O)-R₆. Preferably, R₆ is isopropyl.

25 According to another preferred embodiment, W is -C(O)-C(O)-OR₆. Preferably, R₆ is hydrogen, (C1-C12)-aliphatic, (C6-C10)-aryl, (C3-C10)-cycloalkyl or -cycloalkenyl, (C3-C10)-heterocyclyl or (C5-C10)heteroaryl. More preferably, R₆ is H or methyl.

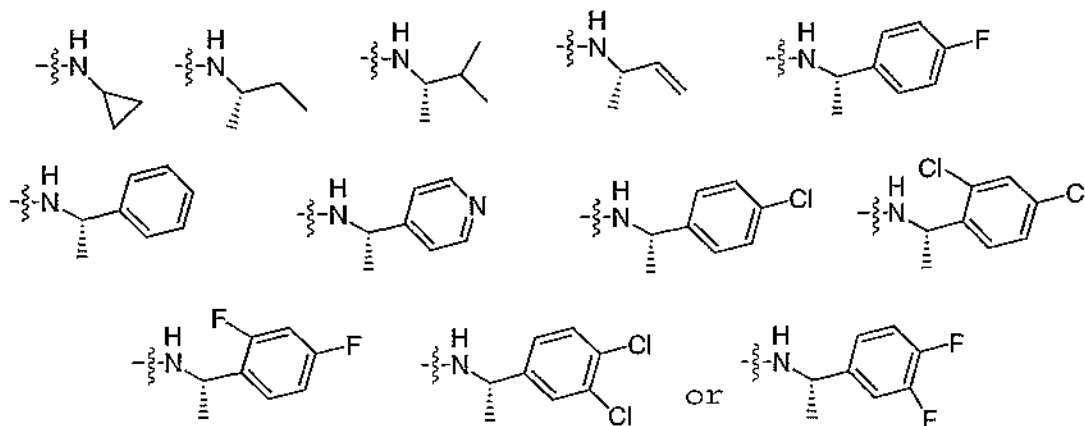
- 23 -

According to another preferred embodiment, W is $-C(O)-C(O)-N(R_6)_2$. Preferably, R_6 is hydrogen, (C3-C10)-cycloalkyl or -cycloalkenyl, or (C3-C10)-heterocyclyl.

In another preferred embodiment of formula I is
 5 where W is $C(O)-C(O)-N(R_6)_2$, the NR_6R_6 portion of the W moiety is $-NH-(C3-C6)$ cycloalkyl, $-NH-CH(CH_3)-(C6-C10)$ aryl or $-NH-CH(CH_3)-(C3-C10)$ heterocyclyl, or $-NH-CH(CH_3)-(C5-C10)$ heteroaryl, wherein said aryl, heterocyclyl, or heteroaryl is optionally substituted with halogen.

10 Alternatively, the NR_6R_6 portion is $-NH-(C3-C6)$ cycloalkyl, $-NH-CH(CH_3)-(C6-C10)$ aryl, or $-NH-CH(CH_3)-(C5-C10)$ heteroaryl, wherein said aryl or said heterocyclyl is optionally substituted with halogen; or NR_6R_6 is $-NH-(C3-C6)$ cycloalkyl, $-NH-CH(CH_3)-(C6-C10)$ aryl,
 15 or $-NH-CH(CH_3)-(C3-C10)$ heterocyclyl, wherein said aryl or said heterocyclyl is optionally substituted with halogen.

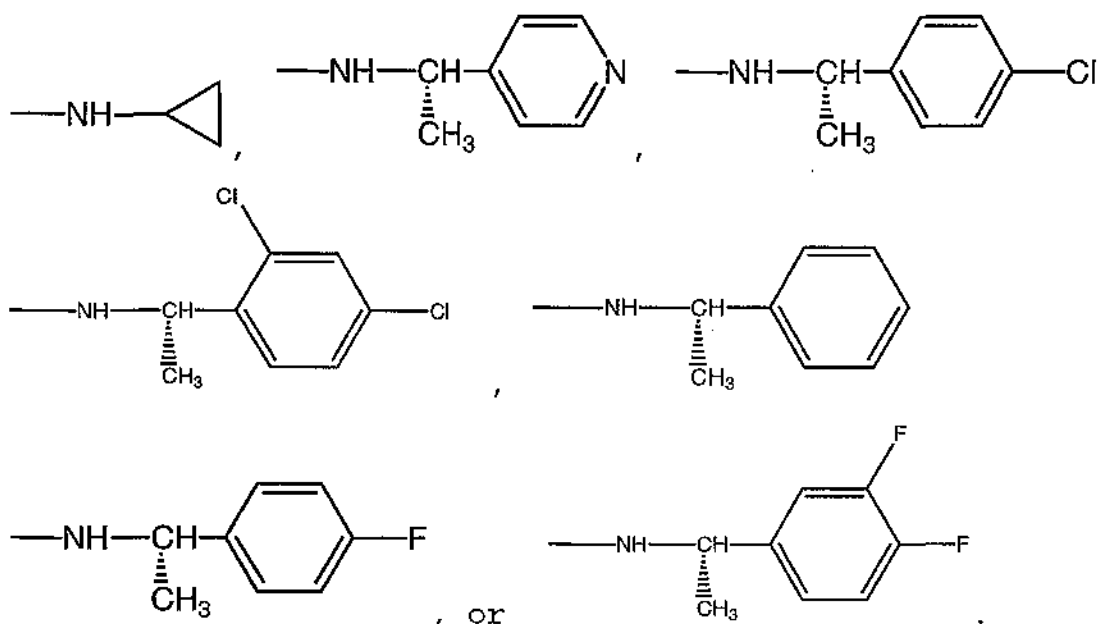
In other preferred embodiment of formula I, NR_6R_6 in W is:



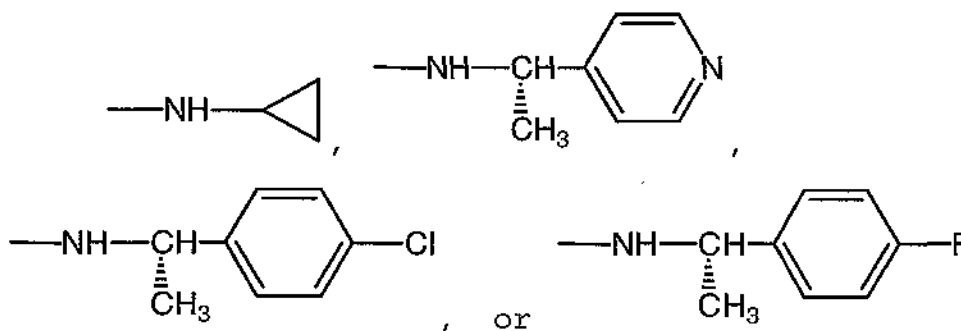
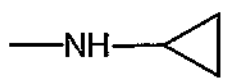
20

More preferably, NR_6R_6 is:

- 24 -



5

Even more preferably, NR_6R_6 is:Most preferably, NR_6R_6 is:

10

In a preferred embodiment of the present invention, X is $-[CH_2]_o-$, $-[CJ'J']_o-$, $-[CH_2]_m-O-$, $-[CH_2]_m-S(O)_2-$, $-[CH_2]_m-SO-$, $-[CR_{20}R_{20}]_m-NR_{21}-$, or $-[CR_{20}R_{20}]_m-NJ'J'-$.

15 In a more preferred embodiment of the present invention, X is $-CR_{20}R_{20}-$; $-O-$; $-S(O)_2$; or NR_{21} .

Preferred embodiments of R_{20} are selected from hydrogen, $-C_1-C_6$ -aliphatic and $-O-(C_1-C_6$ -aliphatic); or each R_{20} is taken together with the carbon atoms to which

- 25 -

they are bound to form a (C3-C6)cycloalkyl. Preferably, these aliphatic groups are alkyl groups.

Preferred embodiments of R_{21} are selected from hydrogen and $-C(O)-O-R_{22}$.

5 In yet another preferred embodiment m in X is 0.

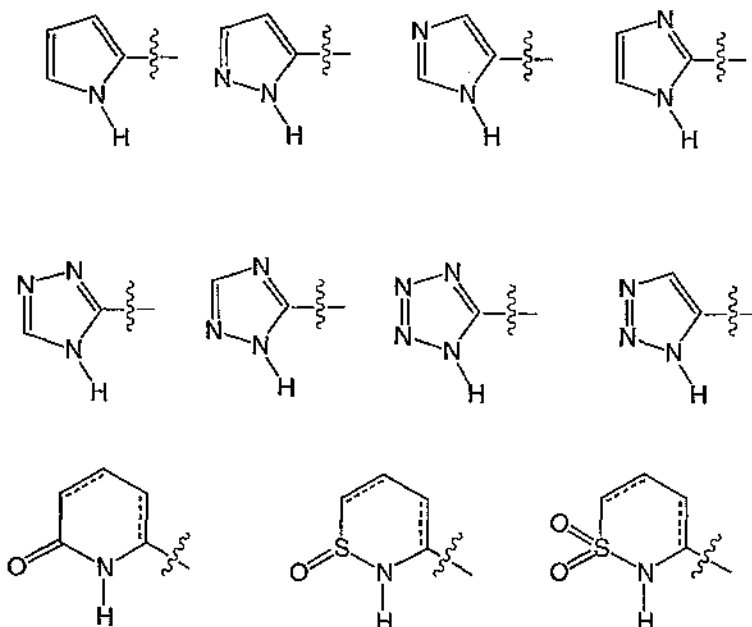
In yet another preferred embodiment, X is $-CH_2-$, $-O-$, $-SO_2-$ or $-NR_{21}-$, wherein R_{21} is hydrogen.

More preferably, X is $-CH_2-$.

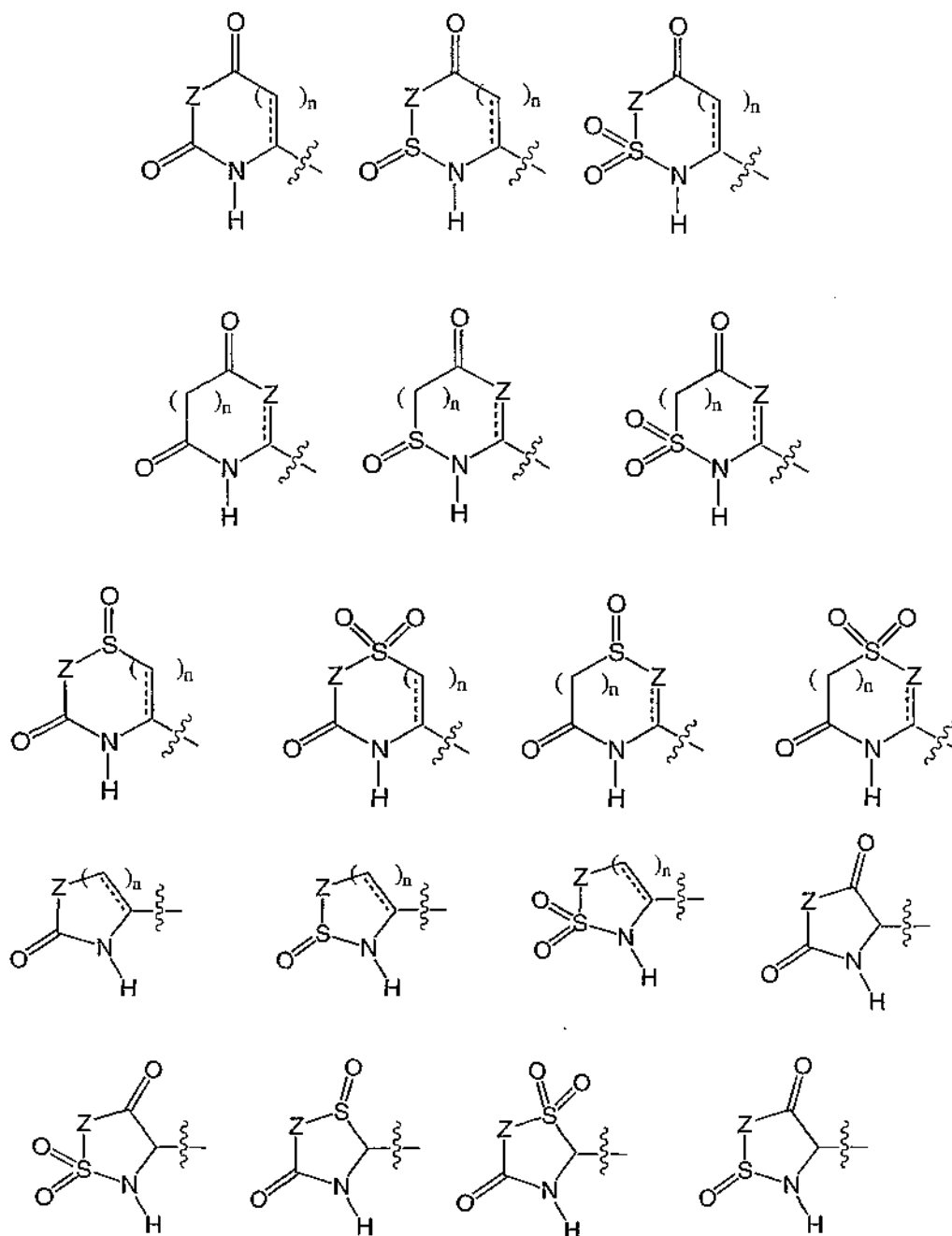
10 Even more preferred is when the bridged bicyclic moiety is fully saturated.

According to another preferred embodiment of this invention, T contains at least one hydrogen bond donor moiety selected from $-NH_2$, $-NH-$, $-OH$, and $-SH$.

15 In a preferred embodiment, T is:



- 26 -

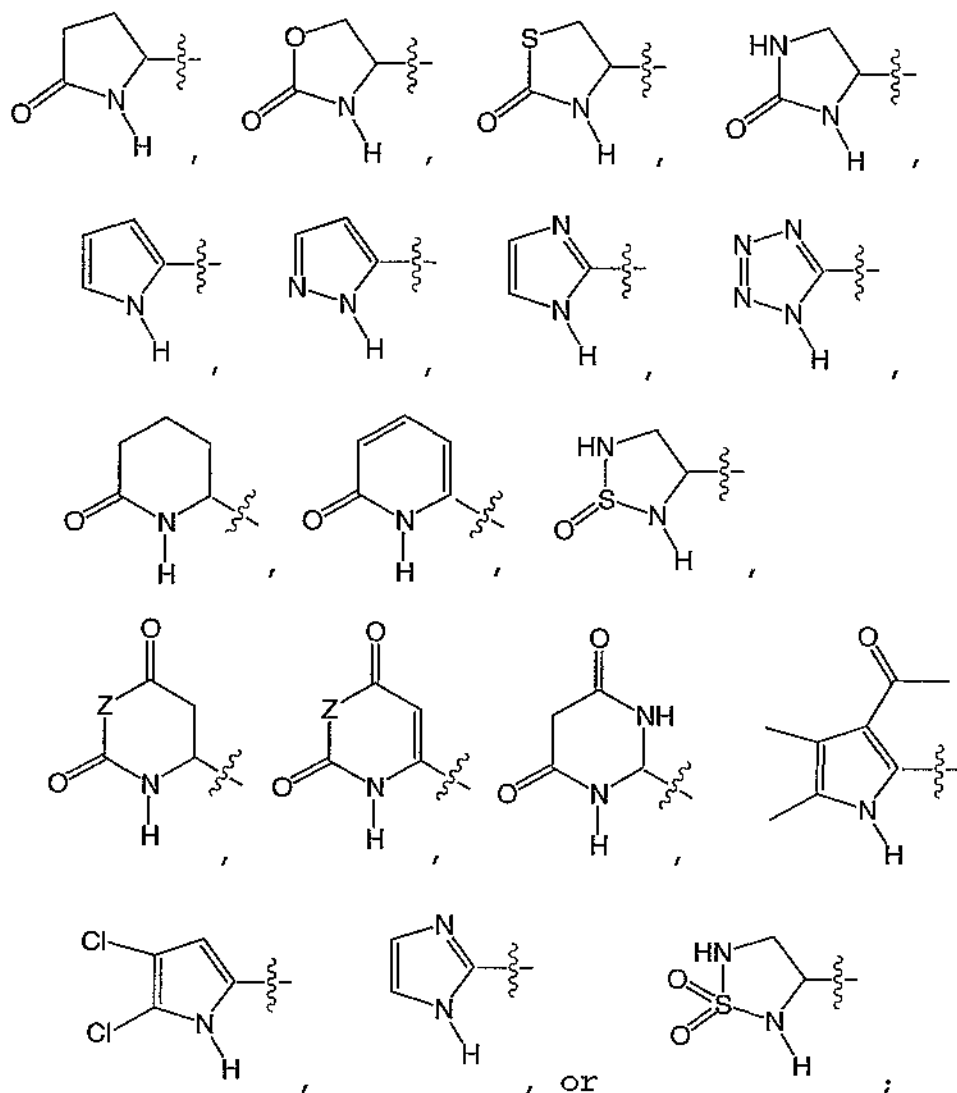


wherein:

- 5 T is optionally substituted with up to 3 J substituents, wherein J is as defined in claim 1;
- Z is independently O, S, NR₁₀, or C(R₁₀)₂;
- n is independently 1 or 2; and
- is independently a single bond or a double bond.

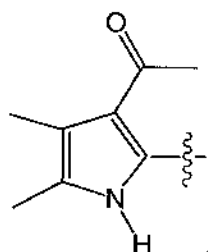
- 27 -

In another preferred embodiment, T is:



wherein Z is as defined above.

More preferably T is



5

According to another preferred embodiment, T is:

- 28 -

(C6-C10)-aryl,
(C6-C10)-aryl-(C1-C12)aliphatic,
(C3-C10)-cycloalkyl or -cycloalkenyl,
[(C3-C10)-cycloalkyl or -cycloalkenyl]-(C1-C12)-
5 aliphatic,
(C3-C10)-heterocyclyl,
(C3-C10)-heterocyclyl-(C1-C12)-aliphatic,
(C5-C10)heteroaryl, or
(C5-C10)heteroaryl-(C1-C12)-aliphatic,

10 wherein each T is optionally substituted with
up to 3 J substituents.

According to yet another preferred embodiment
of this invention, T:

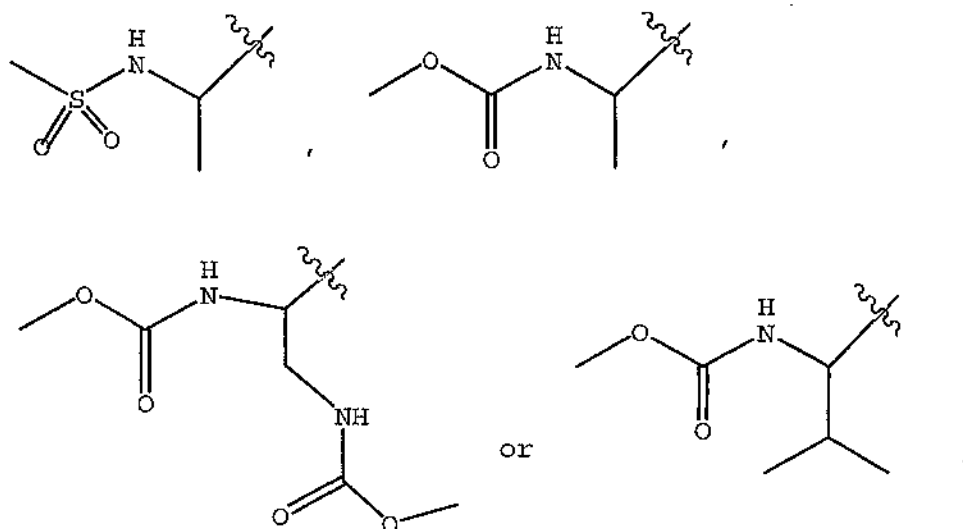
- 30 -

wherein each T is optionally substituted with up to 3 J substituents;

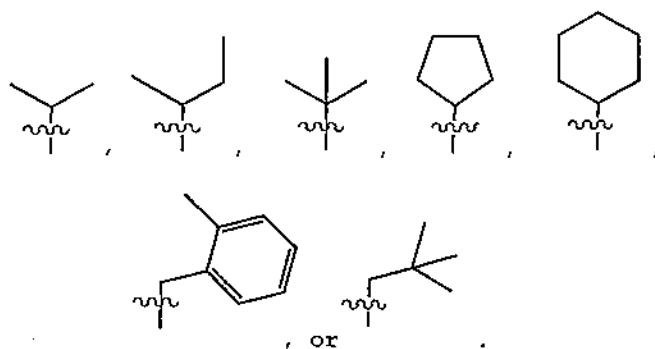
K is a bond, -O-, -S-, -NR₉-, -C(O)-, or -C(O)-NR₉-,
wherein R₉ is hydrogen or C1-C12 aliphatic; and

5 n is 1-3.

More preferably, T is:

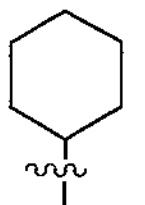


In yet another preferred embodiment, R₁ is:



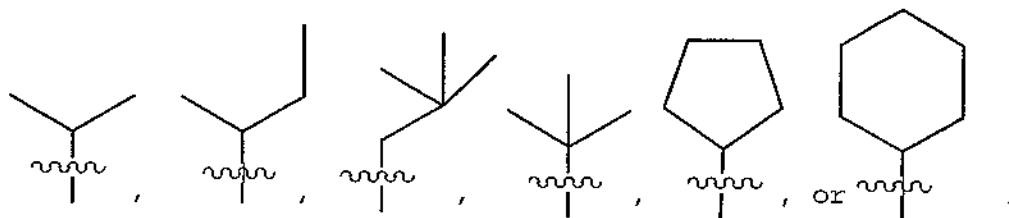
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More preferably, R₁ is:

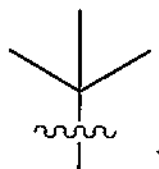


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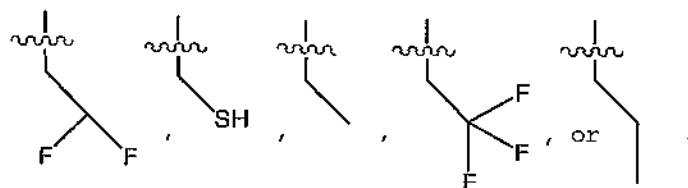
In yet another preferred embodiment, R_3 is:



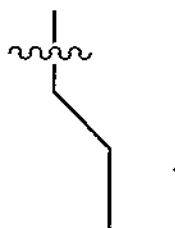
5 More preferably, R_3 is:



In yet another preferred embodiment, R_5 is:



10 More preferably, R_5 is:



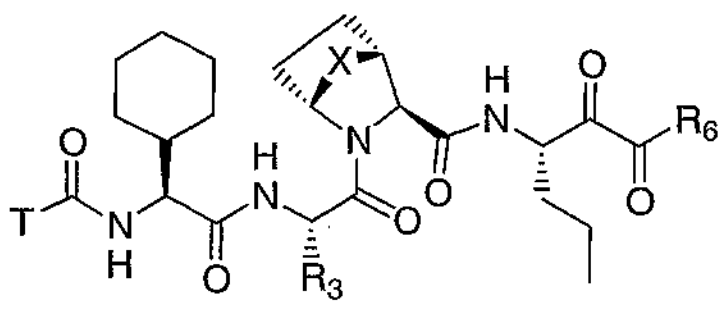
15 In yet another preferred embodiment, R_2 and R_4 are each independently H, methyl, ethyl, or propyl.

More preferably, R_2 and R_4 are each H.

According to a preferred embodiment, V is $-C(O)-NR_8-$. More preferably, V is $-C(O)-NH-$.

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More preferably, the compound of this invention has the structure and stereochemistry depicted below in formula II:



wherein R_3 and R_6 represent the most preferred embodiments set forth above.

Any of the preferred embodiments recited above may be combined to produce a preferred embodiment of this invention.

10

The compounds of this invention may be synthesized by standard chemical schemes well-known in the art. Such schemes are set forth below, but other equivalent schemes, which will be readily apparent to the ordinary skilled organic chemist, may alternatively be used to synthesize various portions of the molecule. For example, compounds of formula I, wherein W is $C(O)OH$ or $C(O)C(O)R_6$ may be prepared according to the methods depicted in schemes 11 and/or 12. More specific synthesis schemes for individual compounds within applicants' invention are set forth in the examples.

