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29th June, 2020

The Controller of Patents
The Patent Office
Boudhik Sampada Bhawan, Plot No. 32,
Sector 14, Dwarka, New Delhi-110078

Re: **REPRESENTATION U/S 25(1) OF THE PATENTS ACT – BY SANKALP REHABILITATION TRUST AGAINST INDIAN PATENT APPLICATION NO. 8533/DELNP/2012 DATED 18/03/2011**
APPLICANT: INSTITUT PASTEUR KOREA AND INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST)

Dear Sir,

We submit herewith a Representation under Section 25(1) of the Patents Act, 2005 along with Form 7A.

The Controller is requested to take the documents on record and proceed further in the matter and keep the Petitioner advised of each and every step taken in the matter.

We crave the leave of the Controller to submit additional documents or evidence or if necessary to support any of the averments in the representation as may be necessitated in the proceeding.

Lastly, we request the Controller to grant an opportunity of being heard before the above representation is finally decided.

Thanking you,

Rajeshwari.

RAJESHWARI H.
RAJESHWARI AND ASSOCIATES
AGENT FOR OPPONENT

BEFORE THE CONTROLER OF PATENTS, THE PATENT OFFICE, NEW DELHI

In the matter of Section 25(1) of The Patents Act,1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application No. 8533/DELNP/2012 dated 18/03/2011 in the name of INSTITUT PASTEUR KOREA AND INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST)

IN THE MATTER OF:

SANKALP REHABILITATION TRUST ….OPPONENT

VS.

INSTITUT PASTEUR KOREA
AND
INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST)

…...APPLICANT

PRE-GRANT OPPOSITION BY SANKALP REHABILITATION CENTRE

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Dated this 29th day of June, 2020

Rajeshwari.

RAJESHWARI H. IN/PA – 358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

To
The Controller of Patents
The Patent Office
New Delhi

FORM 7A
THE PATENTS ACT,
1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[See Rule 55]

We, **SANKALP REHABILITATION TRUST,** having it's registered office at SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002, hereby give representation by way of opposition to the grant of patent in respect of application No: **8533/DELNP/2012 dated 18/03/2011** made by **INSTITUT PASTEUR KOREA and INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST)** on the grounds:

(a) **Section 25(1)(c):** Prior claiming

(b) **Section 25(1)(e):** Lack of inventive step

(c) **Section 25(1)(g):** The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

(d) **Section 25(1)(f):** Invention is not patentable under 3 (d)

(**Detailed grounds are set out in the Opposition as attached**)

My address for service in India is:

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Mobile No: 9910206718

Dated, this 29th day of June, 2020

Rajeshwari.

RAJESHWARI H.
RAJESHWARI AND ASSOCIATES
AGENT FOR OPPONENT

To
The Controller of Patents,
The Patent Office, New Delhi

BEFORE THE CONTROLER OF PATENTS, THE PATENT OFFICE, DELHI

In the matter of Section 25(1) of The Patents Act,1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of Rule 55 of The Patents Rules 2003 as amended by thePatent (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application 8533/DELNP/2012 dated 28/09/2012 in the name of INSTITUT PASTEUR KOREA and INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST)

REPRESENTATION BY:

SANKALP REHABILITATION TRUST

…….. OPPONENT

VS.

INSTITUT PASTEUR KOREA and INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST)

……... APPLICANT

REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION UNDER SECTION 25(1) OF THE PATENTS ACT, 1970

We, SANKALP REHABILITATION TRUST, an Indian organization, hereby submit my representation by way of oppostion to the grant of patent in respect of application no. 8533/DELNP/2012 filed on 28/09/2012 entitled"ANTI-INFECTIVE COMPOUNDS**"** on the following grounds.