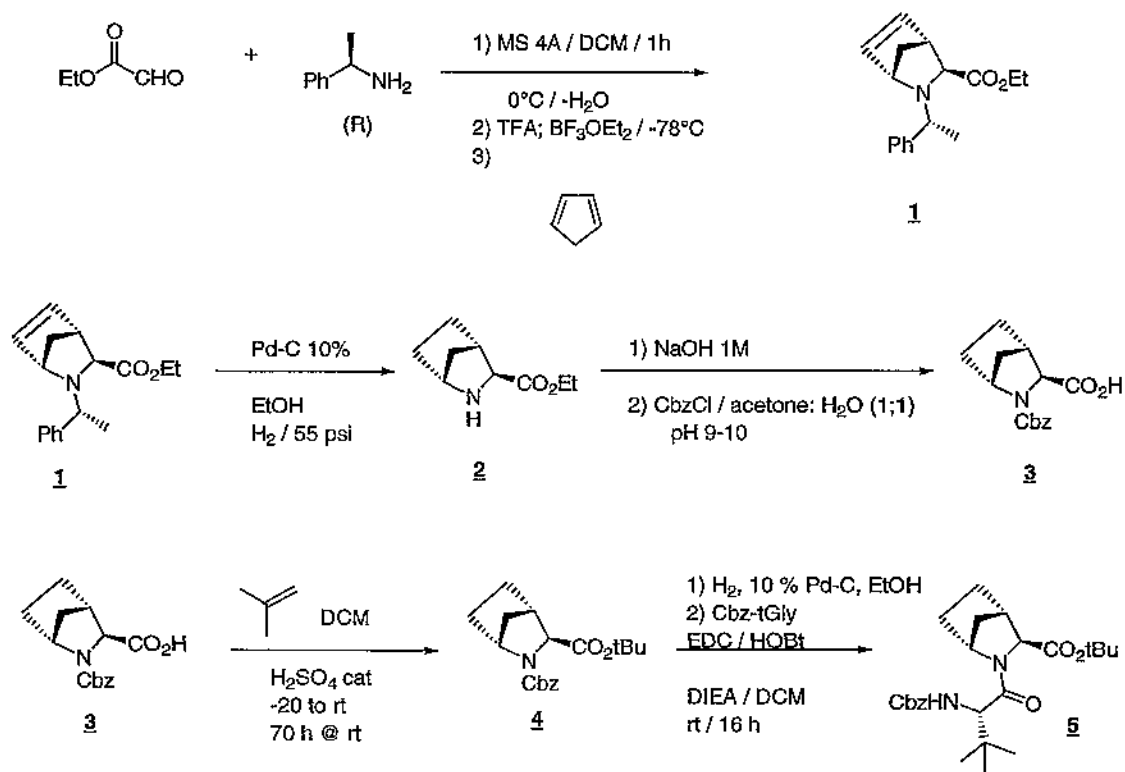
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Scheme 1.

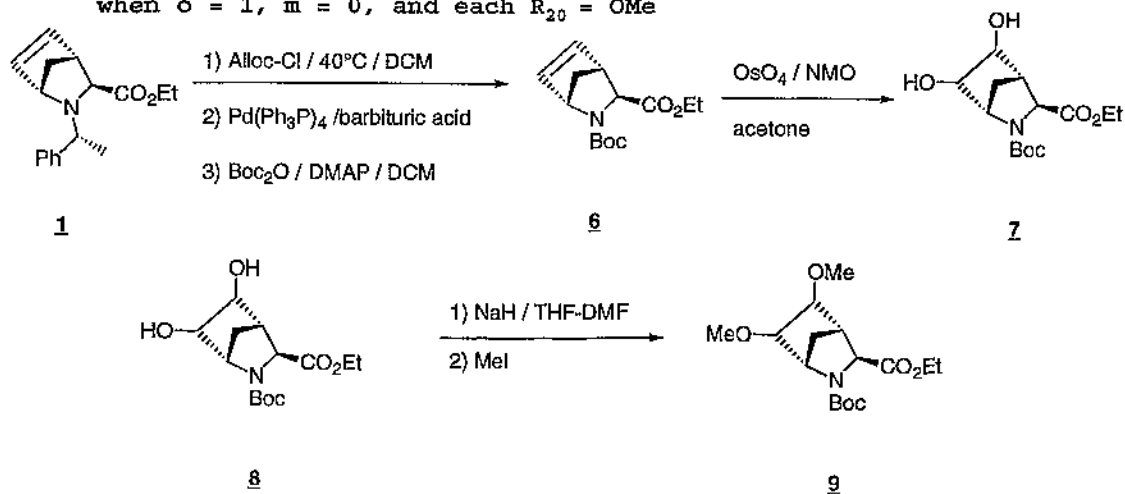
Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid
when $\alpha = 1$, $m = 0$, each $R_{20} = H$, and $R_3 = t\text{-Bu}$



Scheme 2.

Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid
acid

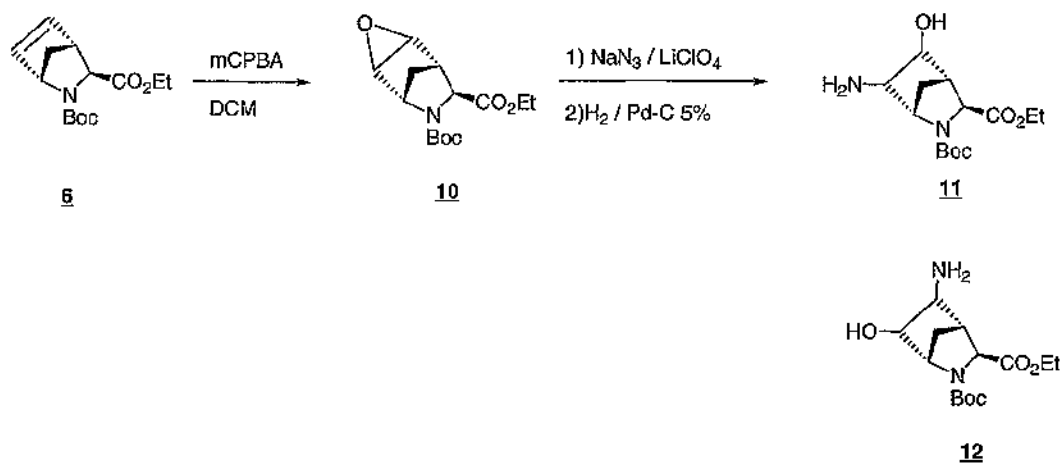
when $\alpha = 1$, $m = 0$, and each $R_{20} = \text{OMe}$



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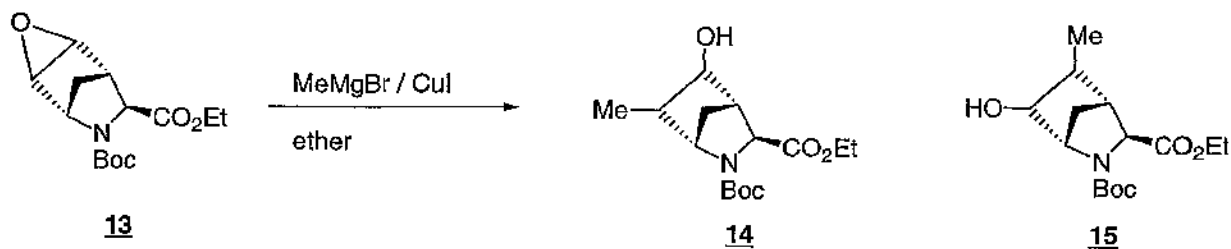
Scheme 3.

Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid

when $o = 1$, $m = 0$, and one $R_{20} = NH_2$ and the other $R_{20} = OH$ 

Scheme 4.

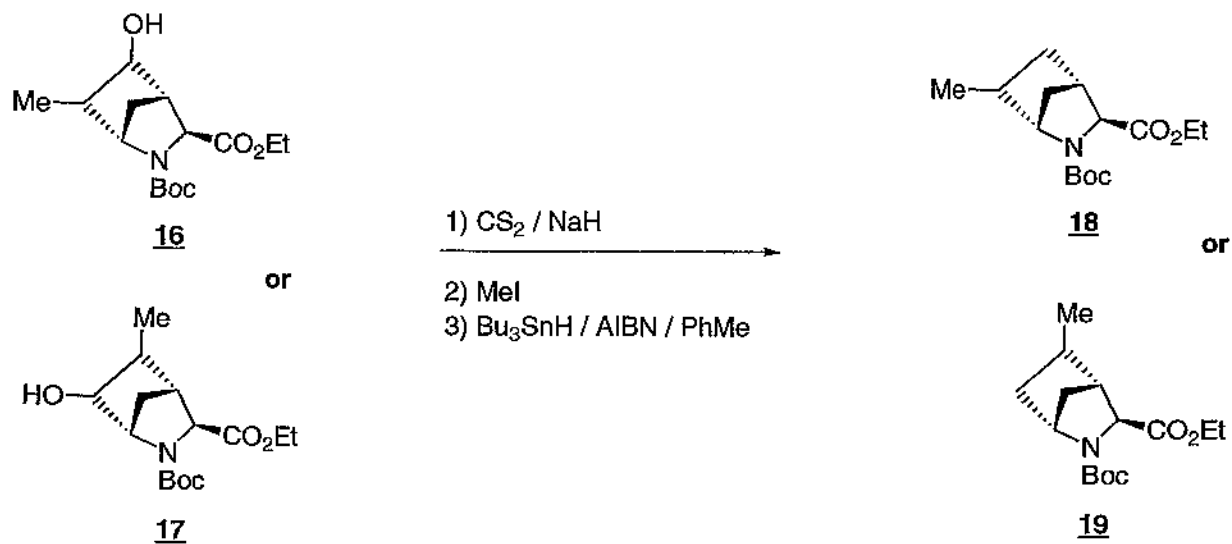
Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid

when $o = 1$, $m = 0$, and one $R_{20} = Me$ and the other $R_{20} = OH$ 

- 35 -

Scheme 5.

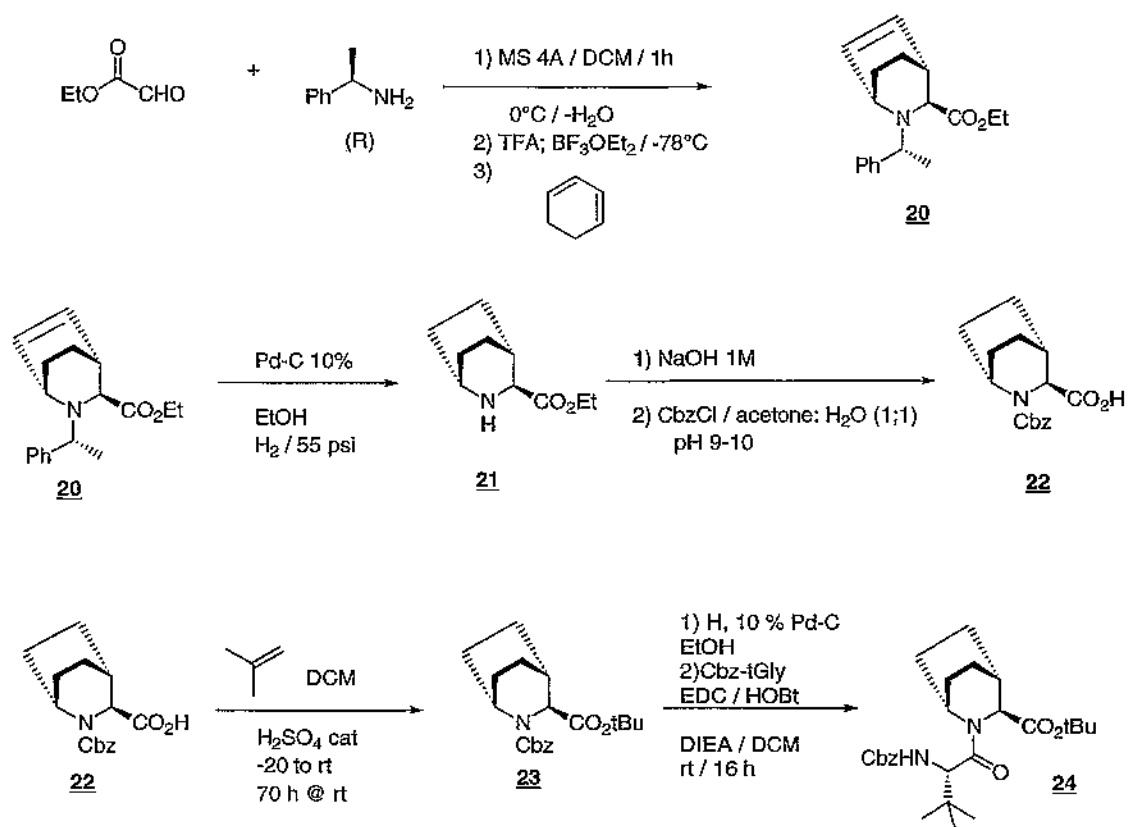
Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid
when $o = 1$, $m = 0$, and one $R_{20} = \text{Me}$ and the other $R_{20} = \text{H}$



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Scheme 6.

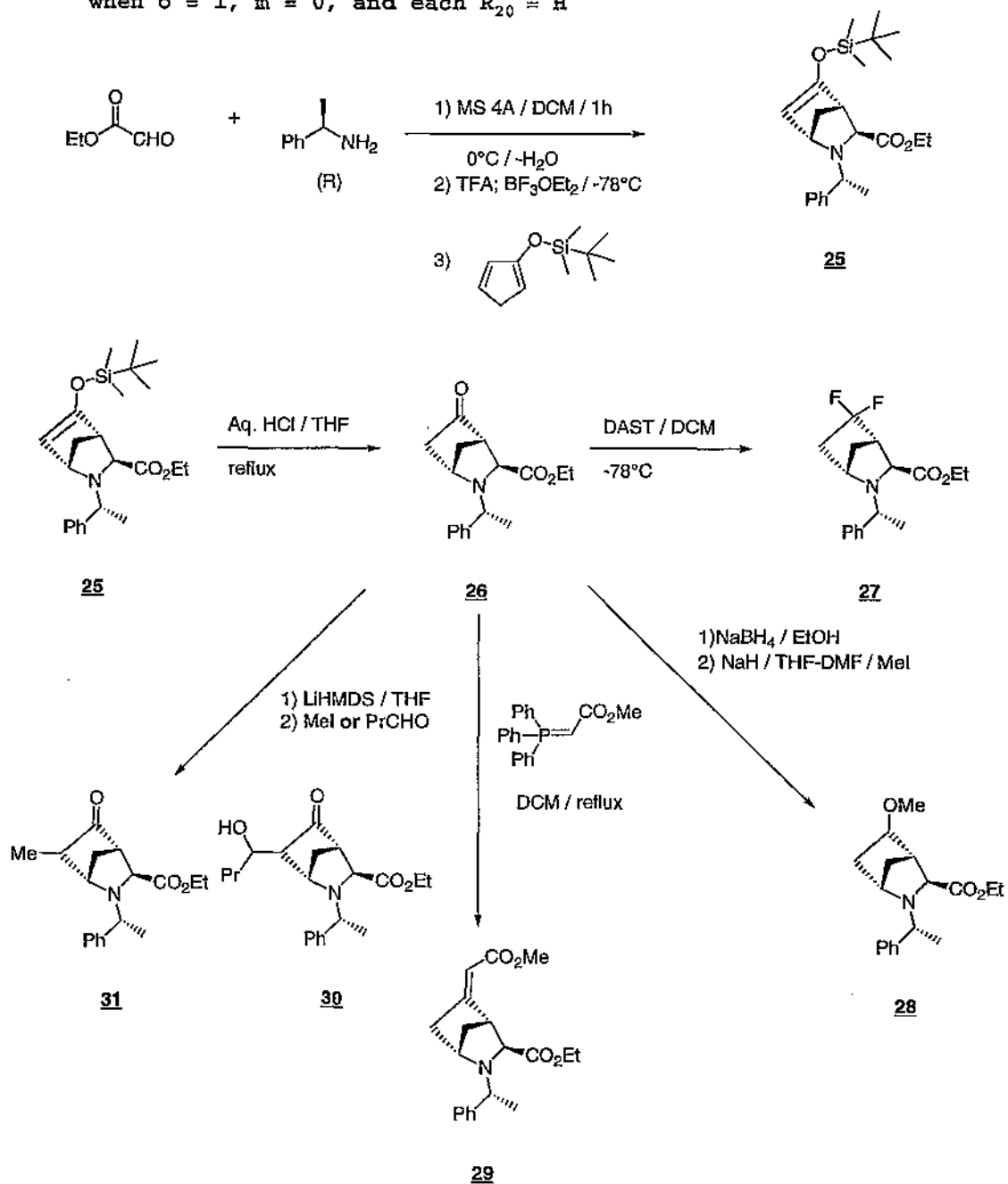
Synthesis of the Azabicyclo[2.2.2] octane-3-carboxylic acid
when $o = 2$, $m = 0$, each $R_{20} = H$, and $R_3 = t\text{-Bu}$



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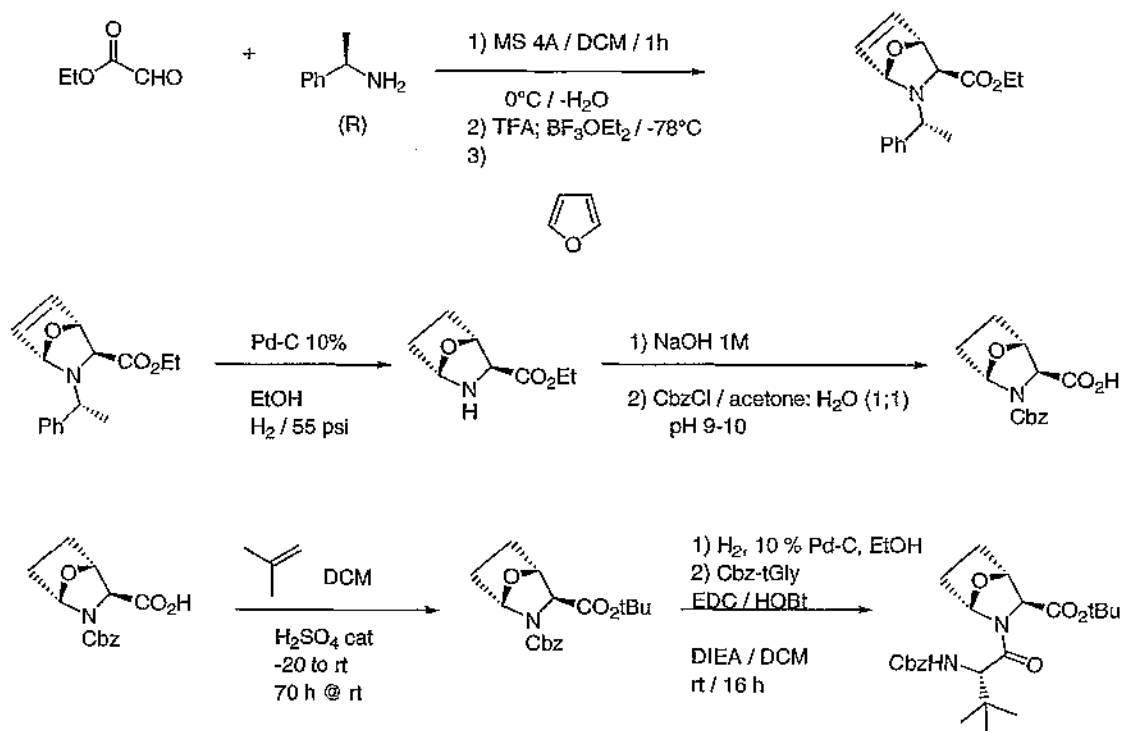
Scheme 7.

Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid
when $o = 1$, $m = 0$, and each $R_{20} = H$



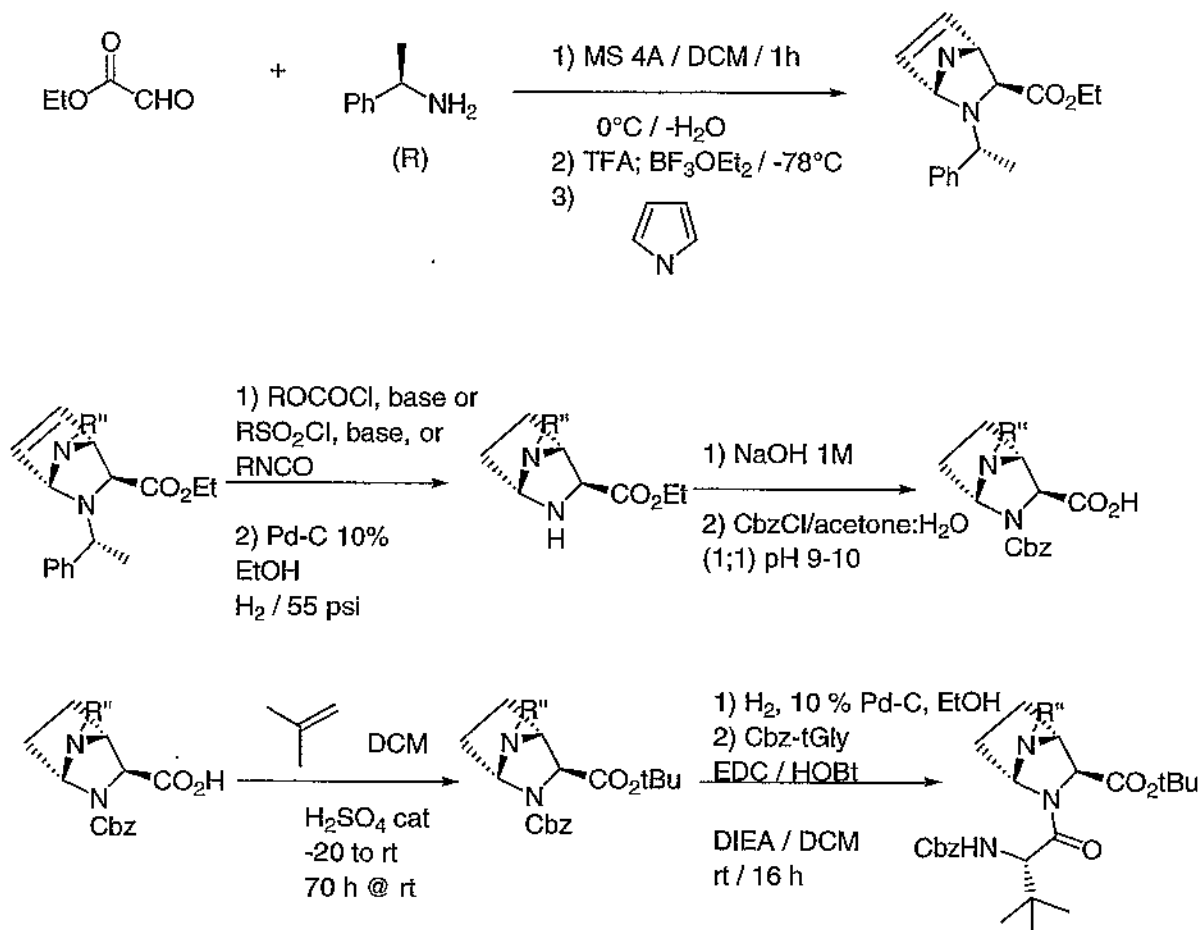
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Scheme 8.
Synthesis of Scaffolds when X is O



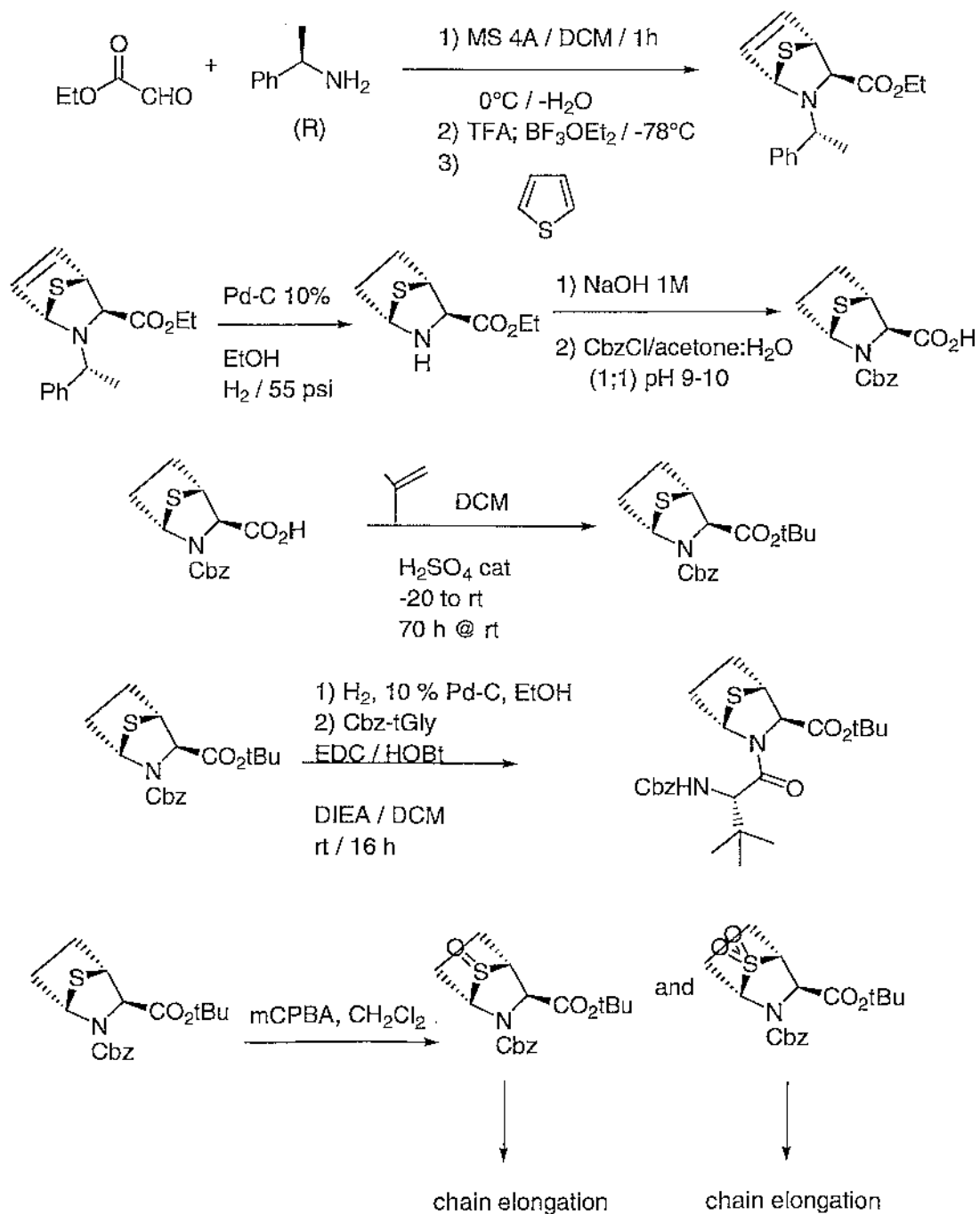
- 39 -

Scheme 9.