STATEMENT OF CASE OF OPPONENT

1. The Opponent has learnt that the Applicant has filed an Indian Patent Application No. 8533/DELNP/2012 (hereinafter "the Impugned Application") on 28/09/2012. The Impugned application was published in the Official Journal of the patent office on 22/01/2016, which is currently pending before the Patent Office. This Impugned application is the national phase entry of PCT (PCT/EP2011/001345), which was filed on

8.03.2011. The Impugned application takes the priority of 61/315,113 US (18.03.2010) and 61/440,937 US (09.02.2011).

GENERAL BACKGROUND ON TUBERCULOSIS

2. TB is a major health problem and its drug resistant forms in particular are an actual concern all over the world. Globally, out of the half-a-million people who develop DR-TB (drug-resistant-tuberculosis) each year, India currently contributes over 25 per cent of the burden. On an annual basis, there are at over 100,000 new cases of DR-TB in India [*see* https://www.thehindubusinessline.com/specials/pulse/dr-tb-patients-need-access-to-new-drugs/article31067811.ece] are annexed herewith as **Annexure-1.** Drug-resistant tuberculosis (DRTB) is common, and the extent of resistance rising, rendering cure and the interruption of transmission increasingly difficult. However, no new drugs have been approved for TB in the forty years prior to 2012. Recently newer TB therapeutics are being researched and under-going clinical trials, which is presumed to be effective therapy to DR-TB treatment.

3. The present patent application no. 8533/DELNP/2012 is relating to the investigational drug telecebec. Telacebec (Q203) is one of the candidates getting close to forming new universal regimen. It is reported to show a synergy with another TB drugs indicating that the combination regimens will be a possibility for future treatment. It is reported that Telacebec (Q203) is an orally active small molecule drug candidate that blocks Mycobacterium tuberculosis growth by inhibiting cytochrome bc1 complex, leading to the depletion of adenosine triphosphate (ATP) synthesis of Mycobacterium tuberculosis. However, accessing these new medication remains a significant challenge.

4. While treatment for DR-TB is provided free of cost by the Government through their TB Control Programme, the cost of the newer drugs and therapies are a significant consideration for introduction of these new drugs as well as scaling up their distribution to patients who need them. Looking at the extraordinary need for these new drugs to reduce treatment failure and death and to enable TB programme in India to ensure availability of new therapies, providing clinical benefits to DR-TB patients, there is increasing need for the Patent Office, another arm of the government, to examine and scrutinize the patent applications relating to TB drugs conscientiously to ensure better availability of affordable medicines.

ACCESS TO MEDICINES AND STRICT INTERPRETATION OF INDIAN PATENTABILITY STANDARDS

5. The Indian Patents (Amendment) Act, 2005 was passed to bring India into compliance with its obligations under TRIPS, and introduced a 20-year product patent regime. However, India is also a signatory to the Doha Declaration on the TRIPS Agreement and Public Health (the Doha Declaration), which reaffirmed the right of WTO members to make use of the flexibilities of the TRIPS Agreement in a manner that is supportive of public health objectives. In this context, the patent offices play a very critical role in making use of such flexibilities to determine the patentability of a claim on a pharmaceutical product or process. Patent examination is a key element that can contribute to or undermine access to medicines.

6. The Opponent respectfully submits that the obligation to promote access to medicines for all must be upheld and that the Patents Act, 1970 must be interpreted to give effect to this aim.

7. The Opponent respectfully submits that the obligation to promote access to medicines for all must be upheld and that the Patents Act must be interpreted to give effect to this aim. The Doha Declaration should be the underlying value system that informs all patent examinations.

8. Furthermore, the Opponent submits that the Doha Declaration has been incorporated into the Patents Act by Parliament through provisions that protect public health. Patents are given to inventions in exchange for advances in science and technology. Where drug companies are granted patents for only minor improvements of existing drugs, they are at liberty to set the prices of the drugs, and often fix prices well beyond the means of the average person in the developing world and in India. Granting patents for such frivolous applications are thus injurious to both scientific advance and to public health.

9. In 2005, while amending the Patents Act, 1970, the members of Parliament decided to deny patent protection to multiple patenting of the same substance or proliferation of patents of the same drug and rejected the practice of "evergreening". In this regard section 3(d) is perhaps the most important provision, which prohibits patents for "a new form of a known substance which does not result in the enhancement of the known

efficacy of that substance" or for the mere discovery of a "new use of a known substance".

10. In this regard, the Supreme Court observed that " …………With regard to the genesis of section 3(d), and more particularly the circumstances in which section 3(d) was amended to make it even more constrictive than before, we have no doubt that the "therapeutic efficacy" of a medicine must be judged strictly and narrowly**.** Our inference that the test of enhanced efficacy in case of chemical substances, especially medicine, should receive a narrow and strict interpretation is based not only on external factors but there are sufficient internal evidence that leads to the same view. It may be noted that the text added to section 3(d) by the 2005 amendment lays down the condition of "enhancement of the known efficacy". Further, the explanation requires the derivative to "differ significantly in properties with regard to efficacy". What is evident, therefore, is that not all advantageous or beneficial properties are relevant, but only such properties that directly relate to efficacy, which in case of medicine, as seen above, is its therapeutic efficacy." [para 180, *Novartis AG* vs *Union of India*, (2013)6SCC1]

11. Apart from section 3(d), it is also important to implement sections 2(1)(j) and (ja) more diligently and strictly to avoid frivolous and unworthy patent applications from being granted a patent. In this regard, the amended provision for inventive step sets a higher two -step standard for determining the inventive step in a patent application. The applicant has an obligation to prove that the feature of the invention has a technical advance or economic significance and the feature is non-obvious to the person skilled in the art. Thus, it is imperative for the patent office to seek scientific evidence for the proving inventive step as well as seeking the applicant to disclose the inventive feature of invention.

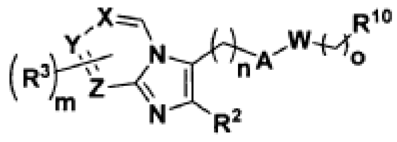
12. The Opponent states that the right to health guaranteed under Article 21 of the Constitution of India is of paramount importance and that medicines required for TB prevention and treatment be made available, so that maximum people can benefit from the treatment and many lives can be saved. Wrongfully granting patents to the Applicant would breach the right to health of a large number of patients living with TB and HIV-TB co-infection. It is submitted that the Hon'ble Patent Controller, may examine the Present Application with strict scrutiny, as its decision will have far reaching effect on the availability of affordable access to treatment for latent TB not only in India but also for countries with a high burden of TB.

The Impugned application is entitled“ANTI-INFECTIVE COMPOUNDS”.

13. The impugned application 8533/DELNP/2012 has been examined by the Indian patent office. The first examination report was generated on 14/01/2019. The applicant has filed the response to the FER and has filed amended the claims.

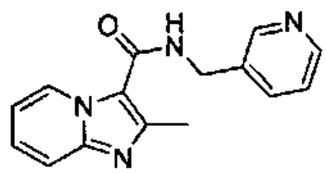
14. The opponent by way of this present pre-grant opposition submits that the claims currently pending on record are not patentable under the provisions provided in this Act. The claims as filed and currently on record are annexed herewith as **Annexure-2.**

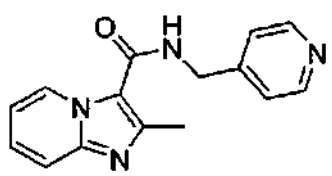
15. **Impugned Patent Application:** The present pre-grant opposition is against Indian Patent Application 8533/DELNP/2012, entitled “ANTI-INFECTIVE COMPOUNDS” and is drawn towards identifying the compounds effective against bacterial infections, in particular Tuberculosis Compoundshaving the general formula Ib (imidazopyridine amide) are disclosed:

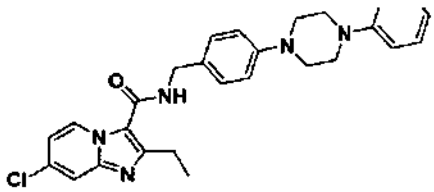


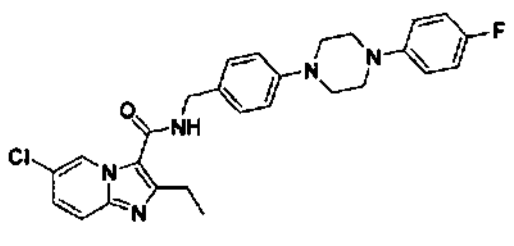
Ib

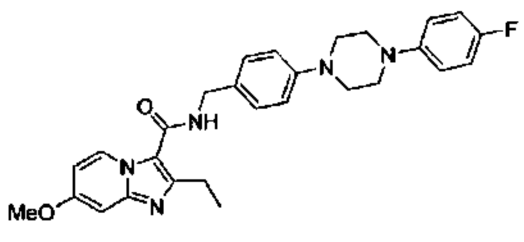
The impugned patent application further discloses few specific compounds which have been given below (few of them)