Synthesis of Scaffolds when X is NR_{21} or NJ wherein R' is R_{21} or J'

- 40 -

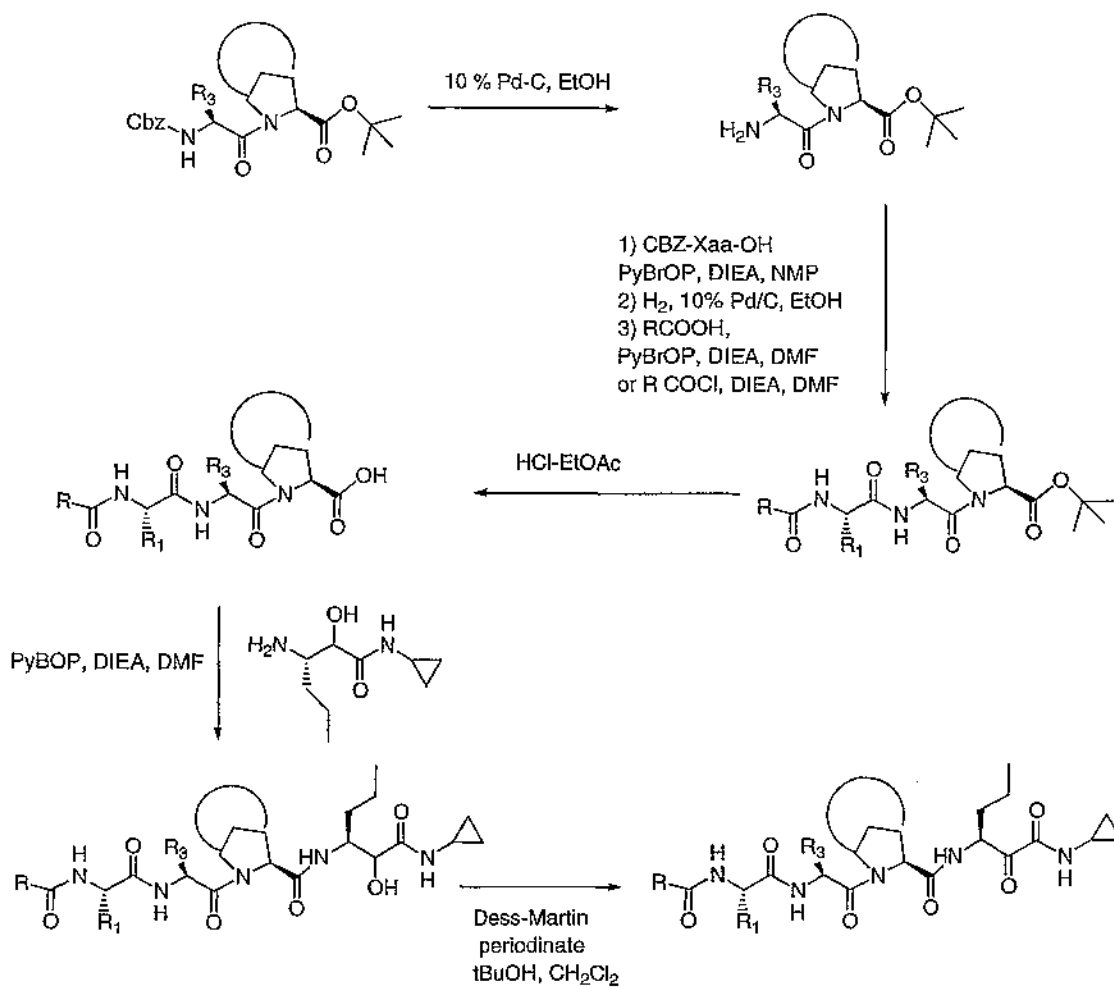
Scheme 10.

Synthesis of Scaffolds when X is SO or SO₂

- 41 -

Scheme 11.

Synthesis of Compounds of Formula I when W is $C(O)C(O)N(R_6)_2$ -
Method A

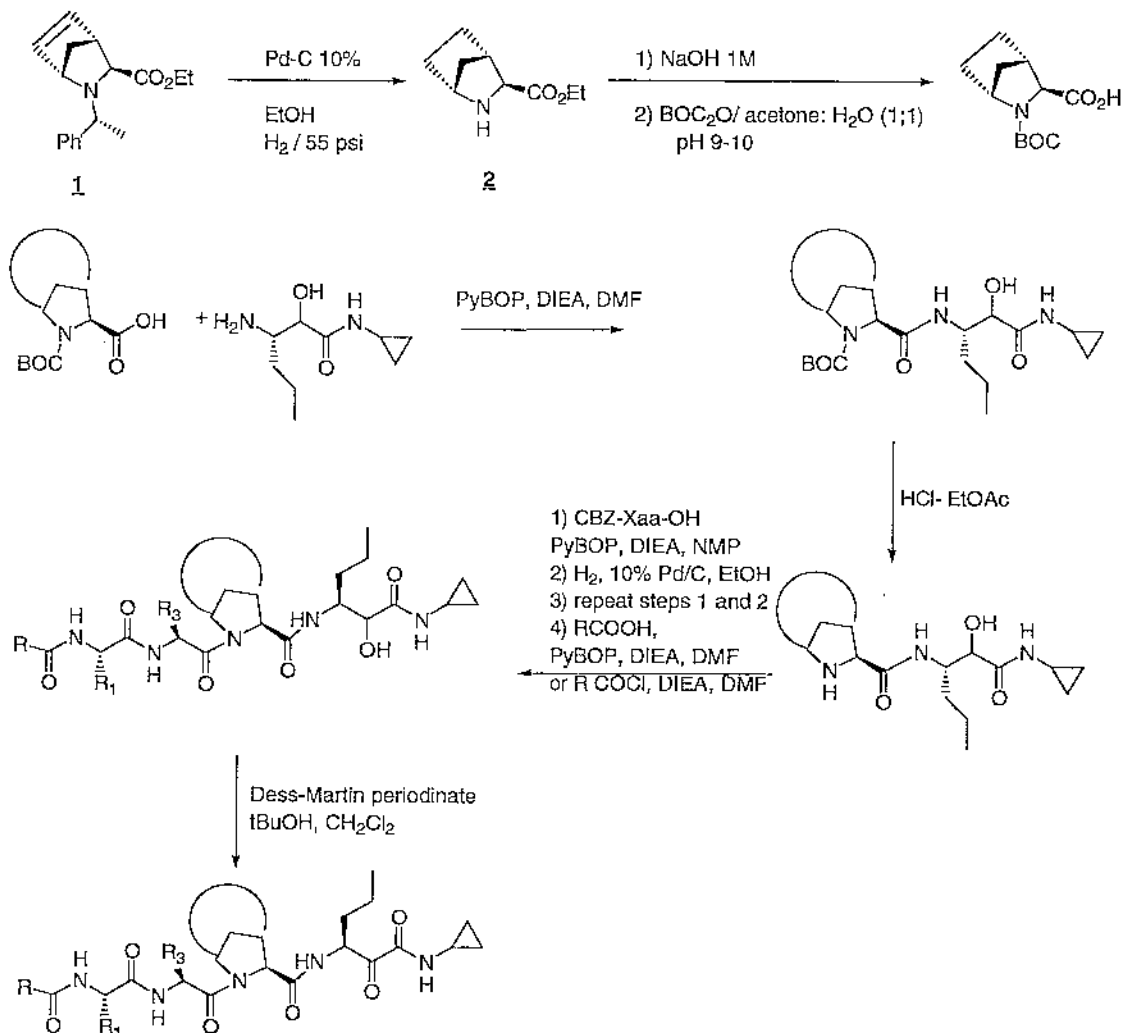


wherein $RC(O)NH-$ corresponds to T-V-

- 42 -

Scheme 12.

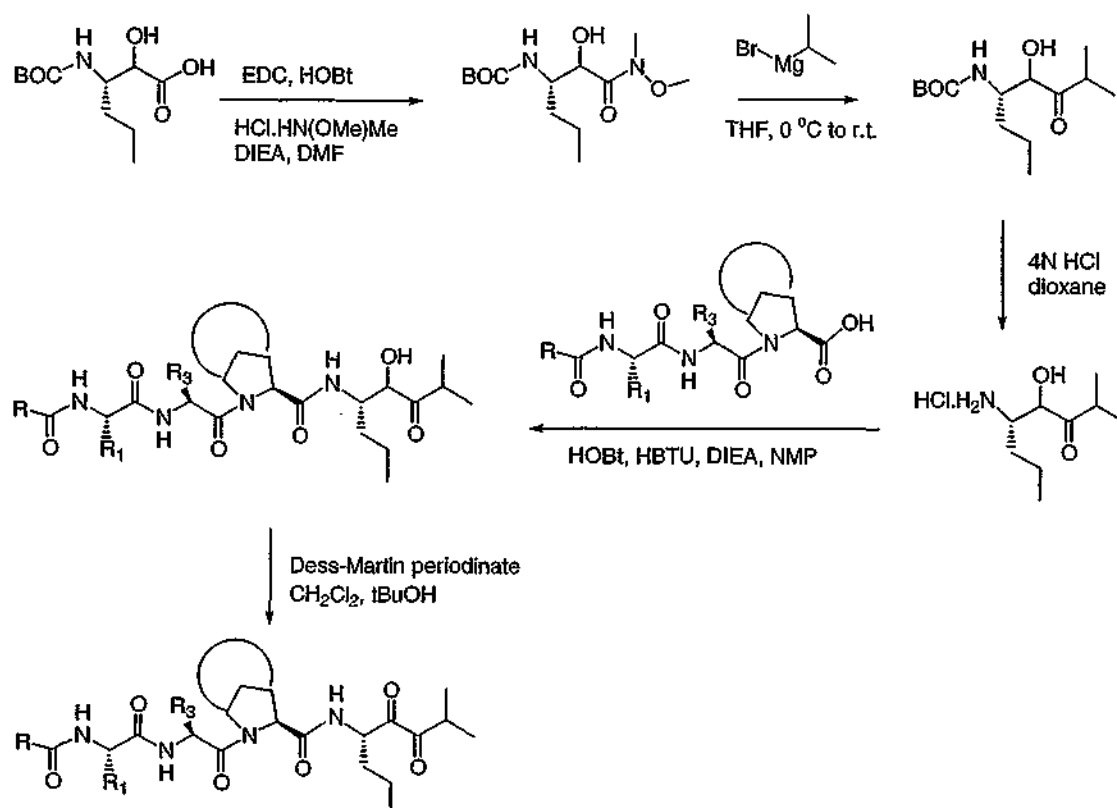
Synthesis of Compounds of Formula I when W is $C(O)C(O)N(R_6)_2$ -
Method B



wherein $RC(O)NH-$ corresponds to T-V-

- 43 -

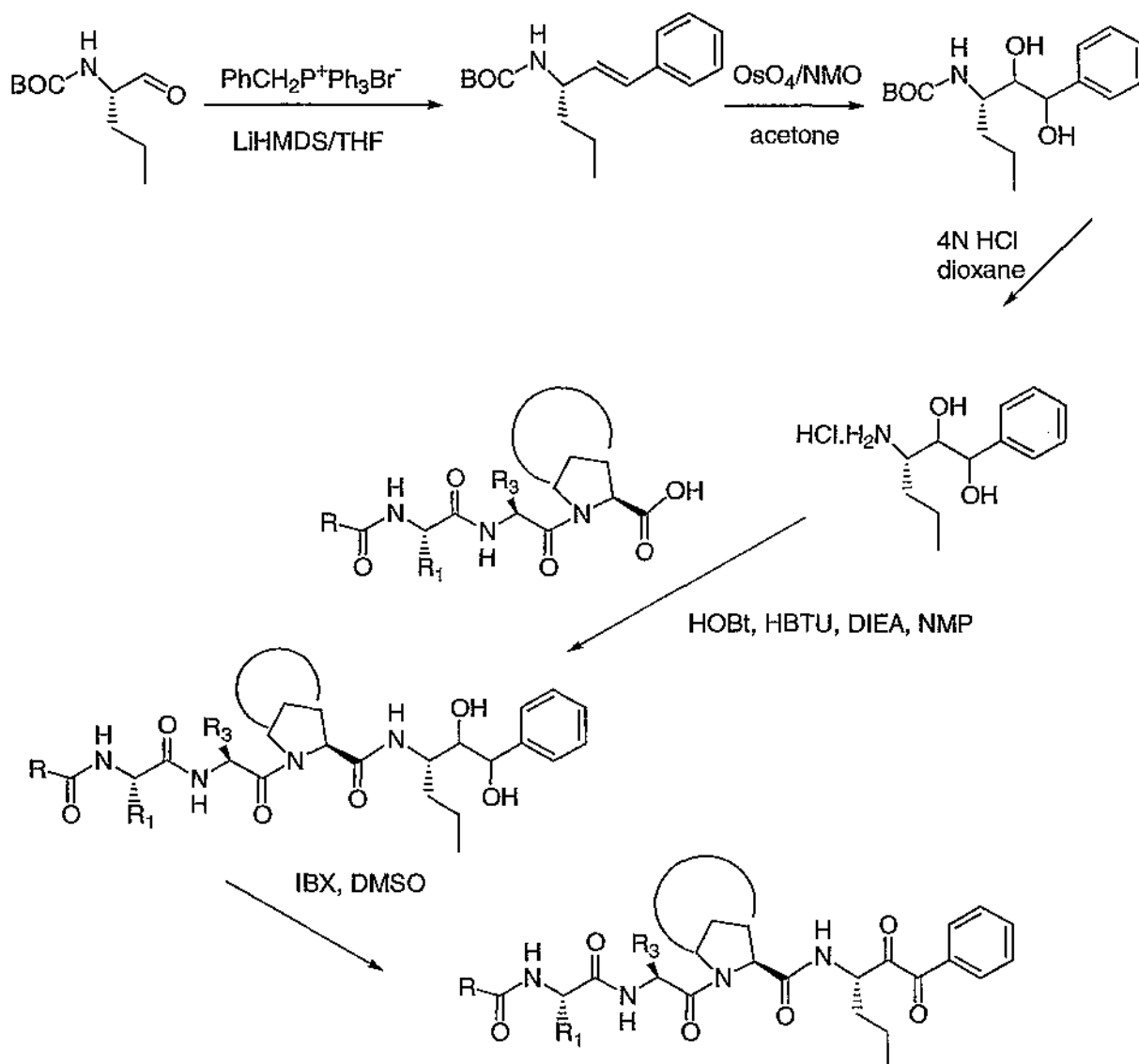
Scheme 13.

Synthesis of Compounds of Formula I when W is $C(O)C(O)R_6$ - Method Awherein RC(O)NH- corresponds to T-V-

- 44 -

Scheme 14.

Synthesis of Compounds of Formula I when W is C(O)C(O)R₆ -
Method B



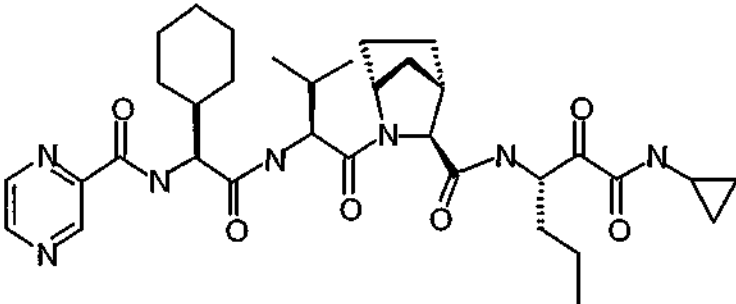
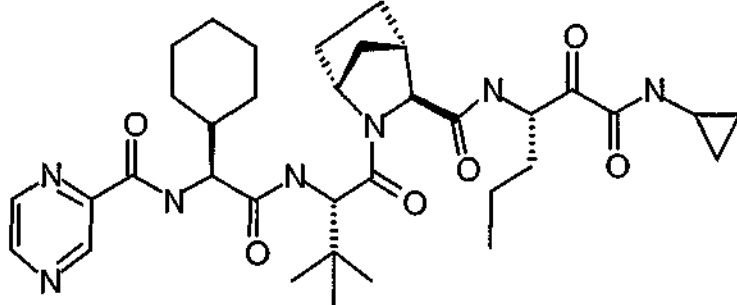
wherein RC(O)NH- corresponds to T-V-

As set forth above, the compounds of
this invention are capable of inhibiting the
activity of HCV NS3-NS4A protease. In order to
5 quantitate the activity of the compounds of this

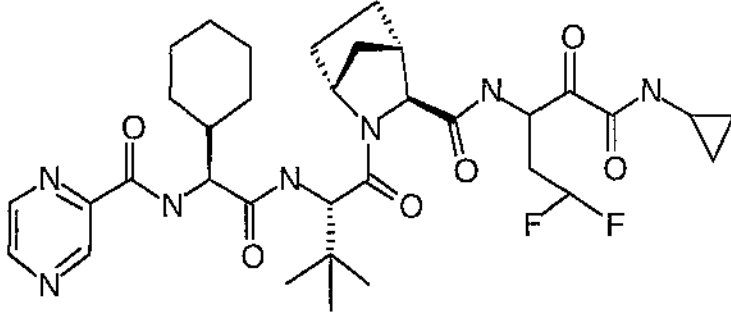
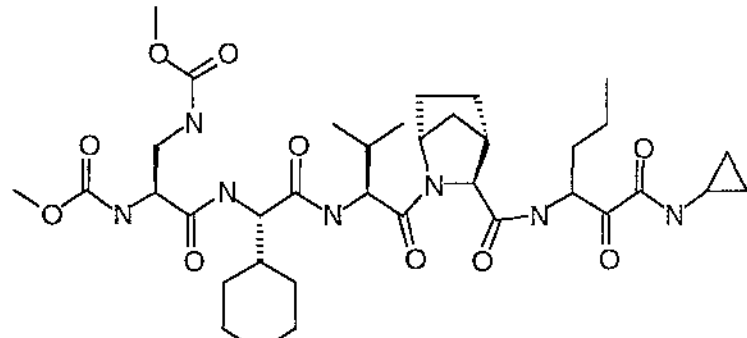
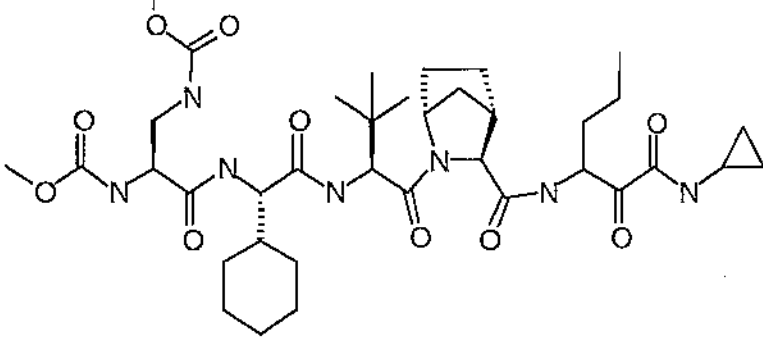
- 45 -

invention, cells containing HCV replicon were incubated with the compounds of this invention, and a Taqman Real Time PCR assay was conducted to determine the percentage inhibition of HCV RNA level and the IC₅₀ were calculated therefrom. The result are shown below in Table 1:

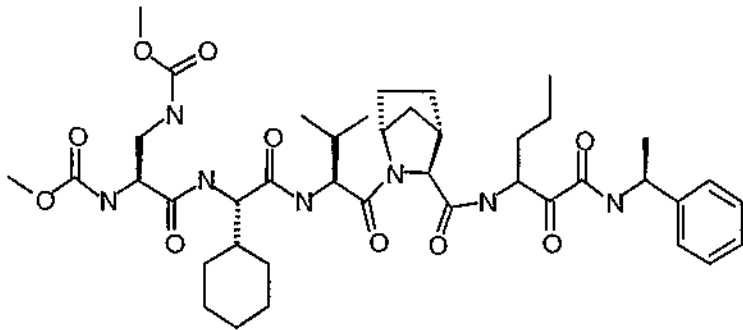
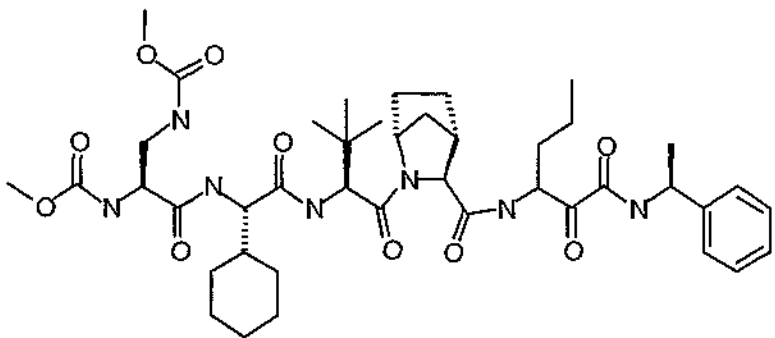
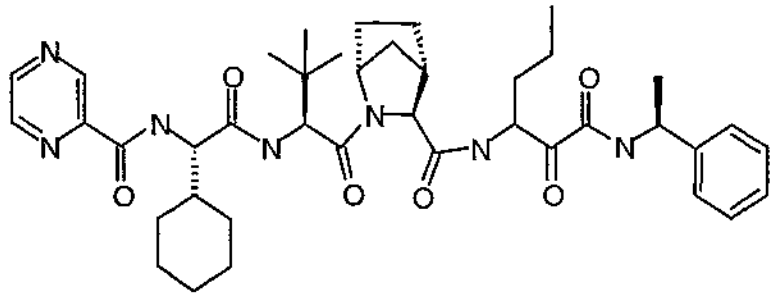
TABLE 1

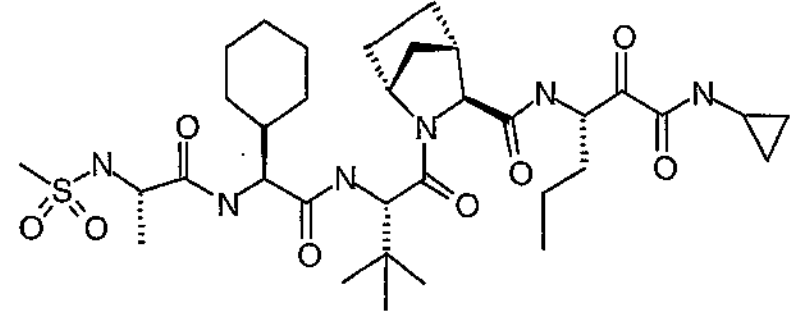
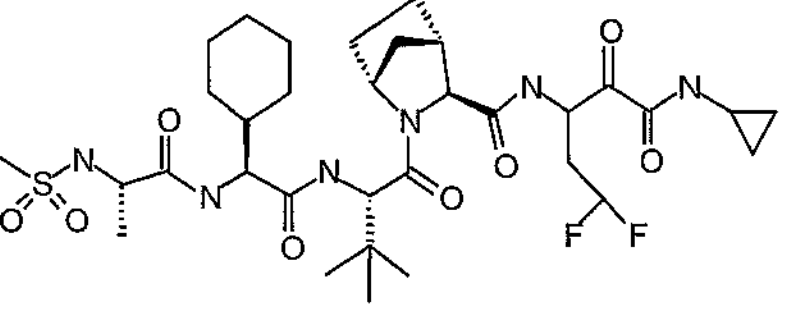
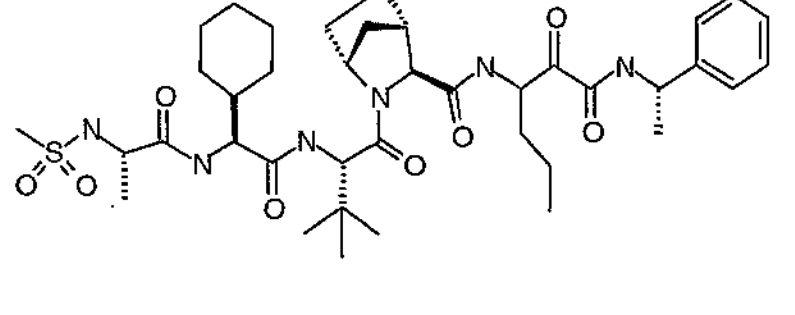
Cmpd No.	Structure	K _i (nM)	IC ₅₀ (nM)
1		220	>1000
2		90	886

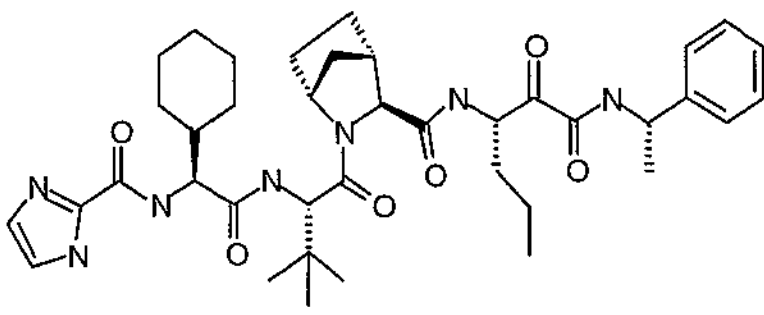
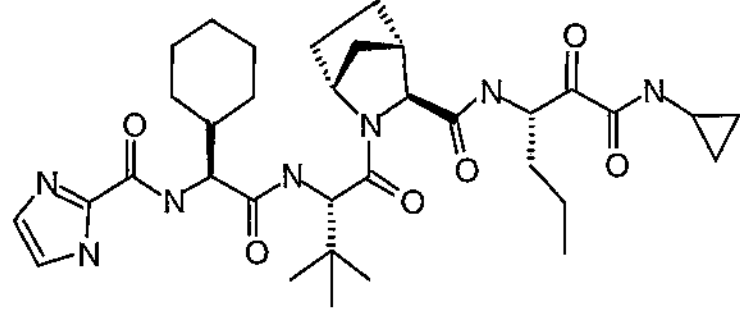
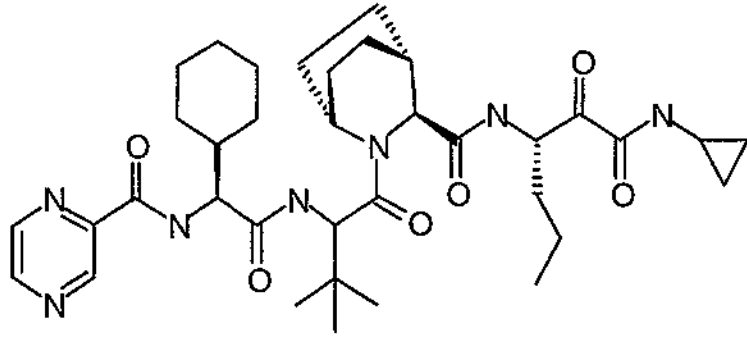
- 46 -

3		63	632
4		95	>10000
5		39	1410

- 47 -

6		96	2650
7		49	449
8		110	679

9		55	4310
10		28	10000
11		50	1230

12		68	412
13		42	251
14		125	1240

- 52 -

succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth.

Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

The compounds utilized in the compositions and methods of this invention may also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

Pharmaceutically acceptable carriers that may be used in these compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of

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saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

10 According to a preferred embodiment, the compositions of this invention are formulated for pharmaceutical administration to a mammal, preferably a human being.

Such pharmaceutical compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally or intravenously.

25 Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and

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solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any
5 bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil,
10 especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable
15 dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other
20 dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to,
25 capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule
30 form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with

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emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions
5 of this invention may be administered in the form of suppositories for rectal administration. These may be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and
10 therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially
15 when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

20 Topical application for the lower intestinal tract may be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical
25 compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid
30 petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical

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compositions may be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited
5 to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions
10 in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated
15 in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well known in the art of pharmaceutical
20 formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

25 Most preferred are pharmaceutical compositions formulated for oral administration.

In a related embodiment, the compositions of this invention additionally comprise another anti-viral agent, preferably an anti-HCV agent. Such anti-viral
30 agents include, but are not limited to, immunomodulatory agents, such as α -, β -, and γ -interferons and pegylated

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derivatized interferon- α compounds; other anti-viral agents, such as ribavirin and amantadine; other inhibitors of hepatitis C proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors); inhibitors of other targets in
5 the HCV life cycle, including helicase and polymerase inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (e.g., VX-497 and other IMPDH inhibitors disclosed in United States Patent 5,807,876, mycophenolic acid and
10 derivatives thereof); or combinations of any of the above.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if
15 necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may,
20 however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the
25 activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of
30 active ingredients will also depend upon the particular described compound and the presence or absence and the

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nature of the additional anti-viral agent in the composition.

According to another embodiment, the invention provides a method for treating a patient infected with a virus characterized by a virally encoded serine protease that is necessary for the life cycle of the virus by administering to said patient a pharmaceutically acceptable composition of this invention. Preferably, the methods of this invention are used to treat a patient suffering from a HCV infection. Such treatment may completely eradicate the viral infection or reduce the severity thereof.. More preferably, the patient is a human being.

In an alternate embodiment, the methods of this invention additionally comprise the step of administering to said patient an anti-viral agent preferably an anti-HCV agent. Such anti-viral agents include, but are not limited to, immunomodulatory agents, such as α -, β -, and γ -interferons and pegylated derivatized interferon- α compounds; other anti-viral agents, such as ribavirin and amantadine; other inhibitors of hepatitis C proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors); inhibitors of other targets in the HCV life cycle, including helicase and polymerase inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (e.g., VX-497 and other IMPDH inhibitors disclosed in United States Patent 5,807,876, mycophenolic acid and derivatives thereof); or combinations of any of the above.

Such additional agent may be administered to said patient as part of a single dosage form comprising

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both a compound of this invention and an additional anti-viral agent. Alternatively the additional agent may be administered separately from the compound of this invention, as part of a multiple dosage form, wherein
5 said additional agent is administered prior to, together with or following a composition comprising a compound of this invention.

In yet another embodiment the present invention provides a method of pre-treating a biological substance
10 intended for administration to a patient comprising the step of contacting said biological substance with a pharmaceutically acceptable composition comprising a compound of this invention. Such biological substances include, but are not limited to, blood and components
15 thereof such as plasma, platelets, subpopulations of blood cells and the like; organs such as kidney, liver, heart, lung, etc; sperm and ova; bone marrow and components thereof, and other fluids to be infused into a patient such as saline, dextrose, etc.

20 According to another embodiment the invention provides methods of treating materials that may potentially come into contact with a virus characterized by a virally encoded serine protease necessary for its life cycle. This method comprises the step of contacting
25 said material with a compound according to the invention. Such materials include, but are not limited to, surgical instruments and garments; laboratory instruments and garments; blood collection apparatuses and materials; and invasive devices, such as shunts, stents, etc.

30 In another embodiment, the compounds of this invention may be used as laboratory tools to aid in the isolation of a virally encoded serine protease. This

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method comprises the steps of providing a compound of this invention attached to a solid support; contacting said solid support with a sample containing a viral serine protease under conditions that cause said protease to bind to said solid support; and eluting said serine protease from said solid support. Preferably, the viral serine protease isolated by this method is HCV NS3-NS4A protease.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

Example 1

Ethyl(1S,3S,4R)-2-[(1R)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (1) (example for $n = 0$, $m = 0$; each $R_{20} = H$) see Scheme 1

(R)-Methylbenzylamine (15 mL; .118 mol; 1.05 eq) was added to a stirred 0°C solution of for example, ethyl glyoxylate 50% in toluene (23 mL; .112 mol; 1.0 eq) in 600 mL of anhydrous DCM containing 27 g of 4A molecular sieve. The reaction mixture was stirred at 0°C for 1 h. then it was lowered to -78°C. The 3 following reagents were sequentially added with 5 min. in between each addition:

TFA (9.08 mL; .118 mmol; 1.05 eq), boron trifluoride etherate (14.93 mL; .118 mol; 1.05 eq) and, for example, cyclopentadiene (16.37 mL; .146 mol; 1.3 eq). The reaction mixture was stirred at -78°C for 5 h before it was allowed to warm to rt. The molecular sieves were separated and the reaction mixture was carefully washed with saturated aqueous sodium hydrogen carbonate (250 mL), brine (250 mL), and dried with magnesium sulfate.

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Concentration and purification by flash chromatography (Hexanes: EtOAc:TEA (89:10:1) afforded (in order of elution) 2.3 g (7.%) of minor endo-isomer and 23.5 g (78%) of the major exo-isomer 1. The compound was characterized using NMR.

Example 2

Ethyl (1S,3S,4R)-2-azabicyclo[2.2.1]heptane-3-carboxylate (2) (example for o = 1, m = 0; each R₂₀ = H)

The aza Diels-Alder adduct 1 (23.5 g; 0.086 mol) was dissolved in 200 mL of absolute ethanol, and, for example, Pd-C 10% (600 mg) was added. The mixture was stirred at rt under hydrogen (55 psi) for 16 h. Filtration through a pad of celite (or nylon/carbon filter combination) and concentration yielded 14.2 g of 2 (97%) as a pale yellow oil which was used directly for the next step. The compound was characterized using NMR.

Example 3

(1S,3S,4R)-2-Benzoylazabicyclo[2.2.1]heptane-3-carboxylic acid 3 (example for o = 1, m = 0, each R₂₀ = H)

Amino ester 2 (3.45 g; 0.0204 mol; 1.0 eq) was added a mixture of, for example, 1N NaOH (71 mL; .143 mol; 3.5 eq) and 71 mL of water and stirred at rt for 4 h (TLC monitoring w/ mixture of EtOAc and 5% TEA). When the saponification is complete, 100 mL of acetone was added and the temperature was lowered to 0°C. Benzyl chloroformate (3.5 mL; 0.0244 mol; 1.2 eq) in 40 mL of acetone was slowly added and the reaction mixture was allowed to stir at rt for 16 h with maintaining the pH to roughly 9 to 10 with 1N NaOH. The acetone was removed and 200 mL of water was added. The aqueous phase was washed with ether (3X 200 mL) and the aqueous phase acidified to pH 2-3 with 2N HCl. Extraction of the product with (3X

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250 mL) of EtOAc, drying (Na_2SO_4) and concentration *in vacuo* provided 3.85 g (70%) of amino acid 3. The compound was used directly for the next step. The compound was characterized using NMR.

5

Example 4

***tert*-Butyl (1*S*, 3*S*, 4*R*)-2-Benzoylazabicyclo[2.2.1]heptane-3-carboxylate (4)** (example for $o = 1$, $m = 0$, each $R_{20} = \text{H}$)

In a sealed tube, 140 μL of concentrated sulfuric acid was added to a solution of acid 3 (3.86g; 0.014 mol) in 30 mL
10 of DCM. The solution was brought to -20°C and saturated with isobutylene, causing a volume increase of 14 mL. After 70 h at rt, the cap was remove to release the pressure and the solution was added to 25 mL of water containing sodium carbonate sufficient to neutralize all
15 acid. The compound 4 was used directly for the next step without further purification. The compound was characterized using NMR.

Removal of the Cbz group with hydrogenation under 1 atm of hydrogen using Pd-C10% in ethanol gave, after 5 h, the
20 desired aminoester intermediate in quantitative yield. The crude compound was coupled to *tert*-butylglycine shown in the next step.

Example 5

***tert*-Butyl glycine coupling to product 5** (example for $o =$
25 1 , $m = 0$, each $R_{20} = \text{H}$, $R_3 = t\text{-Bu}$)

To a solution of Cbz-*tert*-butyl glycine (3.33 g; 0.0126 mol; 1.0 eq) in 20 mL of DCM at 0°C was added, for
example, EDC (2.89 g; 0.015 mol; 1.2 eq), HOBT (2.5 g; 0.0163 mol; 1.3 eq) and DIEA (6.57 mL; 0.038 mol; 3.0 eq).
30 The resulting mixture was stirred at 0°C for 15 min. after which, the above amino ester was slowly added in 10 mL of DCM. The resulting reaction mixture was stirred at rt for

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16 h. Concentrated to a residue that was redissolved in EtOAc. Successive washes with 0.5N HCL, satd' aqueous NaHCO₃ and brine gave after drying (Na₂SO₄) and concentration *in vacuo* the desired product which was subjected to flash chromatography (20% EtOAc/ 80% hexanes) to provide pure 5. The compound was characterized using NMR. The rest of the synthesis was done using standard amino acid coupling which were reported in previous patent.

10

Example 6

Ethyl (1S,3S,4R)-2-[(1R)-1-phenylethyl]-2-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (1) (example for $o = 1$, $m = 0$; each R₂₀ = H) see Scheme 2

15

The preparation of the azabicyclo[2.2.2]oct-5-ene was achieved using the same experimental as above with the procedural change that 1,3-cyclohexadiene was used instead of cyclopentadiene. The rest of the synthesis was done using standard amino acid coupling which have been reported.

20

Example 7

Cells containing hepatitis C virus (HCV) replicon were maintained in DMEM containing 10% fetal bovine serum (FBS), 0.25 mg per ml of G418, with appropriate supplements (media A).

25

On day 1, replicon cell monolayer was treated with a trypsin:EDTA mixture, removed, and then diluted media A into a final concentration of 100,000 cells per ml. 10,000 cells in 100 μ l are plated into each well of a 96-well tissue culture plate, and culture overnight in a tissue culture incubator at 37°C.

30

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On day 2, compounds (in 100% DMSO) were serially diluted into DMEM containing 2% FBS, 0.5% DMSO, with appropriate supplements (media B). The final concentration of DMSO was maintained at 0.5% throughout the dilution series.

The media on the replicon cell monolayer was removed, and then media B containing various concentrations of compounds was added. Media B without any compound was added to other wells as no compound controls.

Cells were incubated with compound or 0.5% DMSO in media B for 48 hours in a tissue culture incubator at 37°C.

At the end of the 48-hour incubation, the media was removed, and the replicon cell monolayer was washed once with PBS and stored at -80°C prior to RNA extraction.

Culture plates with treated replicon cell monolayers were thawed, and a fixed amount of another RNA virus, such as Bovine Viral Diarrhea Virus (BVDV) was added to cells in each well. RNA extraction reagents (such as reagents from RNeasy kits) were added to the cells immediately to avoid degradation of RNA. Total RNA was extracted according the instruction of manufacturer with modification to improve extraction efficiency and consistency. Finally, total cellular RNA, including HCV replicon RNA, was eluted and stored at -80°C until further processing.

A Taqman real-time RT-PCR quantification assay was set up with two sets of specific primers and probe. One was for HCV and the other was for BVDV. Total RNA

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extractants from treated HCV replicon cells were added to the PCR reactions for quantification of both HCV and BVDV RNA in the same PCR well. Experimental failure was flagged and rejected based on the level of BVDV RNA in each well. The level of HCV RNA in each well was calculated according to a standard curve that is run in the same PCR plate. The percentage of inhibition or decrease of HCV RNA level due to compound treatment was calculated using the DMSO or no compound control as 0% of inhibition. The IC₅₀ (concentration at which 50% inhibition of HCV RNA level is observed) was calculated from the titration curve of any given compound.

The IC₅₀ values inhibitory activity of some of the compounds of the present invention is shown in Table 1 above.

Example 8

The K_i determinations were performed as follows. The K_i values for some compounds of the present invention are recited above in Table 1.

HPLC Microbore method for separation of 5AB substrate and products

NH₂-Glu-Asp-Val-Val-(alpha)Abu-Cys-Ser-Met-Ser-Tyr-COOH

Stock solution of 20 mM 5AB was made in DMSO w/ 0.2M DTT.

This was stored in aliquots at -20 C.

Buffer: 50 mM HEPES, pH 7.8; 20% glycerol; 100 mM NaCl
Total assay volume was 200 µL

	X1 (µL)	Conc. in assay
Buffer	155	see above
5 mM KK4A	1	25 µM

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1 M DTT	1	5 mM
DMSO or inhibitor	3	1.5% v/v
0.25 μ M tNS3	20	25 nM
200 μ M 5AB (initiate)	20	20 μ M

The buffer was combined with KK4A, DTT, and tNS3; 177 μ L of this solution was distributed each into wells of 96 well plate and incubated at 30 °C for ~5-10 min.

- 5 3 μ L of appropriate concentration of test compound dissolved in DMSO (DMSO only for control) was added to each well and incubate at 30 °C for 15 min.

Reaction was initiated by addition of 20 μ L of 200 μ M 5AB substrate (20 μ M concentration is equivalent or slightly
10 lower than the K_m for 5AB) and incubated for 20 min at 30 °C. The reaction was terminated by addition of 50 μ L of 10% TFA 200 μ L aliquots were transferred to HPLC vials The SMSY product was isolated from substrate and KK4A by the method which follows.

15

Microbore separation method

Instrumentation:

Hewlett Packard 1100

Degasser G1322A

- 20 Binary pump G1312A

Autosampler G1313A

Column thermostated chamber G1316A

Diode array detector G1315A

- Column: Phenomenex Jupiter; 5 micron C18; 300 angstroms;
25 150x2 mm; P/O 00F-4053-B0

Column thermostat: 40 °C

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Injection volume: 100 μ L

Solvent A = HPLC grade water + 0.1% TFA

Solvent B = HPLC grade acetonitrile + 0.1% TFA

Time (min)	%B	Flow (ml/min)	Max press.
0	5	0.2	400
12	60	0.2	400
13	100	0.2	400
16	100	0.2	400
17	5	0.2	400

5

Stop time: 17 min

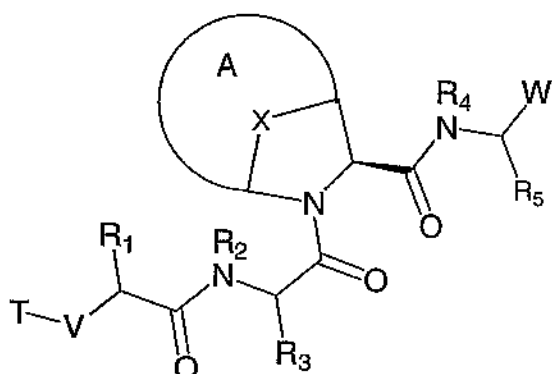
Post-run time: 10 min

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CLAIMS

What is claimed is:

- 5 1. A compound of the formula (I):



(I)

10 wherein:

A, together with X and the atoms to which X is bound, is a 4- to 7-membered aromatic or non-aromatic ring having up to 4 heteroatoms independently selected from N, NH, O, SO, or SO₂; wherein said ring is optionally
 15 fused to a (C6-C10)aryl, (C5-C10)heteroaryl, (C3-C10)cycloalkyl or (C3-C10)heterocyclyl; wherein A has up to 3 substituents selected independently from J;

X is -[CH₂]_o-, -[CJ'J']_o-, -[CH₂]_m-O-, -[CH₂]_m-S(O)₂-,
 -[CH₂]_m-SO-, -[CH₂]_m-S-, -[CR₂₀R₂₀]_m-NR₂₁-, or -[CR₂₀R₂₀]_m-
 20 NJ''-, wherein:

R₂₁ is hydrogen or -C(O)-O-R₂₂;

o is 1 or 2;

R₂₂ is -(C1-C6)alkyl, -(C2-C6)alkenyl, or
 -(C2-C6)alkynyl;

25 m is 0 or 1;

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J is halogen, -OR', -NO₂, -CF₃, -OCF₃, -R', oxo, -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂;

J' is halogen, -OR', -NO₂, -CF₃, -OCF₃, -R', -OR',
5 -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂;

J'' is -OR', -CF₃, -OCF₃, -R', oxo, -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂, wherein each R' is
10 independently:

hydrogen,
-(C1-C12) aliphatic,
-(C3-C10) cycloalkyl or -cycloalkenyl,
-(C1-C12) aliphatic-[(C3-C10) cycloalkyl or
15 -cycloalkenyl],
-(C6-C10) aryl,
-(C1-C12) aliphatic-(C6-C10) aryl,
-(C3-C10) heterocyclyl,
-(C1-C12) aliphatic-(C6-C10) heterocyclyl,
20 -(C5-C10)-heteroaryl, or
-(C1-C12)-aliphatic-(C5-C10) heteroaryl;

R₁ and R₃ are independently:

-(C1-C12) aliphatic,
-(C3-C10)-cycloalkyl or -cycloalkenyl,
25 -(C1-C12)-aliphatic-[(C3-C10)-cycloalkyl or -cycloalkenyl],
-(C6-C10)-aryl,
(C1-C12) aliphatic-(C6-C10) aryl,
-(C3-C10)-heterocyclyl,
30 -(C1-C12) aliphatic-(C6-C10) heterocyclyl,
-(C5-C10) heteroaryl, or
-(C1-C12) aliphatic-(C5-C10) heteroaryl,

- 70 -

wherein each of R_1 and R_3 is independently and optionally substituted with up to 3 substituents independently selected from J;

wherein up to 3 aliphatic carbon atoms in R_1 and R_3 may be replaced by a heteroatom selected from O, NH, S, SO, and SO₂ in a chemically stable arrangement;

R_2 and R_4 are independently hydrogen,

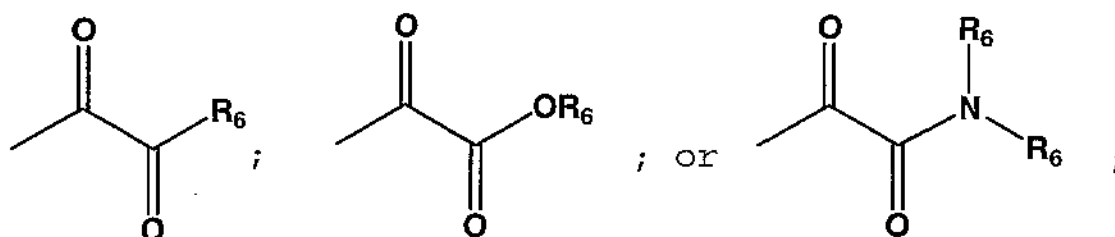
-(C1-C12)aliphatic,
-(C1-C12)aliphatic-(C3-C10)cycloalkyl, or
-(C1-C12)aliphatic-(C6-C10)aryl,

wherein each of R_2 and R_4 is independently and optionally substituted with up to 3 substituents independently selected from J;

wherein up to two aliphatic carbon atoms in R_2 and R_4 may be replaced by a heteroatom selected from O, NH, S, SO, and SO₂;

R_5 is -(C1-C12)aliphatic, wherein any hydrogen is optionally replaced with halogen, and wherein any hydrogen or halogen atom bound to any terminal carbon atom of R_5 is optionally substituted with sulfhydryl or hydroxy;

W is: -C(O)OH;



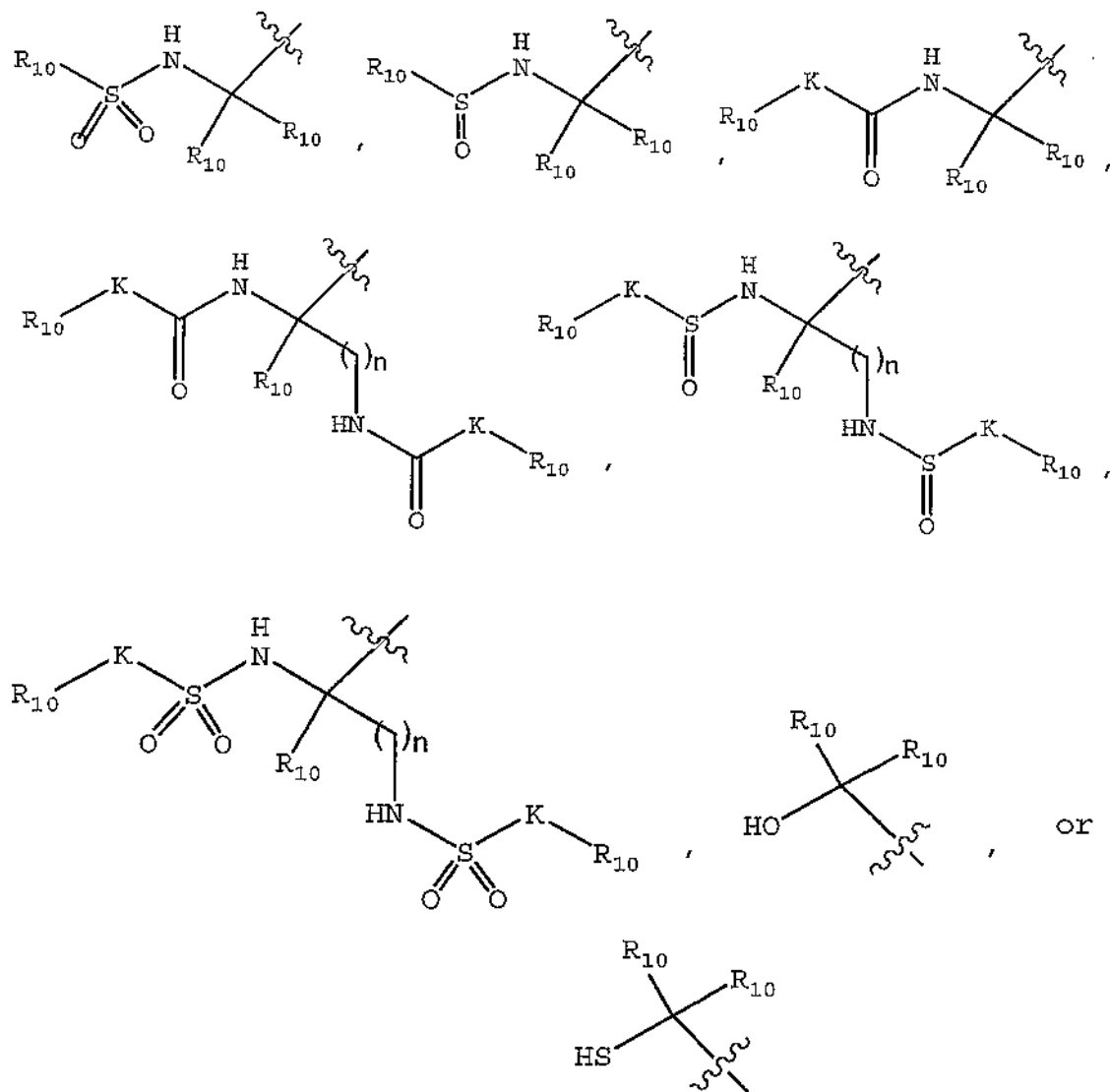
wherein each R_6 is independently:

hydrogen,
-(C1-C12)aliphatic,

- 71 -

- (C6-C10) aryl,
 - (C6-C10) aryl- (C1-C12) aliphatic,
 - (C3-C10)-cycloalkyl or -cycloalkenyl,
 - (C1-C12)-aliphatic-[(C3-C10)-cycloalkyl or
 5 -cycloalkenyl],
 - (C3-C10) heterocyclyl,
 - (C3-C10) heterocyclyl- (C1-C12) aliphatic,
 - (C5-C10) heteroaryl, or
 - (C1-C12) aliphatic- (C5-C10) heteroaryl, or
 10 two R₆ groups, which are bound to the same nitrogen
 atom, form together with that nitrogen atom, a
 - (C3-C10) heterocyclic ring;
 wherein R₆ is optionally substituted with up to 3 J
 substituents or with a suitable electron withdrawing
 15 group;
 V is -C(O)N(R₈)-, -S(O)N(R₈)-, -S(O)₂N(R₈)-, a bond,
 -CH(R₈)-, -N(R₈)-, -O-, -O-CH(R₈)-, -S-, -S-CH(R₈), -C(O)-,
 -C(O)-O-, -C(O)-S-, -C(O)-CH(R₈)-, -S(O)-, -S(O)-CH(R₈),
 -S(O)-N(R₈)-CH(R₈), -S(O)₂-, -S-(O)₂-CH(R₈)-, or -S(O)₂-N(R₈)-
 20 CH(R₈);
 wherein R₈ is hydrogen or - (C1-C12) aliphatic;
 T is:
 - (C6-C10) aryl,
 - (C1-C12) aliphatic- (C6-C10) aryl,
 25 - (C3-C10)-cycloalkyl or -cycloalkenyl,
 - (C1-C12) aliphatic-[(C3-C10)-cycloalkyl or
 -cycloalkenyl],
 - (C3-C10) heterocyclyl,
 - (C1-C12) aliphatic- (C3-C10) heterocyclyl,
 30 - (C5-C10) heteroaryl, or
 - (C1-C12) aliphatic- (C5-C10) heteroaryl; or
 T is:

- 72 -



5 wherein:

R_{10} is:

hydrogen,

-(C1-C12)aliphatic,

-(C6-C10)aryl,

10 -(C1-C12)aliphatic-(C6-C10)aryl,

-(C3-C10)-cycloalkyl or -cycloalkenyl,

-(C1-C12)aliphatic-[(C3-C10)-cycloalkyl or
-cycloalkenyl],

-(C3-C10)heterocyclyl,

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-(C1-C12)aliphatic-(C3-C10)heterocyclyl,
 -(C5-C10)heteroaryl, or
 -(C1-C12)aliphatic-(C5-C10)heteroaryl,

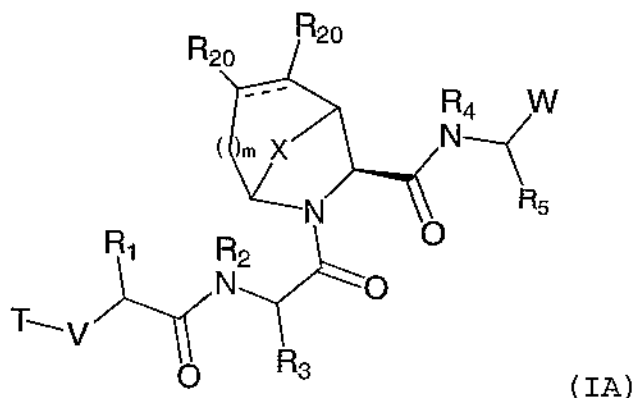
wherein each T is optionally substituted with up to
 5 3 J substituents;

K is a bond, -(C1-C12)aliphatic, -O-, -S-, -NR₉-,
 -C(O)-, or -C(O)-NR₉-, wherein R₉ is hydrogen or -(C1-
 C12)aliphatic;

n is 1-3; and

10 each R₂₀ is independently hydrogen, -(C1-C6)aliphatic
 or -O-((C1-C6)aliphatic); or each R₂₀ is taken together
 with the carbon atoms to which they are bound to form a
 (C3-C6)cycloalkyl.

15 2. The compound according to claim 1, wherein
 the compound of formula (I):



wherein the variables are as defined
 20 above.

3. The compound according to claim 1 or
 claim 2, wherein:

X is -[CH₂]₀-, -[CH₂]_m-O-, -[CH₂]_m-S(O)₂, or -[CR₂₀R₂₀]_m-
 25 NR₂₁; wherein:

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R_{21} is hydrogen or $-C(O)-O-R_{22}$;

o is 1 or 2;

R_{22} is $-(C1-C6)alkyl$, $-(C2-C6)alkenyl$, or
 $-(C2-C6)alkynyl$;

5 m is 0 or 1;

R_5 is $-(C2-C7)alkyl$ optionally substituted with
 halogen;

each R_{20} is independently hydrogen, $-(C1-C6)alkyl$ or
 $-O-((C1-C6)alkyl)$; or each R_{20} is taken together with the
 10 carbon atoms to which they are bound to form a $(C3-$
 $C6)cycloalkyl$;

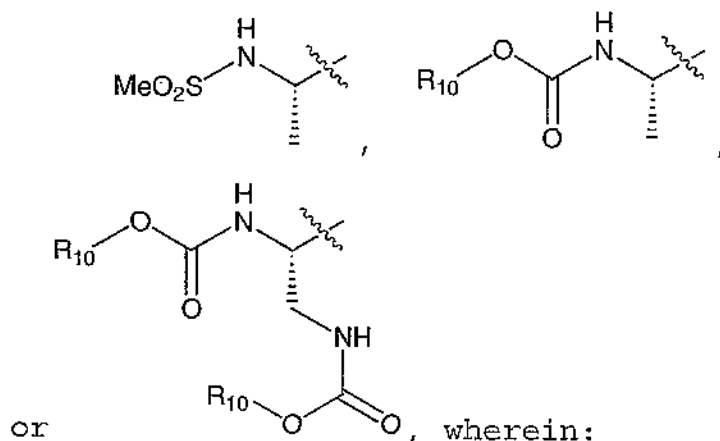
R_3 and R_1 are independently $-(C1-C10)alkyl$,
 $-(C3-C7)cycloalkyl$, or $-((C1-C6)alkyl)-((C3-$
 $C7)cycloalkyl)$;

15 V is a bond, $-CH(R_8)-$, $-N(R_8)-$, $-O-$, $-O-CH(R_8)-$, $-S-$,
 $-S-CH(R_8)-$, $-C(O)-$, $-C(O)-O-$, $-C(O)-S-$, $-C(O)-CH(R_8)-$,
 $-C(O)N(R_8)-$, $-S(O)-$, $-S(O)-CH(R_8)-$, $-S(O)N(R_8)-$,
 $-S(O)-N(R_8)-CH(R_8)-$, $-S(O)_2-$, $-S-(O)_2-CH(R_8)-$, $-S(O)_2N(R_8)-$, or
 $-S(O)_2-N(R_8)-CH(R_8)-$;

20 wherein R_8 is hydrogen or $-(C1-C3)alkyl$;

T is $-(C6-C10)aryl$, $-(C5-C10)heteroaryl$,
 $-(C3-C6)cycloalkyl$, $-(C3-C10)heterocyclyl$, $-(C1-C6)alkyl-$
 $(C6-C10)aryl$, $-(C1-C6)alkyl-(C5-C10)heteroaryl$,
 $-(C1-C6)alkyl-(C3-C6)cycloalkyl$, $-(C1-C6)alkyl-$
 25 $(C3-C10)heterocyclyl$, $-(C2-C6)alkenyl-(C6-C10)aryl$,
 $-(C2-C6)alkenyl-(C5-C10)heteroaryl$, $-(C2-C6)alkenyl-$
 $(C3-C6)cycloalkyl$, $-(C2-C6)alkenyl-(C3-C10)heterocyclyl$,

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R_{10} is -(C1-C4)alkyl; and

W is -C(O)OH or -C(O)-C(O)- R_6 , wherein:

5 R_6 is -(C1-C6)alkyl, -(C6-C10)aryl,
 -(C3-C6)cycloalkyl, -(C5-C10)heteroaryl,
 -(C3-C10)heterocyclyl, or

W is -C(O)-C(O)NR₆R₆, wherein:

NR₆R₆ is -NH-((C1-C6)alkyl),
 10 -NH-((C3-C6)cycloalkyl), -NH-CH(CH₃)-aryl, -NH-CH(CH₃)-
 (C5-C10)heteroaryl or -NH-CH(CH₃)-(C3-C10)heterocyclyl,
 wherein said aryl, heteroaryl, or heterocyclyl is
 optionally substituted with a suitable electron
 withdrawing group.

15

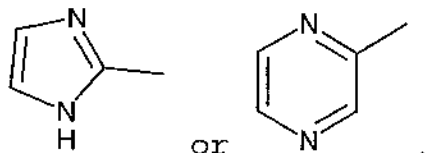
4. The compound according to claim 3, wherein
 V is -NH-.

5. The compound according to claim 3, wherein
 20 V is -C(O)-.

6. The compound according to claim 3,
 wherein T is a -(C5-C10)heteroaryl.

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7. The compound according to claim 6, wherein
T is:



5 8. The compound according to claim 3, wherein
R₁ is -CH₂-CH(CH₃)-CH₃, -C(CH₃)₃, -CH(CH₃)₂,
-CH(CH₃)-CH₂-CH₃, or cyclohexyl.

9. The compound according to claim 8, wherein
10 R₁ is cyclohexyl.

10. The compound according to claim 3, wherein
R₃ is -C(CH₃)₂, -CH(CH₃)₂, -CH(CH₃)-CH₂-CH₃, or cyclohexyl.

15 11. The compound according to claim 10,
wherein R₃ is -C(CH₃)₃ or -CH(CH₃)₂.

12. The compound according to claim 3, wherein
each R₂₀ is independently -CH₃ or hydrogen.

20

13. The compound according to claim 12,
wherein each R₂₀ is hydrogen.

14. The compound according to claim 3, wherein
25 R₅ is -CH₂CH₂CH₃, -CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂F, -CH₂CH₂CHF₂, or
-CH₂CH₂CF₃.

15. The compound according to claim 14,

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wherein R_5 is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ or $-\text{CH}_2\text{CH}_2\text{CHF}_2$.

16. The compound according to claim 15,
wherein R_5 is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$.

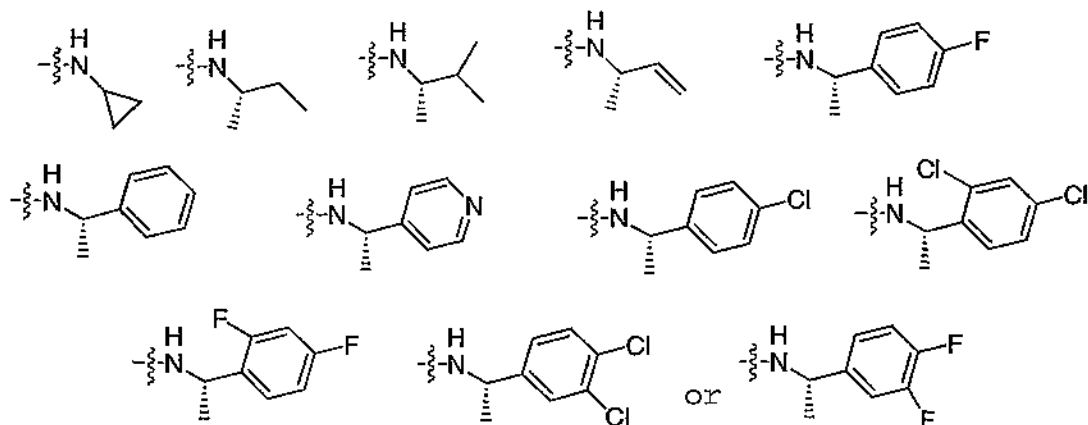
5

17. The compound according to claim 3, wherein
W is $\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_6$.

18. The compound according to claim 3, wherein
10 W is $\text{C}(\text{O})-\text{C}(\text{O})\text{NR}_6\text{R}_6$ and NR_6R_6 is $-\text{NH}-(\text{C}3-\text{C}6)\text{cycloalkyl}$,
 $-\text{NH}-\text{CH}(\text{CH}_3)-(\text{C}6-\text{C}10)\text{aryl}$, $-\text{NH}-\text{CH}(\text{CH}_3)-(\text{C}3-$
 $\text{C}10)\text{heterocyclyl}$, or $-\text{NH}-\text{CH}(\text{CH}_3)-(\text{C}5-\text{C}10)\text{heteroaryl}$,
wherein said aryl, heterocyclyl, or heteroaryl is
optionally substituted with halogen.

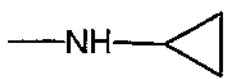
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19. The compound according to claim 18,
wherein NR_6R_6 is:



20

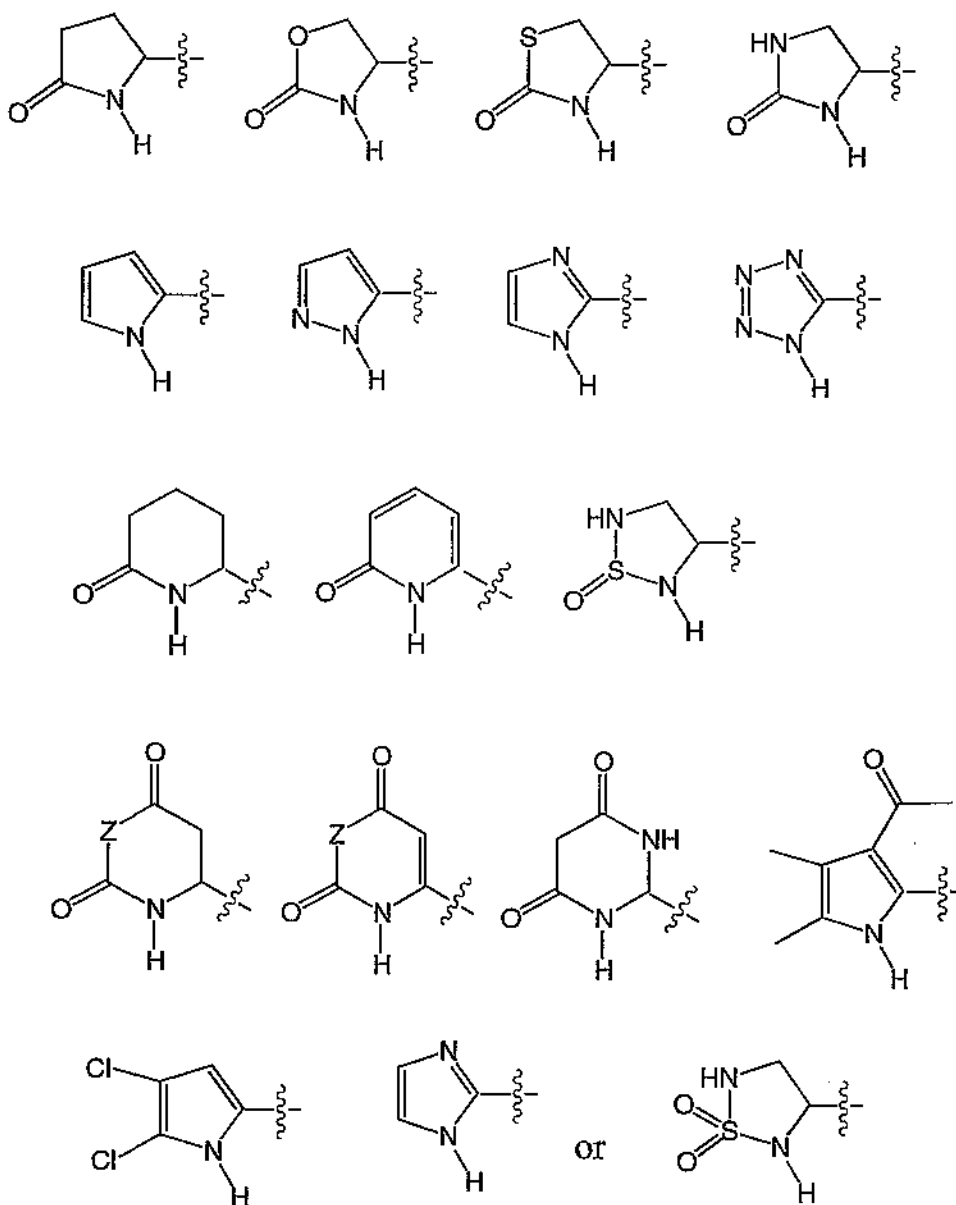
20. The compound according to claim 19,
wherein NR_6R_6 is:



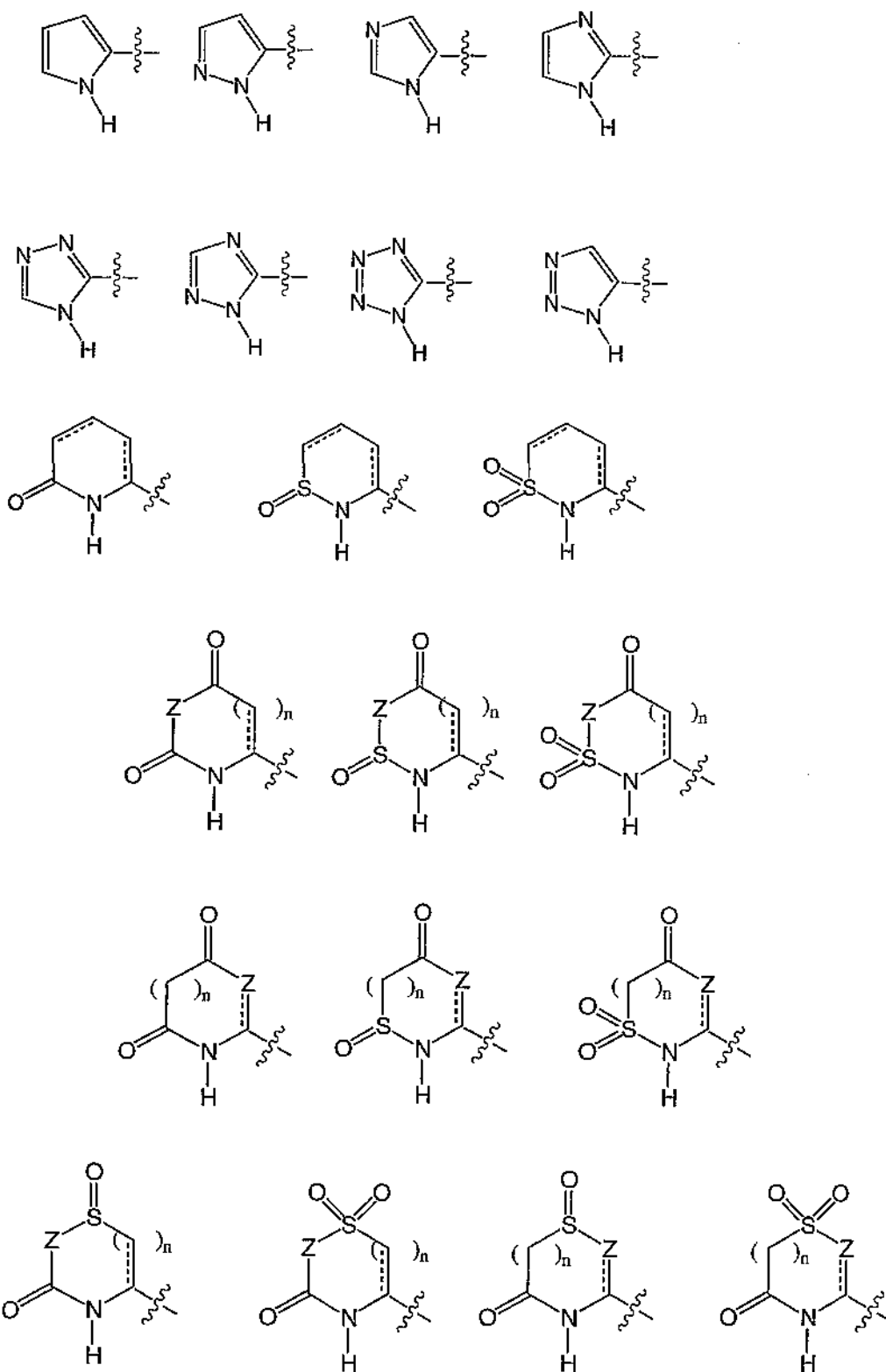
- 78 -

21. The compound according to claim 1 or claim 2, wherein T contains at least one hydrogen bond donor moiety selected from -NH_2 , -NH- , -OH , and -SH .

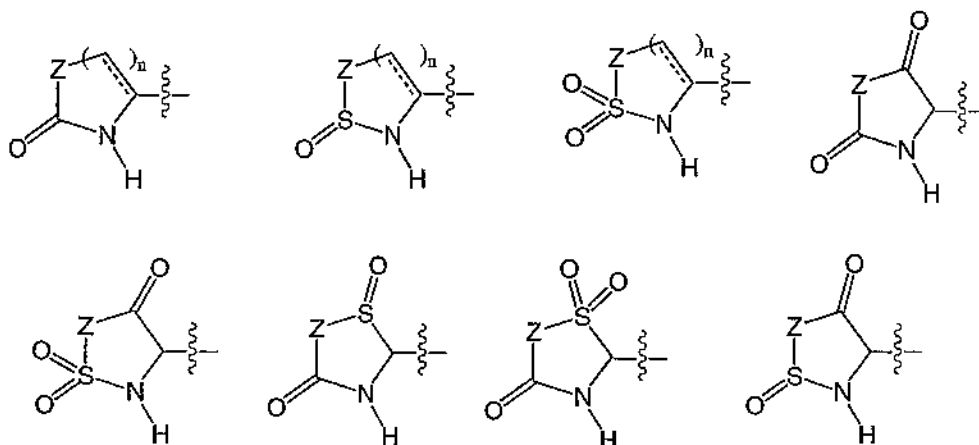
5 22. The compound according to claim 21, wherein T is:



- 79 -



- 80 -

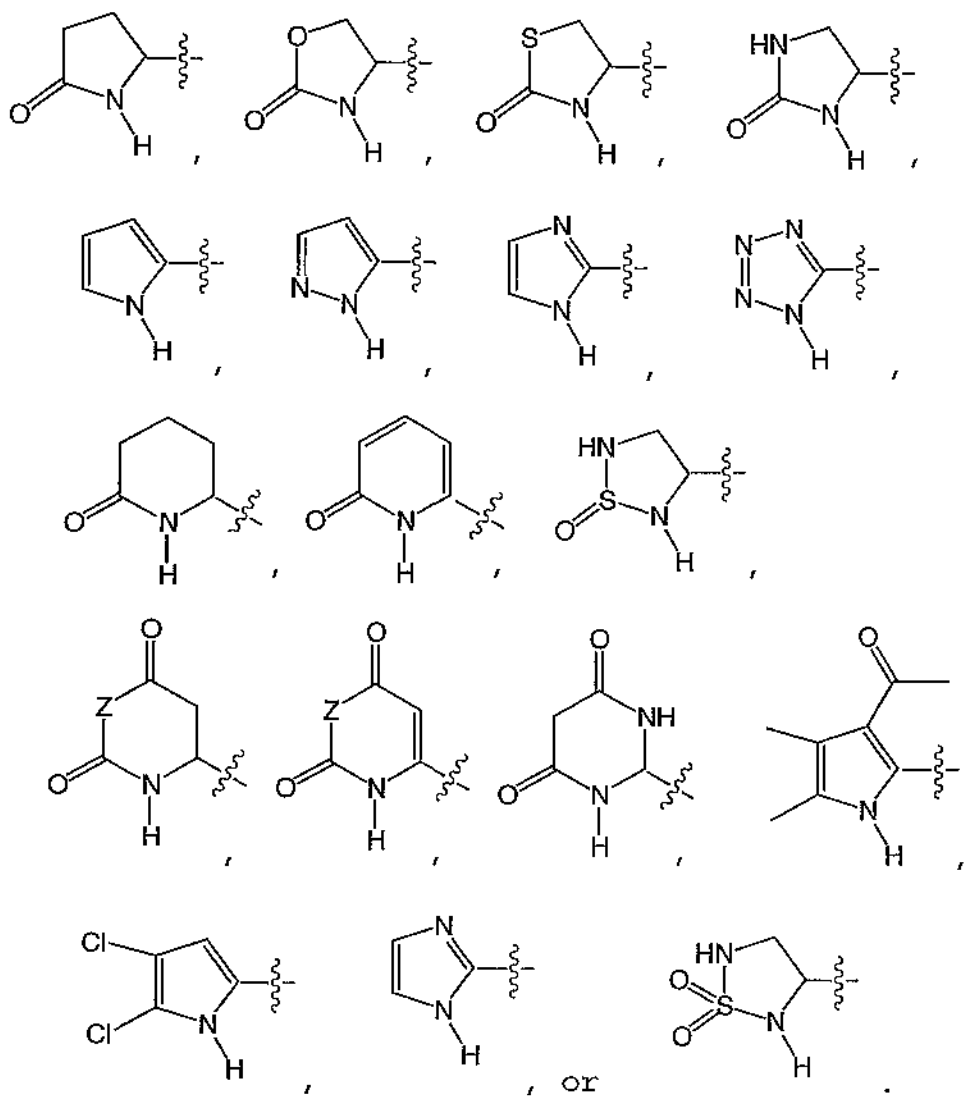


wherein:

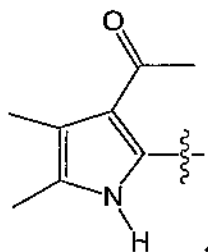
- T is optionally substituted with up to 3 J
 5 substituents, wherein J is as defined in claim 1;
 Z is independently O, S, NR₁₀, or C(R₁₀)₂;
 n is independently 1 or 2; and
 ----- is independently a single bond or a double bond.

- 10 23. The compound according to claim 22, wherein T
 is:

- 81 -



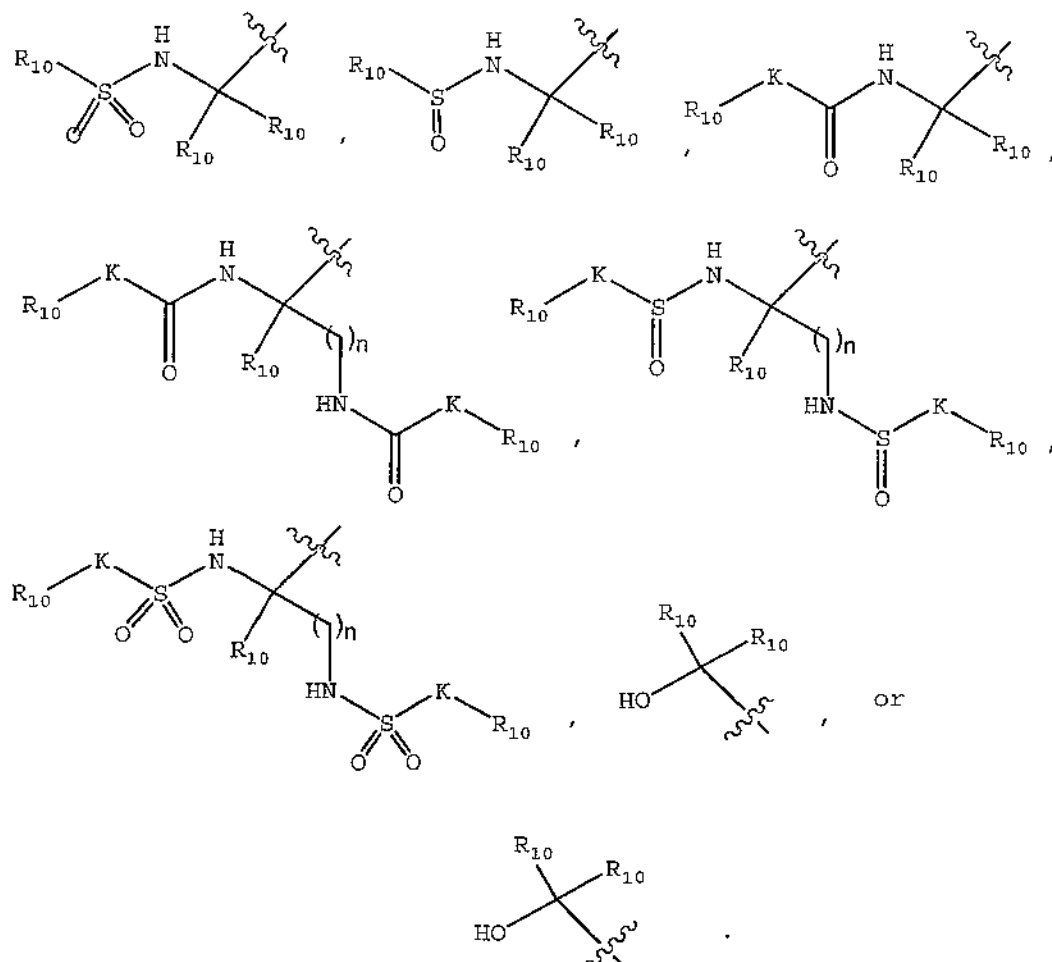
24. The compound according to claim 23,
wherein T is



5

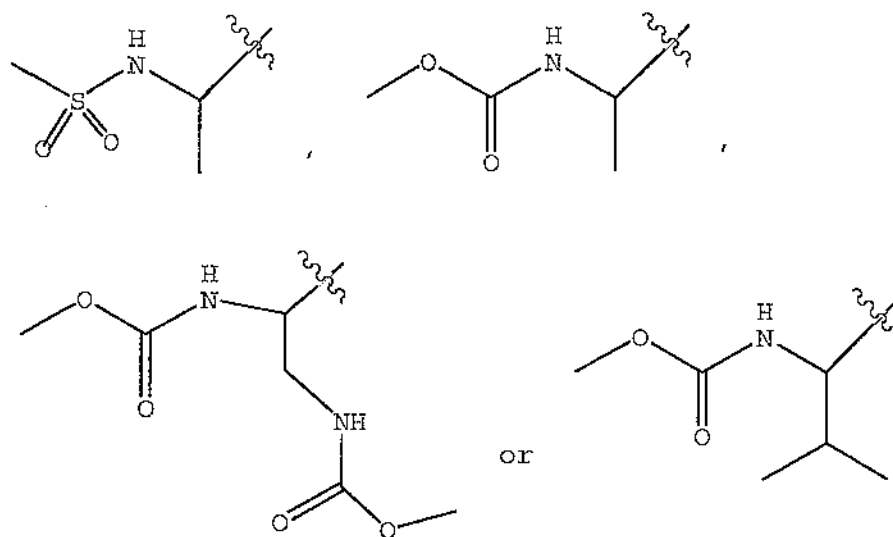
25. The compound according to claim 21,
wherein T is:

- 82 -

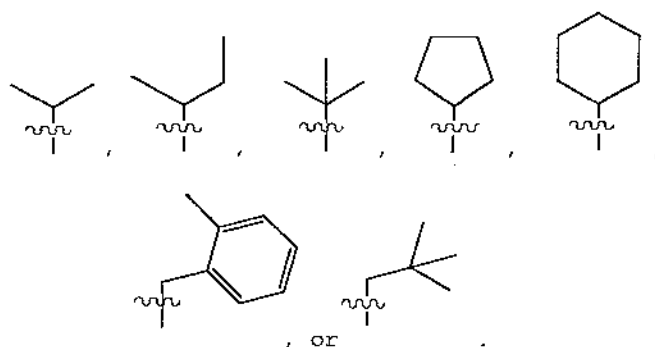


- 5 26. The compound according to claim 25,
wherein T is:

- 83 -

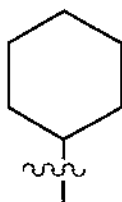


27. The compound according to claim 1 or claim 2, wherein R_1 is:



5

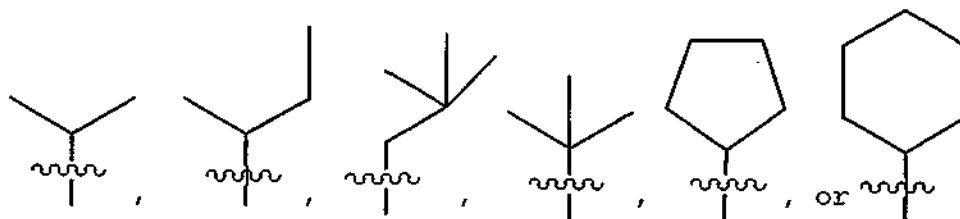
28. The compound according to claim 27, wherein R_1 is:



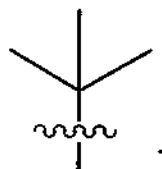
10

29. The compound according to claim 1 or claim 2, wherein R_3 is:

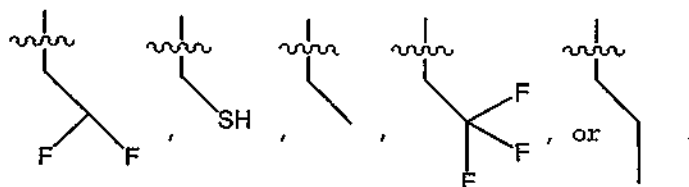
- 84 -



30. The compound according to claim 29,
 5 wherein R_3 is:

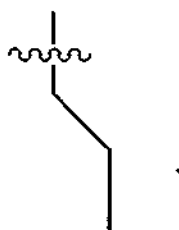


31. The compound according to claim 1 or
 claim 2, wherein R_5 is:



10

32. The compound according to claim 31,
 wherein R_5 is:



15

33. The compound according to claim 1 or
 claim 2, wherein R_2 and R_4 are each independently H,
 methyl, ethyl, or propyl.

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34. The compound according to claim 33,
wherein R_2 and R_4 are each H.

35. The compound according to claim 1 or 2,
5 wherein X is $-\text{[CH}_2\text{]}_o-$, $-\text{[CJ'J']}_o-$, $-\text{[CH}_2\text{]}_m-\text{O}-$, $-\text{[CH}_2\text{]}_m-$
 S(O)_2- , $-\text{[CH}_2\text{]}_m-\text{SO}-$, $-\text{[CR}_{20}\text{R}_{20}]_m-\text{NR}_{21}-$, or $-\text{[CR}_{20}\text{R}_{20}]_m-\text{NJ''}-$.

36. A composition comprising a compound
according to any one of claims 1-35 or a pharmaceutically
10 acceptable salt, derivative or prodrug thereof in an
amount effective to inhibit a serine protease; and a
acceptable carrier, adjuvant or vehicle.

37. The composition according to claim 36,
wherein said composition is formulated for administration
15 to a patient.

38. The composition according to claim 37,
wherein said composition comprises an additional agent
selected from an immunomodulatory agent; an antiviral
20 agent; a second inhibitor of HCV protease; an inhibitor
of another target in the HCV life cycle; or combinations
thereof.

39. The composition according to claim 38,
25 wherein said immunomodulatory agent is α -, β -, or γ -
interferon; the antiviral agent is ribavarin or
amantadine; or the inhibitor of another target in the HCV
life cycle is an inhibitor of HCV helicase, polymerase,
or metalloprotease.

30

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40. A method of inhibiting the activity of a serine protease comprising the step of contacting said serine protease with a compound according to any one of claims 1-35.

5 41. The method according to claim 40, wherein said protease is an HCV NS3 protease.

42. A method of treating an HCV infection in a patient comprising the step of administering to said patient a composition according to claim 37 or claim 38.

10 43. The method according to claim 42, comprising the additional step of administering to said patient an additional agent selected from an immunomodulatory agent; an antiviral agent; a second inhibitor of HCV protease; an inhibitor of another target
15 in the HCV life cycle; or combinations thereof; wherein said additional agent is administered to said patient as part of said composition according to claim 37 or as a separate dosage form.

20 44. The method according to claim 43, wherein said immunomodulatory agent is α -, β -, or γ -interferon; said antiviral agent is ribavirin or amantadine; or said inhibitor of another target in the HCV life cycle is an inhibitor of HCV helicase, polymerase, or metalloprotease.

25 45. A method of eliminating or reducing HCV contamination of a biological sample or medical or laboratory equipment, comprising the step of contacting

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said biological sample or medical or laboratory equipment with a composition according to claim 36.

46. The method according to claim 45, wherein
said sample or equipment is selected from blood, body
5 fluids other than blood, biological tissue, a surgical
instrument, a surgical garment, a laboratory instrument,
a laboratory garment, a blood or other bodily fluid
collection apparatus; a blood or other bodily fluid
storage material.

INTERNATIONAL SEARCH REPORT

In ☐ national Application No
PCT/US 02/22027

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K5/10 C07D471/08 C07D453/06 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 09558 A (BOEHRINGER INGELHEIM CA LTD ;GOUDREAU NATHALIE (CA); GHIRO ELISE () 24 February 2000 (2000-02-24) cited in the application compounds 1-511 page 1, line 3 -page 1, line 7; claims -----	1-46
A	US 4 720 484 A (VINCENT MICHEL ET AL) 19 January 1988 (1988-01-19) examples 8-14 -----	1-35

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

25 November 2002

Date of mailing of the international search report

03/12/2002

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Authorized officer

Schmid, A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/22027

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 40-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Int nat Application No

PCT/US 02/22027

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Fluorine in Medicinal Chemistry

Hans-Joachim Böhm,* David Banner, Stefanie Bendels, Manfred Kansy, Bernd Kuhn, Klaus Müller, Ulrike Obst-Sander, and Martin Stahl^[a]

Fluorinated compounds are synthesized in pharmaceutical research on a routine basis and many marketed compounds contain fluorine. The present review summarizes some of the most frequently employed strategies for using fluorine substituents in medicinal chemistry. Quite often, fluorine is introduced to improve the metabolic stability by blocking metabolically labile sites. However, fluorine can also be used to modulate the physi-

cochemical properties, such as lipophilicity or basicity. It may exert a substantial effect on the conformation of a molecule. Increasingly, fluorine is used to enhance the binding affinity to the target protein. Recent 3D-structure determinations of protein complexes with bound fluorinated ligands have led to an improved understanding of the nonbonding protein–ligand interactions that involve fluorine.

1. Introduction

Carbon-bound fluorine atoms are unique in organic chemistry. Fluorine is a small atom with a very high electronegativity.^[1] With a van der Waals radius of 1.47 Å,^[2] covalently bound fluorine occupies a smaller volume than a methyl, amino, or hydroxyl group, but is larger than a hydrogen atom (van der Waals radius of 1.2 Å).

While synthetic fluoro-organic chemistry has matured over recent decades, the specific use of fluorine in small-molecule drug-discovery research is more recent. Traditional medicinal chemistry was very much based on the use of natural compounds or closely related derivatives thereof. Traditional Chinese medicines, for example, do not contain fluorinated molecules.^[3] As a consequence, until the 1970s fluorinated compounds were rare in medicinal chemistry.^[4] This has changed quite dramatically over the last 20 years, and fluorinated compounds are nowadays synthesized in pharmaceutical research on a routine basis.^[5–7] According to the World Drug Index (WDI), there are 128 fluorinated compounds with US trade names.^[8] Of the 31 new chemical entities approved in 2002, nine compounds contained fluorine.^[9]

In the present contribution, we select a few examples to illustrate how fluorine substitution is used in contemporary medicinal chemistry. We are not attempting to provide an exhaustive review of the subject. Instead, we will discuss representative examples and comment on how we see the use of fluorine evolving.

Current strategies for the introduction of fluorine atoms center on the following topics:

- 1) Metabolic stability is one of the key factors in determining the bioavailability of a compound. Rapid oxidative metabolism by the liver enzymes, in particular the P450 cytochromes, is often found to limit bioavailability. A frequently employed strategy to circumvent this problem is to block the reactive site by the introduction of a fluorine atom. There are many examples^[10–14] illustrating that the replacement of an oxidizable C–H group by a C–F group increases metabolic stability of the molecule.
- 2) Fluorine can change the basicity of a compound. Highly basic groups can have a limiting effect on the bioavailabili-

ty. A fluorine atom introduced close to a basic group reduces its basicity; this results in better membrane permeation of a compound and thus improved bioavailability.

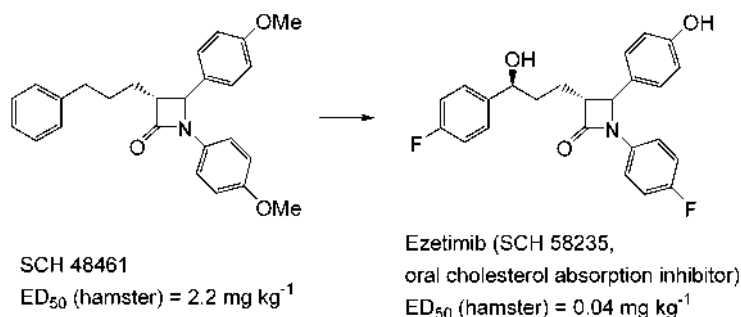
- 3) Increasingly, fluorine substituents are introduced to increase the binding affinity of a compound. For example, most of the NK1 antagonists currently in clinical development contain a 3,5-di(trifluoromethyl)phenyl group to increase binding affinity.^[15] In a recent review on the use of QSAR and computer-aided design methods, Wermuth described the 3,5-di(trifluoromethyl)phenyl group as “magic”^[16] because it is found in many published NK1 antagonists and classical QSAR does not account for this strong effect of fluorine.

2. Improving Metabolic Stability with Fluorine

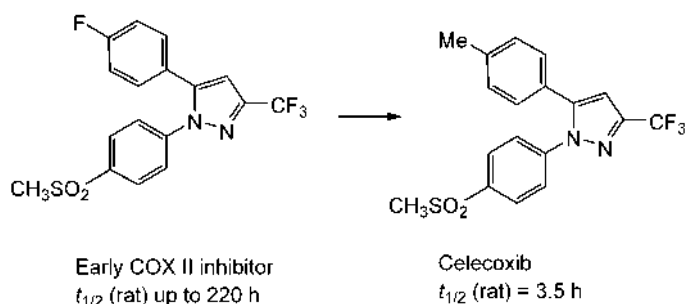
Low metabolic stability is a recurring challenge in many drug-discovery projects. Lipophilic compounds have a tendency to be oxidized by liver enzymes, in particular cytochrome P450. There are several strategies to counter this issue. One of them is to make the molecule more polar. An alternative strategy is to block the metabolically labile site with a fluorine substituent and hope that the small fluorine atom will not impair the binding to the target protein. Indeed, this approach is frequently employed and has led to many successful compounds.^[10–14]

A particularly nice example is the discovery of the cholesterol-absorption inhibitor Ezetimibe (Scheme 1).^[12–13] Starting from the moderately potent compound SCH48461, blockade of two metabolically labile sites in the molecule by fluorine substituents contributed significantly to the discovery of SCH58235 (Ezetimibe), which is a very potent compound that

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Scheme 1. Development of Ezetimibe (SCH58235) by optimization of the lead SCH48461.^[12,13] As part of the optimization, two metabolically labile sites are blocked by fluorine substituents.



Scheme 2. Development of the COX 2 inhibitor Celecoxib.^[14] Replacement of a fluorine group by a methyl group reduces the very long half-life to an acceptable level.

was recently approved by the FDA. Introduction of fluorine atoms prevent oxidation of the phenyl ring to phenol and dealkylation of the methoxy group.

Another interesting recent example demonstrating the strong effect of fluorine on metabolic stability, is the discovery of the cyclo-oxygenase 2 (COX 2) inhibitor Celecoxib (Scheme 2).^[10,14] In this case, the extremely high metabolic stability of the lead compound, which results in a very long biological half life, could be reduced to more acceptable levels by replacing a fluorine atom by a metabolically labile methyl group.

Interestingly, there are also a few cases known for which the introduction of a fluorine substituent does not prevent oxidation at that site.^[5,17,18] This phenomenon is observed in particular for phenyl rings with a nitrogen substituent in the *para* position to the fluorine substituent. During P450-catalyzed oxidation, a rearrangement takes place in which the fluorine atom moves to an adjacent carbon and the phenol metabolite is formed *para* to the nitrogen substituent.

3. The Effect of Fluorine on Physicochemical Properties

3.1 The effect of fluorine on the pK_a

As the most electronegative atom, fluorine has a very strong effect on the acidity or basicity of nearby functional groups.

Depending on the position of the fluorine substituent relative to the acidic or basic group in the molecule, a pK_a shift of several log units can be observed. For example, the pK_a's of acetic acid and its α -fluorinated analogues are 4.76 (CH₃COOH), 2.59 (CH₂FCOOH), 1.24 (CHF₂COOH), and 0.23 (CF₃COOH).^[15] Likewise, the basicities of ethylamine and its β -fluorinated analogues, measured by the pK_a's of the protonated amines, decrease in an approximately linear fashion upon introduction of fluorine, the pK_a's being 10.7 (CH₃CH₂NH₂), 8.97 (CH₂FCH₂NH₂), 7.52 (CHF₂CH₂NH₂), and 5.7 (CF₃CH₂NH₂).^[19] Similarly, a fluorine substituent at the 3 and 4 position of a piperidine ring lowers the pK_a by about 2 log units.^[20–21]

Quite often, a change in the pK_a has a strong effect on both the pharmacokinetic properties of the molecule and its binding affinity. For example, a strongly basic group may be required for binding within a certain lead series, but at the same time this basic group may also be found to result in compounds with low bioavailability due to the limited ability of a strong basic group to pass through membranes. The drug discovery project team is then faced with the challenge of finding an optimum between these conflicting effects.

This challenge is very nicely highlighted by the work of van Niel et al.^[22] on the discovery of novel fluorinated indole derivatives as selective 5HT_{1D} receptor ligands. The incorporation of fluorine was found to significantly reduce the pK_a of the compounds, and this reduction of basicity, with a concomitant weakening of the affinity to the receptor, was shown to have a strong beneficial influence on oral absorption (Figure 1).

3.2 The effect of fluorine on molecular lipophilicity

Lipophilicity is a key molecular parameter in medicinal chemistry. Typically, groups of substantial lipophilicity on the ligand are required to obtain a good binding affinity to the target protein.^[23] However, a high lipophilicity typically results in a reduced solubility and a number of other undesirable properties for a compound. Therefore, the right balance between a required lipophilicity and a certain minimal overall polarity of the molecule is one of the recurring challenges for medicinal chemists.

We investigated the effect of replacing a hydrogen by a fluorine atom on the lipophilicity of a compound. We selected 293 pairs of molecules from the Roche in-house database with measured log*D* values that just differ by one fluorine atom. Log*D* is the logarithmic coefficient of the distribution of the compound between octanol and water at a given pH (typically 7.4). A histogram of changes in log*D* upon one H/F exchange is shown in Figure 2. The plot reveals a Gaussian distribution with the maximum slightly higher than 0. On average, the substitution of a hydrogen atom by fluorine increases lipophilicity slightly, by roughly 0.25 log units. This is in line with expectations and atomic increments published by others.^[24] Interest-

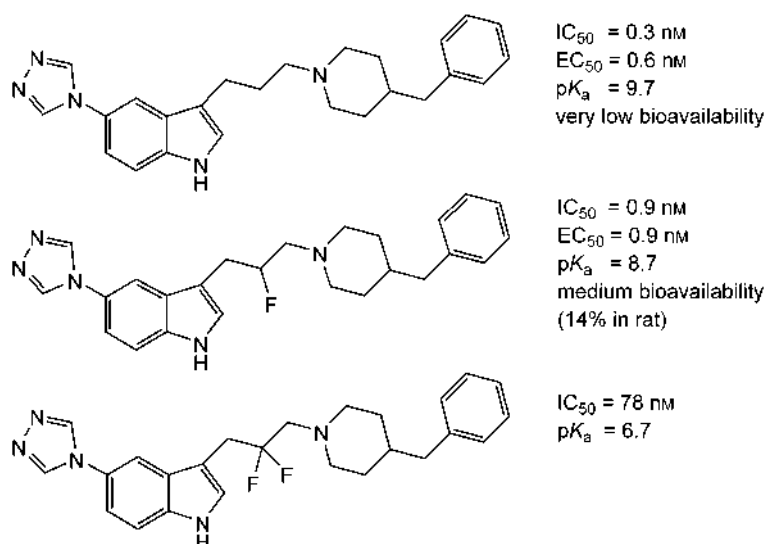


Figure 1. Effect of pK_a value on the bioavailability and receptor binding for a set of $5HT_{1D}$ agonists.^[22] The nonfluorinated parent compound is a very potent receptor ligand, but has very low bioavailability. The monofluorinated compound has a lower pK_a that is still compatible with the requirements for receptor binding, but now results in a compound of substantially increased bioavailability. The difluoro compound has a pK_a of 6.7. This compound is no longer basic enough to achieve high binding affinity for the $5HT_{1D}$ receptor.

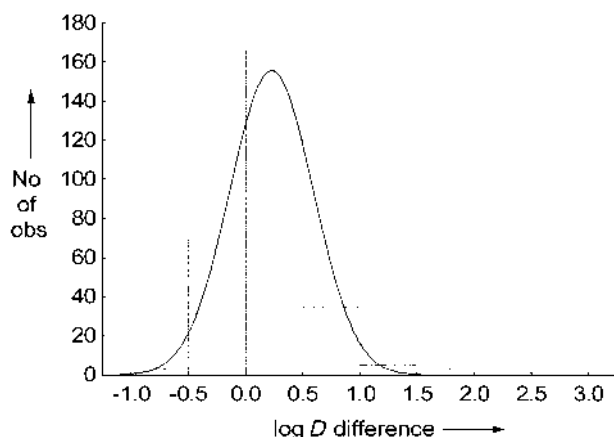
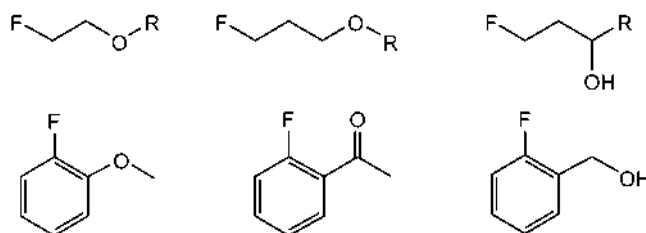


Figure 2. Histogram of change in $\log D$ observed upon substitution of a hydrogen atom by a fluorine atom. On average, $\log D$ is increased by roughly 0.25.

ingly, the tail of the Gaussian distribution extends to values below zero. In other words, there are quite a number of cases for which an H to F substitution decreases lipophilicity. A closer inspection of these cases reveals that there are a few recurring structural patterns that appear to correlate with this effect. The substructures are shown in Scheme 3. At the present, we cannot offer a conclusive explanation for this effect. Interestingly, the compounds are characterized by the presence of an oxygen atom close to the fluorine. We carried out conformational analyses for 14 compounds with a negative $\log D$ shift associated with one single H/F exchange. All compounds were found to have at least one low-energy conformer with an O...F distance smaller than 3.1 Å. In order to better understand this observation, we calculated the solvation free energies for

ethylbenzene, *ortho*-fluoroethylbenzene, acetophenone, and *ortho*-fluoroacetophenone in water and in chloroform (we used chloroform instead of *n*-octanol for technical reasons) by using an ab initio quantum-chemical method.^[25] These results indicate that, for ethylbenzene, the fluorine substituent has little effect on the solvation energy both in water and in chloroform, whereas for acetophenone, the fluorine substituent enforces the solvation energy in water more strongly than in chloroform. Taken together with the results from the conformational analysis, one possible explanation, is that fluorine in close vicinity to an oxygen atom increases the overall polarity of the molecule, leading to a more pronounced gain in solvation energy in the polar medium relative to the nonpolar solvent. However, it is also possible that the fluorine polarizes the neighboring oxygen atoms and this leads to stronger hydrogen bonds between the oxygen and neighboring water molecules.

The concept of increased lipophilicity due to H/F exchange does not appear to hold in general and should therefore be used with care. Moreover, our results might point to strategies to reduce the lipophilicity of a compound while, at the same time, increasing its metabolic stability.



Scheme 3. Chemical substructures observed in compounds for which a fluorine substituent decreases $\log D$.

We have also examined the other end of the Gaussian distribution shown in Figure 2, which contains compounds with a much stronger positive shift in $\log D$ than expected for a single H/F exchange. Most of these compounds contain one or more basic nitrogen atoms. The fluorine substituent reduces the basicity of the nitrogen functionality, leading to an increased $\log D$ which was measured at pH 7.4.

In interpreting the data, we should keep in mind that our data set of 293 molecular pairs might contain a certain structural bias. Therefore, it is very likely that further substructural elements will be discovered that will also give rise to interesting effects of a fluorine substituent on lipophilicity.

4. The Effect of a F Substituent on Molecular Conformation

A fluorine substituent can lead to a change in the preferred molecular conformation. Again, this effect can be explained by

the size and electronegativity of fluorine. Based on a van der Waals radius of 1.47 Å for fluorine, the volume of a trifluoromethyl group is roughly twice that of a methyl group. As a result, the effect of fluorine substitution on molecular conformation is quite subtle and sometimes difficult to predict.

For example, methoxybenzenes without *ortho* substituents favor a planar conformation. We have carried out a search for trifluoromethoxybenzenes without substituents in the *ortho* positions using the November 2003 release of the Cambridge Structural Database (CSD)^[26] and found six entries.^[27] None of them has the $-\text{OCF}_3$ group in the plane of the phenyl ring. For five entries, the dihedral angle C–C–O–C is around 90°, while for one crystal structure the dihedral angle is about 36°. Interestingly, similarly twisted conformations are also found for aryl-bound difluoroalkoxy groups. Spectroscopic studies and high-level quantum-mechanical calculations further show that preference for the planar arrangement in anisole ($\Delta E \sim 3 \text{ kcal mol}^{-1}$) is inverted to the orthogonal orientation in trifluoromethylanisole ($\Delta E \sim -0.5 \text{ kcal mol}^{-1}$).^[28]

These observations can have important consequences in a lead-optimization program. Clearly, the OCF_3 group is not just a simple isosteric replacement of a OCH_3 group, because it adopts a different conformation. The R group in $\text{Ph}-\text{OCF}_2-\text{R}$ will point in a different direction from that of the R group in $\text{Ph}-\text{OCH}_2-\text{R}$. A nice example illustrating this point is the work by Massa et al.^[29] on inhibitors of cholesteryl ester transfer protein (CETP) containing 3-tetrafluoroethoxy substituents. This paper suggests that the steric and electronic properties of $\text{Ph}-\text{OCF}_2\text{CF}_2\text{H}$ are very similar to 2-phenyl-furan, which according to Massa et al.^[29] is also nonplanar. From a medicinal chemistry perspective, this is a very interesting finding because mono-substituted furan is generally considered to be an undesirable group due to its metabolic instability and its potential to generate reactive metabolites. The $\text{OCF}_2\text{CF}_2\text{H}$ side chain is therefore a promising route forward to converting a biologically active furane into a more stable group.

5. The Role of Fluorine in Protein–Ligand Interactions

Fluorine can have significant effects on the binding affinity in protein–ligand complexes. This effect can be direct by interaction of the fluorine with the protein, or it can be indirect by modulation of the polarity of other groups of the ligand that interact with the protein.

Frequently, it is found that a fluorine substituent leads to a slight enhancement of the binding affinity due to an increased lipophilicity of the molecule (see section 3.2) that results in an increased (nonspecific) affinity for the protein. If F increases the affinity by lipophilic interactions, then one will typically see a gradual increase of the affinity for the series $\text{H}-\text{F}-\text{Cl}-\text{Br}$. Indeed, such behavior has been frequently reported, for example, in ref. [30], and it is indicative of unspecific lipophilic interactions of fluorine. However, sometimes within the $\text{H}-\text{F}-\text{Cl}-\text{Br}$ series, the observed binding affinity is maximum for F, for example in ref. [31]. This behavior may be consistent with the oc-

currence of specific polar interactions involving F or simply indicate that only limited space is available in the protein cavity.

Probably the strongest indirect effect of fluorine on binding affinity is the change of basicity or acidity of the ligand molecule. One example is the set of $5\text{HT}_{1\text{D}}$ agonists described by van Niel et al.^[22] discussed above (Figure 1). Another striking example is the binding of $\text{CX}_3\text{SO}_2\text{NH}_2$ ($\text{X}=\text{H}$ or F) to carbonic anhydrase II (CA II).^[32] CA II is a metalloenzyme with a zinc cation in the active site. It is known from 3D X-ray structure determination that the deprotonated sulfonamide group binds at the active site through a direct interaction of the negatively charged $\text{R}-\text{SO}_2\text{NH}^-$ group and the positively charged Zn^{2+} cation. $\text{CH}_3\text{SO}_2\text{NH}_2$ is an extremely weak acid with a pK_a of 10.5 and binds to CA II with $K_i=100 \mu\text{M}$. $\text{CF}_3\text{SO}_2\text{NH}_2$ is much more acidic due to the electron-withdrawing effect of the three fluorine atoms and has a pK_a of 5.8; at neutral pH, $\text{CF}_3\text{SO}_2\text{NH}_2$ is dissociated. As an anion, it binds to carbonic anhydrase more strongly with $K_i=2 \text{ nM}$. This simple fluoroaliphatic sulfonamide is thus almost as potent an inhibitor of carbonic anhydrase as some more complex heteroaromatic compounds that have been in use for the treatment of glaucoma for more than 50 years. That the binding affinity to carbonic anhydrase is directly linked to the pK_a of the sulfonamides is evidenced by a linear correlation between the acid pK_a (ranging from 5.8 to 11.1) and the binding constant K_i (ranging from 2 nM to 250 μM).^[32]

Benzylic α,α -difluorophosphonates, α,α -difluorosulfonates, and α,α -difluorocarboxylates have been described as inhibitors of the protein tyrosine kinase 1B (PTB1B).^[33,34] Difluoro compounds are relatively good inhibitors of PTB1B, while the non-fluorinated counterparts are very poor inhibitors. X-ray crystallographic and kinetic studies suggest that this effect is due to direct interactions of at least one of the fluorine atoms with the enzyme active site. The effect appears not to be attributable to pK_a shifts.^[33,34]

The enzyme carbonic anhydrase II has also been used to study direct protein–ligand interactions involving fluorine.^[35–38] Abbate et al.^[35] synthesized analogues of the CA II inhibitor methazolamide. The perfluorobenzoyl analogue binds almost ten times more strongly to CA II than methazolamide. The X-ray crystallographic structure determination reveals a stacking interaction between the perfluorophenyl ring of the inhibitor and the aromatic ring of Phe131.

A similar interaction of fluoroaromatic inhibitors of human CA II was studied by Doyon et al.^[36] and by Kim et al.^[37–38] Fluorination of a phenyl side chain interacting with the side chain of Phe131 improves the binding affinity.

5.1 The role of F in polar interactions

Olsen et al. have demonstrated for a set of fluorine-substituted thrombin inhibitors that $\text{C}-\text{F} \cdots \text{C}=\text{O}$ interactions can play an important role in protein–ligand interactions and can lead to significantly increased binding affinities.^[39] A fluorine scan of thrombin inhibitors led to the discovery of a monofluorinated compound that binds five times more strongly to thrombin

than the nonfluorinated parent compound. The binding mode of the fluorinated compound was determined by X-ray structure analysis and shows that the F atom is in remarkably close contact with the H-C $_{\alpha}$ -C=O moiety of Asn98 of thrombin. The authors suggest that this H-C $_{\alpha}$ -C=O fragment should be considered fluorophilic because it offers several favorable polar interactions with F.

Interestingly, a very similar structural arrangement has also been observed in some other protein-ligand complexes with fluorinated ligands, for example in many fluorinated inhibitors of p38 kinase.^[40–42] One example^[42] is shown in Figure 3. A similar interaction pattern for fluorine was also observed for a factor Xa inhibitor.^[43]

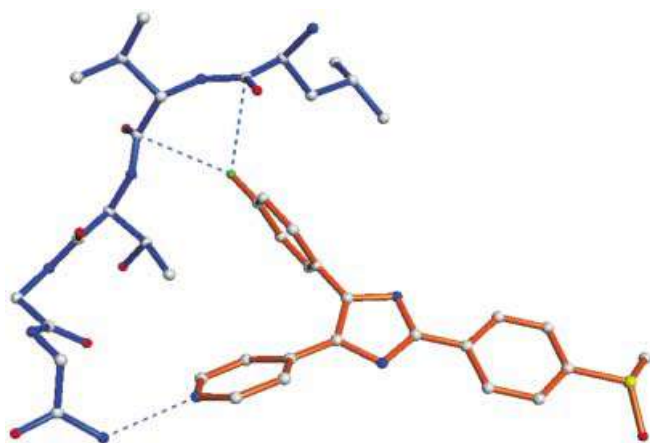


Figure 3. Binding of a fluorinated inhibitor to p38 kinase (pdb refcode 1au9^[41]). The fluorine is in close proximity to two carbonyl groups of the protein. The distances between the fluorine atom and the carbon atoms of the C=O units are 3.21 and 3.47 Å. Oxygen atoms are in red, nitrogen atoms in blue, carbon atoms are light gray, fluorine atoms are green, and sulfur atoms are shown in yellow.

5.2 Does fluorine form hydrogen bonds?

The question of whether covalently bound fluorine atom engages in hydrogen bonds in protein-ligand complexes has been the subject of quite a considerable debate. Dunitz^[44] has pointed out that the number of cases in small-molecule crystal structures in which a covalently bound fluorine atom engages in a nonbonding interaction that could legitimately be termed a hydrogen bond is very small. In most cases, the interactions of C-F units appear to be better described in terms of weak polar interactions.

We would like to report one example from our own work. In

our effort to discover novel serine protease inhibitors with antithrombotic activities, we synthesized a pair of molecules (Figure 4) that differ just by one fluorine atom. The fluorinated

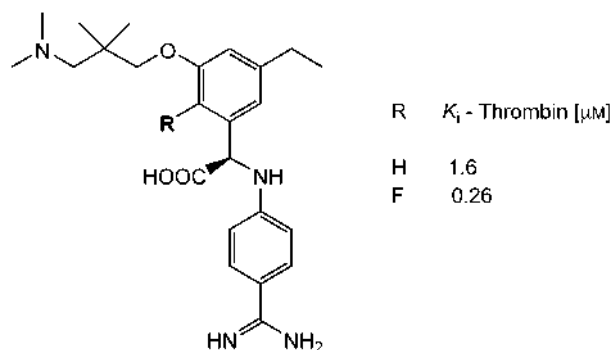


Figure 4. Structure and binding affinity of a pair of thrombin inhibitors with and without fluorine substituent.

compound is a good inhibitor of thrombin with $K_i = 260$ nM. The compound without fluorine is six times less potent ($K_i = 1.6$ μ M). We determined the X-ray structures of both compounds bound to human thrombin. They are shown side-by-side in Figure 5. Interestingly, there is a conformational change of the ligand on going from R=H to R=F. In the fluorinated compound, the fluorine is within hydrogen-bonding distance of the N-H group of Gly216 of thrombin, although the distance is somewhat at the upper end of what would be considered to be geometrically compatible with a hydrogen bond ($R_{FN} = 3.47$ Å). Therefore, this interaction mode certainly constitutes a favorable dipolar interaction. Whether one wants to call this a hydrogen bond remains a matter of personal taste.

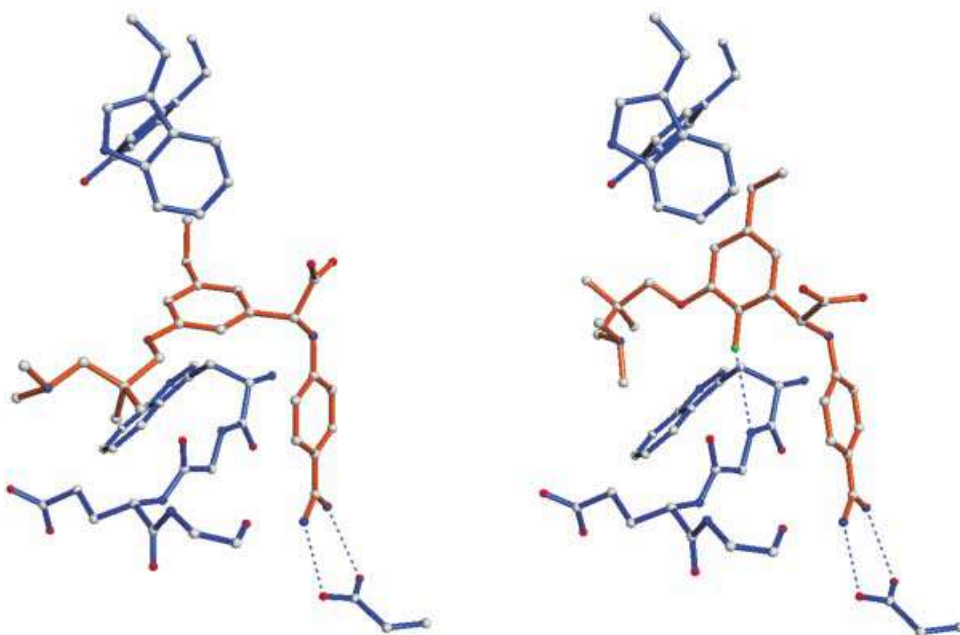
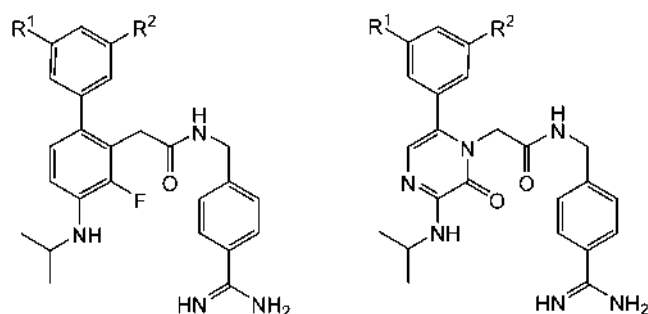


Figure 5. Structure of two inhibitors with and without fluorine bound to thrombin. In the right-hand structure, the F...N distance is 3.47 Å.

A similar interaction of fluorine with a protein N–H group in a series of inhibitors for the serine protease complex Tissue Factor/Factor VIIa (TF/VIIa) has been described by Parlow et al.^[45–47]. They report a fluorinated compound (Figure 6) with



K_i - Tissue Factor VIIa = 0.34 μ M
(R^1 =NH₂, R^2 =H)

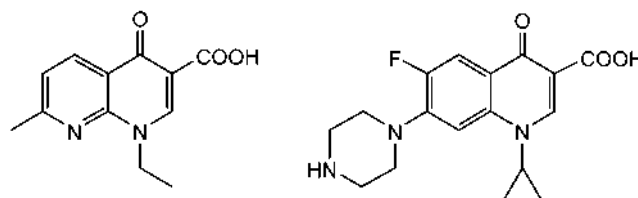
Figure 6. Structure of two inhibitors of the serine protease factor VIIa with pyrazinone and benzene core structures.

a benzene core that is a good inhibitor of TF/VIIa with K_i = 340 nM.^[45] The X-ray structure of the protein–ligand complex reveals a hydrogen bond between the fluorine and the N–H group of Gly216 of the protein with (R_{FN} = 3.4 Å). However, Parlow et al. also report that the fluorinated compound has a weaker binding affinity than the pyrazinone inhibitors, which form strong hydrogen bonds to the N–H group of Gly216 through the pyrazinone carbonyl group.^[46]

6. Fluorine as Key Component in Drugs

As indicated in the Introduction, there are now many marketed drugs containing one or more fluorine atoms. In many cases, fluorine was introduced to modulate the molecular properties, for example, as described in Section 2 for Ezetimibe.^[12–13] In the case of fluorouracil,^[48] the unique properties of fluorine are exploited to generate a potent irreversible inhibitor of thymidylate synthase (actually, the active compound is a metabolite that is formed in vivo).

The discovery of the fluoroquinolones as antibacterials is a striking example of the strong effect of fluorine atoms on molecular properties.^[31,49,50] Fluoroquinolones are highly active and safe antibacterial agents that are widely used. The usage of a first generation of molecules, exemplified by nalidixic acid (Scheme 4), was limited by a rather narrow antibacterial spectrum and a comparatively weak activity. These problems could be overcome by the discovery of the fluoroquinolones such as ciprofloxacin (Scheme 4). The role of the fluorine atom has been investigated in detail by Domagala et al.^[49] A comparison of several fluoroquinolones and their nonfluorinated parent compounds revealed that i) F increases binding affinity by a factor of 2–17, ii) F reduces plasma protein binding leading to a higher free fraction of the drug, and iii) F increases cell pene-



Scheme 4. Chemical structures of the DNA gyrase inhibitors nalidixic acid (left) and ciprofloxacin (right).

tration by a factor of 1–70. The combination of these effects results in a dramatically improved antibacterial activity. Interestingly, the same effect is also found when the fluorine atom is introduced into the first generation compound nalidixic acid.^[50]

Conclusion

Fluorinated compounds are frequently synthesized in modern medicinal chemistry and have led to a large number of highly effective drugs. Most frequently, fluorine is introduced to block a metabolically labile site in the molecule. Increasingly, fluorine is also introduced to modulate the physicochemical properties and to increase binding affinity by exploiting specific interactions of F with the target protein.

Modern fluorine-organic chemistry has dramatically widened the synthetic repertoire for the specific introduction of fluorine into organic molecules. Our continuously improving understanding of the diverse physicochemical, biophysical, and pharmacological effects of H/F substitution offers interesting new opportunities in medicinal chemistry.

Acknowledgements

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Keywords: basicity • fluorine • lipophilicity • metabolic stability • protein–ligand interactions

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Mechanism of Action and Antiviral Activity of Benzimidazole-Based Allosteric Inhibitors of the Hepatitis C Virus RNA-Dependent RNA Polymerase

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The RNA-dependent RNA polymerase of hepatitis C virus (HCV) is the catalytic subunit of the viral RNA amplification machinery and is an appealing target for the development of new therapeutic agents against HCV infection. Nonnucleoside inhibitors based on a benzimidazole scaffold have been recently reported. Compounds of this class are efficient inhibitors of HCV RNA replication in cell culture, thus providing attractive candidates for further development. Here we report the detailed analysis of the mechanism of action of selected benzimidazole inhibitors. Kinetic data and binding experiments indicated that these compounds act as allosteric inhibitors that block the activity of the polymerase prior to the elongation step. Escape mutations that confer resistance to these compounds map to proline 495, a residue located on the surface of the polymerase thumb domain and away from the active site. Substitution of this residue is sufficient to make the HCV enzyme and replicons resistant to the inhibitors. Interestingly, proline 495 lies in a recently identified noncatalytic GTP-binding site, thus validating it as a potential allosteric site that can be targeted by small-molecule inhibitors of HCV polymerase.

Hepatitis C virus (HCV) is the causative agent of the majority of chronic liver disease throughout the world. More than 170 million individuals are estimated to be infected with this virus (27). The size of the HCV epidemic and the limited efficacy of current therapy (based on the use of alpha interferon) have stimulated intense research efforts towards the development of antiviral drugs that are both better tolerated and more effective. The most widely established strategy for developing novel anti-HCV therapeutics aims at the identification of low-molecular-weight inhibitors of essential HCV enzymes.

RNA-dependent RNA polymerase (RdRP) activity, carried out by the NS5B protein, is essential for virus replication (13) and has no functional equivalent in uninfected mammalian cells. It is thus likely that specific inhibitors of this enzyme can be found that block HCV replication with negligible associated toxicity. The NS5B RdRP has been expressed in a variety of recombinant forms (2, 4). The production of highly soluble forms of the enzyme (12, 24), devoid of the C-terminal membrane anchoring domain (23), has allowed considerable progress toward the determination of the enzyme's three-dimensional structure and mechanism of action. The crystal structure of NS5B revealed a classical "right hand" shape, showing the characteristic fingers, palm, and thumb subdomains (1, 7, 14). More recently, the three-dimensional struc-

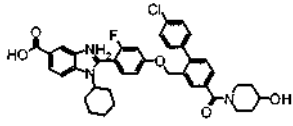
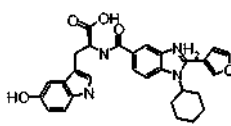
ture of the HCV polymerase was solved in complex with RNA (20) as well as in a complex with nucleoside triphosphates (6). Three distinct nucleotide-binding sites were observed in the catalytic center of HCV RdRP whose geometry was remarkably similar to that observed in the initiation complex of the RNA phage $\Phi 6$ RdRP (8), strengthening the proposal that the two enzymes initiate replication *de novo* by similar mechanisms. An unexpected result of this study was the observation of a GTP-binding site on the enzyme surface at the interface between the finger and thumb domains, 30 Å away from the polymerase catalytic center (6). This previously unidentified GTP pocket was proposed to be a potential allosteric regulatory site that could modulate alternative interactions between the two domains during the conformational change of the enzyme required for efficient initiation. The presence of a unique nucleotide-binding site away from the enzyme catalytic center could potentially provide an attractive target for allosteric inhibitors of the HCV polymerase reaction.

A number of structurally diverse nonnucleoside inhibitors (NNI) of the HCV polymerase have now been reported (10). Among these, two promising compound series that share a common benzimidazole scaffold have been described (P.-L. Beaulieu, G. Fazal, J. Gillard, G. Kukulj, and V. Austel, July 2002, World Intellectual Property Organization; H. Hashimoto, K. Mizutani, and A. Yoshida, Dec. 2001, World Intellectual Property Organization). Interestingly, an orally bioavailable benzimidazole analogue (JTK-003) is currently under investigation in early clinical trials (18). We have synthesized two benzimidazole-containing inhibitors of the HCV RdRP that are representative of each series. We show that these compounds act as allosteric inhibitors that block the activity of

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TABLE 1. Potency, selectivity, and mechanism of inhibition of compounds A and B

Compound	Structure	IC ₅₀ (μM) of compound for NS5B		Kinetics of inhibition versus UTP ^a	
		GBV-B	HCV	K _i (μM)	K _{ii} (μM)
A		NA ^b	0.28 ± 0.1 ^c	0.12 ± 0.14	0.13 ± 0.16
B		NA	0.25 ± 0.05	0.15 ± 0.10	0.20 ± 0.10

^a K_i and K_{ii} values were derived from a replot of slopes and 1/V_{max}, respectively, of double-reciprocal plots.

^b NA, not active at 50 μM.

^c Data are means ± standard deviations.

the polymerase prior to the polymerization step. By taking advantage of the recently developed subgenomic replication system (15), we demonstrate that at least one compound of this class is able to interfere with the replication of the HCV RNA in cell culture. Replicon clones that are resistant to inhibition were selected that allowed the identification of the possible inhibitor interaction site on the enzyme. This site, which we show to be common to the two compounds tested, corresponds to the previously identified surface GTP-binding site and thereby validates its relevance as a target for allosteric inhibitors of the HCV polymerase.

MATERIALS AND METHODS

Compound synthesis. Compound A (2-[4-({4'-chloro-4-[(4-hydroxypiperidin-1-yl) carbonyl]-1,1'-biphenyl-2-yl)methoxy}-2-fluorophenyl]-1-cyclohexyl-1H-benzimidazole-5-carboxylic acid) and compound B (N-[[1-cyclohexyl-2-(3-furyl)-1H-benzimidazol-5-yl]carbonyl]-5-hydroxy-L-tryptophan) were synthesized as previously described (Hashimoto et al., World Intellectual Property Organization; Beaulieu et al., World Intellectual Property Organization).

Plasmids. pHCVNeo17.B (25) encodes an HCV replicon identical to I377neo/NS3-3'/wt (15) but containing the adaptive mutations E176G in NS3 and a AAA triplet (coding for K) insertion after the GTG triplet, coding for V67 in NS5A. All other replicon plasmids were derived from pHCVNeo17.B and contain the following mutations: pHCVNeo17.BR1 and pHCVNeo17.BR2, replacement of CCG codon for P495 in NS5B with CTG (coding for L) or GCG (coding for A), respectively; pHCVNeo17.D, replacement of ATC codon for I585 in NS5B with GTC (coding for T); pHCVNeo17.DR2, replacement of CCG codon for P495 with CTG (coding for L) and of ATC codon for I585 with GTC (coding for T).

pT7-NS5BΔC55 contains the HCV-BK sequence coding for the NS5B protein lacking 55 C-terminal residues (residues 1 to 536) in the pT7-7 expression vector. pT7-GB/NS5BΔC23 encodes a GB virus B (GBV-B) NS5B protein lacking 23 C-terminal residues (residues 1 to 567).

NS5B expression and purification. Expression of the HCV and GBV-B NS5B proteins in *Escherichia coli* BL21(DE3) and purification of the proteins were carried out as described previously (5).

Polymerase assays. Primer-dependent assays were performed with either the heteropolymeric RNA template Dcoh (4) or the homopolymeric template-primer couple poly(A)-oligo(U)₁₈ as previously described (24). Compounds were dissolved and diluted in dimethyl sulfoxide. Unless otherwise specified, compounds, polymerase, and template RNA were incubated at room temperature (RT) for 25 min before the addition of nucleoside triphosphates (NTPs). Alternatively, compounds were added to the preformed polymerase-template complex (15 min at RT) and incubated at RT for 10 min before the addition of NTPs. Elongation proceeded for 1 h at RT and the activity was measured as acid-insoluble radioactivity. Fifty percent inhibitory concentration (IC₅₀) values were calculated by using a three-parameter logistic equation, and inhibition data were fitted by use of Kaleidagraph software.

Kinetic parameters were calculated from a least-square fit of initial rates as a function of substrate concentration, assuming Michaelis-Menten kinetics.

Inhibition mechanisms were determined by performing substrate titration experiments. In the single-turnover experiments, elongation reactions were started by the addition of nucleotides and 50 ng of heparin per μl.

Polymerase-inhibitor binding. The polymerase-inhibitor complex was monitored essentially as previously described (21). Polymerase and compound (10 μM each) were mixed in 60 μl of incubation buffer (20 mM Tris-HCl [pH 7.5], 3 mM dithiothreitol, 100 mM NaCl, 0.03% *n*-octyl-β-D-glucopyranoside, 10% glycerol) with or without 15 μM poly(A)-oligo(U)₁₈. After a 10-min incubation at RT, the mixture was applied to a gel filtration G-25 spin column (Pharmacia) prewashed with incubation buffer. The eluate, containing the protein-inhibitor complex and the unbound protein, was recovered by centrifugation for 2 min at 1,450 × *g*. The eluting protein was quantified by Bradford assay (Bio-Rad), and the inhibitor was quantified by mass spectrometry as follows. The column eluate (0.4 μl) was injected into a reverse-phase C₁₈ column coupled online with an ion trap mass spectrometer (LCQ DECA; Thermoquest, San Jose, Calif.) operated with selected reaction monitoring. The flow from the column was split 1:10 towards the electrospray ionization (ESI) inlet of the ion trap mass spectrometer and the diode array detector. All spectra were acquired at unit resolution and 0.3% mass accuracy. The inhibitor was quantitated from a five-point calibration curve.

Tissue culture, replication analysis selection, and sequencing of resistant replicons. Huh-7 and HBI10A cells were cultured as previously described (25). Transient transfections by electroporation of in vitro-transcribed RNAs were performed using cells that are highly competent for HCV replication, obtained by curing HBI10A cells of the endogenous replicons with human alpha interferon 2b as described previously (25). The effect of compounds on viral replication was monitored by cell enzyme-linked immunosorbent assay (cell-ELISA) (25) or by in situ RNase protection assay (isRPA) (9). Clones resistant to compound A were selected as previously described (25). HBI10A cells were plated at 3 × 10³/cm² and cultured in the presence of 1 mg of G418 per ml and increasing concentrations of compound A, from 1.6 to 4 μM. Approximately 15 days after beginning selection, small colonies of cells resistant to the inhibitor and the antibiotic became visible and were isolated. Replicon RNAs extracted from resistant clones were retrotranscribed, amplified by PCR, and sequenced by automated sequencing.

Transient-transfection assays were performed as described previously (25). Replication efficiency was determined 96 h after transfection by cell-ELISA and was expressed as the ratio between the absorbance value of the sample transfected with a given RNA and the absorbance value of mock-transfected cells. The values were normalized to the transfection efficiency measured by cell-ELISA 24 h after transfection. Each experiment was performed in triplicate, and average absorbance values were used for calculations.

RESULTS

Effect of benzimidazole-based inhibitors on NS5B polymerase activity. Compounds A and B were chosen as representative examples of benzimidazole-based inhibitors of the HCV

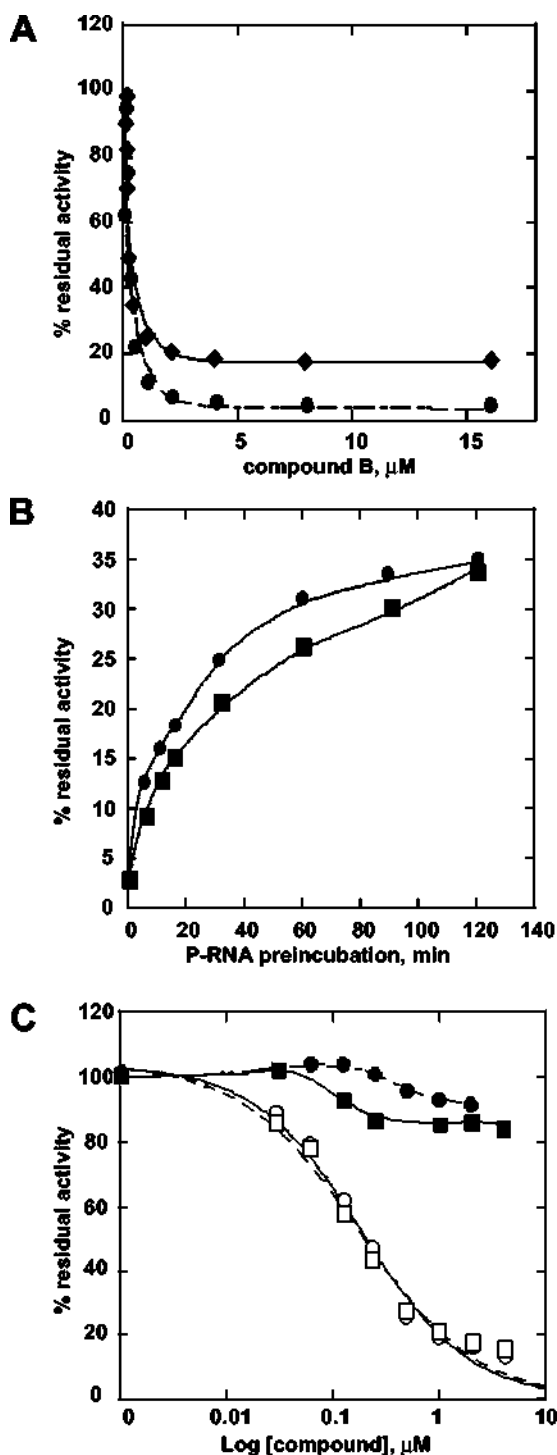


FIG. 1. Inhibition by compounds A and B. (A) Dependence of inhibition curves on polymerase-RNA (P-RNA) complex formation. Increasing amounts of compound B (30 nM to 16 μM) were added to polymerase and heteropolymeric RNA (DcoH) that were (♦) or were not (●) preincubated for 15 min at RT. (B) Effect of P-RNA preincubation time. NS5BΔC55 and DcoH template were preincubated from 0 to 120 min before the addition of 4 μM compound A (■) or compound B (●). The residual activity was expressed as the percentage of that obtained at each time point in the absence of inhibitor. (C) Inhibition curves for compound A and compound B under single-cycle conditions. NS5BΔC55 and the DcoH template (20 nM) were preincubated for 15 min at RT before the addition of compounds from 30 nM

polymerase (Beaulieu et al., World Intellectual Property Organization; Hashimoto et al., World Intellectual Property Organization). Both compounds were confirmed to strongly inhibit HCV RdRP activity in a dose-dependent manner. We measured similar IC_{50} values of about 0.25 μM using either homopolymeric poly(A)-oligo(U)₁₈ template-primer or heteromeric RNA (Table 1; see below). The inhibitor potency was independent of the form of recombinant polymerase used, as both full-length and C-terminally truncated NS5BΔC21 and ΔC55 enzymes were inhibited, with similar IC_{50} values (data not shown). Compounds A and B were highly selective against HCV polymerase and did not inhibit the closely related GBV-B RdRP (Table 1). In assays using poly(A)-oligo(U)₁₈ as template-primer, both compounds appeared to be noncompetitive with respect to UTP (Table 1). Moreover, increasing amounts of template-primer RNA did not affect the inhibition potency, suggesting that RNA binding does not interfere with the enzyme-compound interaction. Consistent with their structural similarities, the two compounds appeared clearly competitive with each other when tested in direct competition assays (not shown). Taken together, these results suggest that both the compounds interact with the polymerase at a site distinct from the catalytic center.

Order of addition. We observed that the order of reagent addition in the RdRP reaction affected the shapes of the inhibition curves. Inhibition experiments were performed by either preincubating the enzyme with the RNA template prior to addition of the inhibitors or by omitting the preincubation step (for compound B, see Fig. 1A; for compound A, data not shown). Similar IC_{50} values were measured in both cases, but complete inhibition of the enzymatic activity could not be attained if the inhibitors were added to a preformed enzyme-RNA complex. In this case, a significant fraction of the polymerase activity was not inhibited, even at very high compound concentrations. A possible explanation for this finding is that the fraction of the enzyme engaged with the RNA in a preelongation complex is protected from the action of the inhibitor. In line with this interpretation, when the NS5B polymerase and the RNA template were preincubated for increasing times before the addition of compounds, at a concentration 15-fold above the IC_{50} values, the percentage of residual activity increased as a function of preincubation time (Fig. 1B). Interestingly, polymerase activity in the absence of inhibitor also increased with the enzyme-RNA preincubation time (data not shown), likely reflecting the formation of a productive preelongation complex.

Inhibition under single-cycle conditions. The RdRP assays described above were performed under continuous polymerization conditions whereby the polymerase performs multiple sequential rounds of processive RNA synthesis. The inhibited activity after preincubation of enzyme and template might therefore result from those polymerase molecules that dissociated from the template during the reaction and were thus susceptible to inhibition. In order to assess directly whether

to 4 μM. Elongation was started by the addition of nucleotide mixture (5 μM each plus 4 μCi of [³H]UTP) with (■, compound A; ●, compound B) or without (□, compound A; ○, compound B) heparin (50 ng/μl).

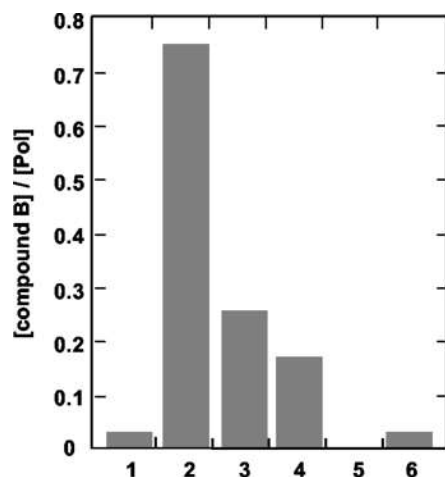


FIG. 2. Polymerase-inhibitor binding. Compound B and polymerases (bars 1 to 4, NS5BΔC55; bar 5, GB/NS5BΔC23; bar 6, NS5BΔC55-P495L) were incubated in the absence (bar 1) or presence (bars 2, 5, and 6) of 15 μ M poly(A)-oligo(U)₁₈. Alternatively, NS5BΔC55 and poly(A)-oligo(U)₁₈ were preincubated for 30 (bar 3) or 60 (bar 4) min before the addition of compound B. Polymerase-inhibitor complexes were separated by gel exclusion chromatography, and the eluted polymerase and compound were quantitated as described in Materials and Methods. Data are reported as molar ratios between eluting compound and polymerase.

compounds A and B could no longer interfere with the enzymatic activity of polymerase molecules already engaged in a preelongation complex, we measured inhibition under conditions that favored single-cycle RNA synthesis. The inhibitors were added to preformed polymerase-RNA complexes and the elongation reaction was started by the addition of nucleotides and heparin (Fig. 1C). Heparin functions as a trapping agent to titrate free enzyme as well as polymerase molecules that dissociate from the template after completion of a processive round of RNA synthesis (3). Under these conditions, we measured only the activity of those polymerase molecules that were engaged in a productive preelongation complex prior to the addition of the trapping agent. As shown in Fig. 1C, both compounds failed to inhibit polymerase activity under these conditions, suggesting their inability to act on preformed enzyme-RNA complexes.

Polymerase-inhibitor interaction. To further investigate the mechanism of inhibition, we performed experiments aimed at the direct characterization of the polymerase-inhibitor interaction. Following preincubation, polymerase-inhibitor complexes were separated from the unbound compound through gel filtration columns. The concentrations of enzyme and inhibitor in the complex were measured by Bradford assay and mass spectrometry, respectively. Due to the low solubility of compound A, these experiments were performed only with compound B. As shown in Fig. 2 (bars 1 and 2), compound B eluted with the enzyme at almost stoichiometric concentrations when incubation was performed in the presence of poly(A)-oligo(U)₁₈ RNA. As expected, compound B did not associate with GBV-B NS5B (Fig. 2, bar 5) or with RNA alone (not shown). This finding suggests that compound B interacts with the purified enzyme in the presence of template RNA. However, when the inhibitor was added after prolonged preincu-

TABLE 2. Effect of compound A on parental and resistant clones

Clone	IC ₅₀ (μ M) for compound A ^a		NS5B mutation(s)
	Cell-ELISA	isRPA	
HBI10A	0.35 \pm 0.15	0.30 \pm 0.2	
10AI1	>5	>5	P495L
10AI2	>5	>5	P495L
10AI12	>5	>5	P495A
10AI14	>5	>5	P495L, I585T

^a Data are means \pm standard deviations.

bation of the polymerase with template RNA, the amount of compound eluting with the enzyme decreased with longer preincubation times, reaching about 20% of the initial value after 60 min (Fig. 2, bars 3 and 4).

This and the previous findings suggest that although the initial interaction of the enzyme with the template RNA appears to be essential for compound B binding, the polymerase-RNA complex undergoes a slow conformational change to a form of the enzyme that is no longer susceptible to inhibition.

Antiviral activity and selection of resistant mutants. The effect of compounds A and B on the replication of HCV subgenomic replicons was determined by using Huh-7 clone HBI10A (19) and was monitored by measuring replicon RNA by isRPA and NS3 protein by cell-ELISA (9, 25). Incubation with compound A resulted in a dose-dependent reduction of both viral RNA and NS3 protein synthesis, with an IC₅₀ of about 0.35 μ M in both assays (Table 2). Conversely, compound B up to 10 μ M showed no inhibition of viral replication (not shown). Compound A was nontoxic and had no effect on cell growth rate up to 10 μ M (not shown), indicating that its direct effect is on viral replication. Taking advantage of the expression of neomycin resistance, we cultured HBI10A cells in the presence of G418 and compound A in order to select inhibitor-resistant replicon variants. Selection yielded several resistant clones that duplicated at the same rate as parental cells and expressed HCV RNA and proteins at comparable levels. More importantly, the IC₅₀ values for compound A on all the selected clones were at least 10-fold higher than that on parental cells (Table 2). The NS5B sequences of four resistant clones were determined. Remarkably, all shared replacement of proline 495 with leucine (P495L) or alanine (P495A), and in addition, clone 10AI14 contained replacement of isoleucine 585 with threonine (I585T) (Table 2). These clones were as sensitive to alpha interferon and the nucleoside inhibitor 2'-C-methyl-adenosine (9) as the parent cells were, indicating that resistance was specific for compound A (not shown). In order to assess their relevance for resistance, the NS5B mutations were segregated in the pHCVNeo17.B replicon. This replicon harbors two adaptive mutations that enhance replication efficiency (25). Among the resulting replicons, pHCVNeo17.BR1 and pHCVNeo17.BR2, bearing mutations P495L and P495A, respectively, were clearly resistant to compound A but replicated less efficiently than the selected clones (Table 3). The IC₅₀ values measured for these replicons were similar to those observed in the resistant cells, indicating that substitutions of P495 were sufficient to confer the resistance phenotype of the selected clones. Conversely, pHCVNeo17.D, bearing an I585T substitution, was still sensitive to inhibition by compound A

TABLE 3. Resistant replicons and enzyme

Replicon or enzyme	NS5B mutation(s)	Replication efficiency (arbitrary units) ^a	IC ₅₀ (μM)	
			Compound A	Compound B
pHCVNEO17 replicons				
B		14.2	0.32	
BR1	P495L	3.1	>5	
BR2	P495A	10.9	2.2	
D	I585T	>20	0.4	
DR1	P495L, I585T	10.6	>5	
Enzyme ΔC55				
	P495L		>20	16 ± 0.8

^a Replication efficiency was determined by cell-ELISA.

and even showed enhanced replication efficiency with respect to the parent replicon. Interestingly, a replicon containing both P495L and I585T (pHCVNeo17.DR1) replicated more efficiently than pHCVNeo17.BR1 and was resistant to inhibition by compound A, suggesting that the I585T substitution was irrelevant for resistance but partially compensated the replication defect due to P495L.

Mechanism of resistance of mutant polymerase. To support the genetic evidence, we introduced the P495L mutation in the NS5BΔC55 protein. The mutant protein showed substantially reduced susceptibility to inhibition by both compounds A and B (Table 3). Conversely, comparable kinetic parameters were measured for the poly(A)-oligo(U)₁₈ RNA for wild-type and mutant proteins ($k_{cat}/K_m = 15,830$ and $9,649 \text{ s}^{-1} \text{ M}^{-1}$, respectively), indicating that the P495L mutation did not significantly affect polymerase activity.

In order to assess whether the P495 mutations conferred resistance by impairing the interaction with the inhibitors, we measured by mass spectrometry the amount of compound B eluting with the purified P495L mutant protein from gel filtration columns. As shown in Fig. 2 (bar 6), compound B was hardly detectable, indicating that the mutant enzyme had a reduced affinity for the inhibitors. This result confirmed that compounds A and B inhibited polymerase activity by binding the enzyme at the same or overlapping sites. Interestingly, P495 is part of a specific noncatalytic GTP-binding site recently identified by X-ray crystallography on the surface of the enzyme, at the interface between the finger and thumb domains (6). Thus, we verified whether GTP was specifically able to interfere with inhibition by compounds A and B by measuring potencies at increasing GTP concentrations. As shown in Fig. 3, the IC₅₀ values increased with increasing GTP concentrations, while they were marginally affected by even high concentrations of CTP. The GTP concentration that produced doubling of the IC₅₀ values was very high (about 1 mM), in agreement with the low-affinity nature of the surface GTP-binding site (5), and did not significantly affect the RdRP activity in our assay (not shown).

DISCUSSION

Although they are derived from independent studies, both HCV polymerase NNIs used in this study share a common cyclohexyl-benzimidazole scaffold that might constitute the active center of the molecule. In light of this similarity, we

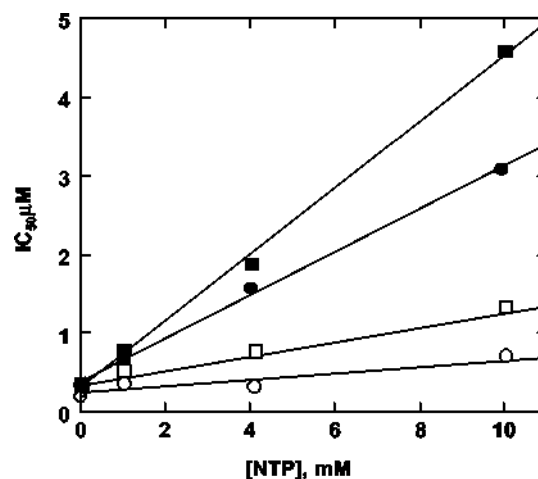


FIG. 3. Effect of GTP and CTP on inhibition potency. The IC₅₀ values for inhibition of NS5BΔC55 on DcoH RNA were measured in the presence of 5 μM and 1, 4, and 10 mM GTP (●, compound A; ■, compound B) or CTP (○, compound A; □, compound B). Reactions were carried out as described in Materials and Methods in the presence of 15 mM MgCl₂, 10 μM UTP, 2 μCi of [³H]UTP, 250 μM ATP, and 250 μM CTP or GTP.

thought that these compounds may inhibit the HCV RdRP through a common mechanism, interacting at the same site of the enzyme. As expected on the basis of their chemical structures, these compounds were found to be noncompetitive with nucleotide substrates. Interestingly, inhibition of RNA synthesis by compounds A and B was not observed in single-turnover experiments, indicating that both are unable to affect the actively elongating enzyme. Their inability to act during the elongation phase excludes the idea that inhibition might be due to alteration of the NS5B processivity by inducing premature dissociation of the enzyme or by altering its translocation along the RNA product.

As is the case for other polymerases, the HCV RdRP catalyzes RNA synthesis through an ordered stepwise mechanism, with RNA template binding occurring first. Each step presumably involves conformational changes of the enzyme leading to the proper positioning of template, the growing RNA chain, and incoming nucleotides in the catalytic center. Our data support a model in which the benzimidazole-containing NNIs act at a step prior to the formation of a productive polymerase-RNA complex. Interestingly, though these compounds do not prevent interaction with the RNA template, prolonged incubation of the enzyme with RNA abolishes the interaction of the inhibitors. We propose, therefore, that by interacting with the enzyme in the polymerase-RNA complex, the compounds might effect a slow conformational transition preceding nucleotide binding that is required for the formation of a productive preelongation complex. However, once the conformational transition has happened, the polymerase may no longer be sensitive to inhibition. This possibility is supported by the observation that when the compounds are added to preformed polymerase-RNA complexes, there is residual enzyme activity even at a saturating inhibitor concentration. This activity may correspond to the fraction of enzyme that has undergone the conformational change and is therefore no longer susceptible

to inhibition. The time course experiments shown in Fig. 1 and 2 are in line with the existence of an intrinsically slow conformational change that occurs within a polymerase-RNA complex and leads to the formation of a productive preelongation complex. The existence of isomerization steps within the enzyme-template-primer complex is well documented for the human immunodeficiency virus (HIV) reverse transcriptase (28), and additional studies would be required to obtain a more direct proof that this is also the case for the HCV RdRP.

As for HIV, the high mutational frequency of HCV is expected to favor the generation of drug-resistant mutants upon long-term treatment with inhibitors of viral enzymes. Thus, resistance studies using tissue culture systems are considered crucial to optimize the resistance profiles of inhibitors and can contribute important information for understanding the mechanism of inhibition. In the absence of a suitable *in vitro* infection model, we took advantage of the recently developed subgenomic replication system (15) to select for replicon clones harboring resistant mutations. This approach has already been successfully used to select mutants resistant to an inhibitor of the viral NS3-4A serine protease (25) and has now allowed us to identify the putative region where compounds A and B interact with the polymerase enzyme. Remarkably, all the selected replicons contained mutations of proline 495 in NS5B, which we demonstrated to be responsible for the acquired resistance to inhibition by both the compounds. Proline 495 in NS5B is conserved in >99% of natural HCV isolates of all strains, suggesting a significant role for the region where P495 lies during HCV replication and possibly explaining the lower replication efficiency of replicons in which its substitutions were segregated. Supplementary mutations might have emerged to compensate for the replication defect in the selected cell clones. In fact, an additional mutation in NS5B, I585T, partially restored the replication ability of replicons containing P495 substitutions. The I585T mutation was able to enhance replication capability even in the absence of the P495 substitution, therefore excluding a direct effect on polymerase enzymatic activity. Interestingly, P495 has been recently identified by X-ray crystallography as one of the key residues involved in the interaction with a noncatalytic GTP molecule on the NS5B surface (6), leading to the speculation that the binding site for benzimidazole-based inhibitors at least partially overlaps with the surface GTP-binding site (Fig. 4). The reduced ability of the mutant enzyme to interact with compound B and the effect of high GTP concentrations on the potency of both compounds A and B strengthen this hypothesis. This model, however, will ultimately require confirmation by structural studies of the polymerase in complex with RNA template and inhibitors.

Though specific, GTP binding at the surface site appears to have no consequence on *in vitro* polymerase activity. In our experiments, while GTP strongly stimulated *de novo* activity of the NS5B polymerase, high GTP concentrations only very modestly enhanced the overall polymerase efficiency on heteromeric templates, which is different from what was previously reported by others (16). We believe that these effects are not exerted by binding at the surface site, as mutations of residues in the surface GTP-binding site neither alter the GTP response of activity nor significantly affect the *de novo* efficiency of NS5B (L. Tomei and A. Biroccio, unpublished ob-

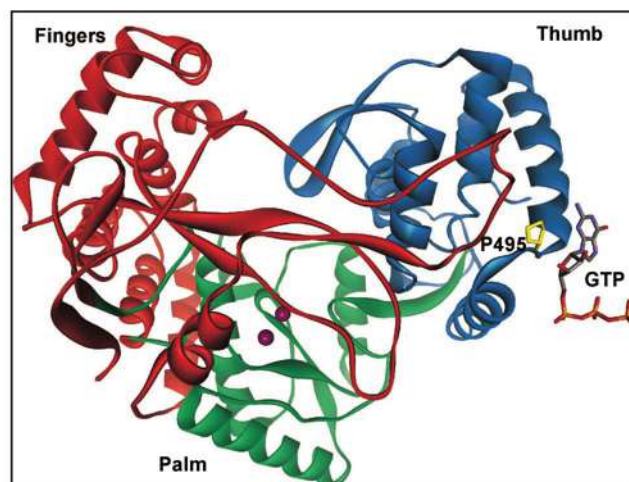


FIG. 4. Location of GTP-binding site and P495. Top view of the NS5B Δ C55 polymerase with finger, palm, and thumb domains in red, green, and blue, respectively. A stick representation shows the non-catalytic GTP in the surface site interacting with P495 (yellow). Divalent Mn^{2+} metal ions in the catalytic center are displayed as violet spheres.

servations). The latter result is in line with recently published observations (22) that point to the initiating-NTP site in the catalytic cavity of the enzyme, not the surface site, as the site at which GTP binding plays a regulatory role for *de novo* activity of NS5B. Whether or not GTP binding at the surface site could be of biological significance *per se*, our finding clearly points to this site as an allosteric pocket on the enzyme surface that may be targeted by small-molecule inhibitors of HCV polymerase activity. Moreover, the observation that replicons carrying P495 substitutions do not replicate efficiently suggests that this region of the molecule might play a key function during viral replication through, for example, the interaction with other viral and/or cellular factors.

The relevance of the thumb domain surface as a target for allosteric inhibitors of the HCV polymerase is becoming increasingly evident. Two series of NNIs of the NS5B enzyme have recently been shown by X-ray crystallography to interact in a hydrophobic pocket at the base of the thumb domain (17, 26; R. A. Love and X. Yu, May 2001, European Patent Office). This site does not overlap with the surface GTP-binding site and is almost 15 Å from it. In contrast to HIV reverse transcriptase, for which all known NNIs have been shown to bind to the same site of the enzyme (11), HCV NS5B apparently contains multiple regions of the thumb domain that are potential targets for allosteric inhibitors. This is of particular relevance in consideration of the possible requirement for a combination therapy regimen based on the use of multiple NNIs.

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L. Tomei and S. Altamura contributed equally to this work.

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