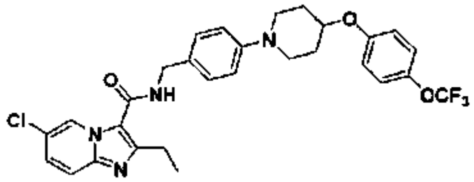


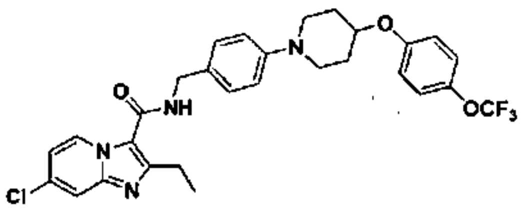












PRIOR ARTS:

The opponent wishes to rely on the following prior art as evidence in support of the grounds of opposition.

i. D1: IN 4917/DELNP/2012; Published on 25/09/2015
ii. D2: Article titled "Functionalized 3-amino-imidazo[1,2-a]pyridines: A novel class of drug-like Mycobacterium tuberculosis glutamine synthetase inhibitors" Bioorganic & medicinal chemistry letters 19(16):4790-3, July 2009
iii. D3: WO2008082490, Publication date: 10.07.2008
iv. D4: Article titled "Synthesis and Antituberculosis Activity of New Hydrazide Derivatives" Arch. Pharm. Chem. Life Sci. 2008, 341, 721 – 724.
v. D5: Article titled "OPC-67683, a Nitro-Dihydro-Imidazooxazole Derivative with Promising Action against Tuberculosis In Vitro and In Mice, PLoS Med. 2006 Nov; 3(11):, Published online 2006 Nov 28.
vi. D6: Article titled "Fused Heterocycles: Synthesis of Some New Imidazopyridines as Anti-Mycobacterial Agents"Turk J Chem 31 (2007) , 617 – 622.
vii. D7: Article titled "Amide bond formation: beyond the myth of coupling reagents Valeur, E., & Bradley, M. (2009). Amide bond formation: beyond the myth of coupling reagents. Chem. Soc. Rev.

Accordingly, the Opponent submits its opposition by way of representation under Section 25(1) in respect of the said Indian Patent Application 8533/DELNP/2012 on the following grounds below, which are without prejudice and in the alternative to each other.

i. It is submitted that all claims of the impugned patent application are liable to be refused on following grounds as below:

(a) Section 25(1)(c): Prior claiming
(b) Section 25(1)(e): Lack of inventive step

(c) Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

(d) Section 25(1)(f): Invention is not patentable under 3 (d)

GROUND I: PRIOR CLAIMING UNDER SECTION 25(1)(c)

1. It is submitted that the invention as claimed in the impugned patent application as set out in amended claims 1 to 6 liable to be refused for prior claiming under Section 25(1)(c) of the Act.

PRIOR CLAIMING BY IN 4917/DELNP/2012

2. The claims of the impugned Patent Application 4917/DELNP/2012 are prior claimed by herein reproduced as IN’4917. The IN’4917 (formerly was filed on 04/06/2012. It has a PCT application PCT/US2010/055728 that was filed on 05/11/2010. The conditions for prior claiming is fulfilled in IN’4917 because:-

    a) IN’4917 claims priority date 05/11/2009, which is prior to the priority date of the impugned patent application i.e. 18.03.2010.

    b) IN’4917 is published after the priority date 18.03.2010of the impugned patent application i.e. published on 25/09/2015 (publication date of the application IN’4917). Corresponding PCT application IN’4917 is also published after the priority date of the impugned patent application i.e. 12.05.2011

    It is submitted that IN’4917 fulfills all tenets of Section 25(1) (c) as set out hereinabove.

Table 1: PRIOR CLAIMING BY IN’4917/WO’145

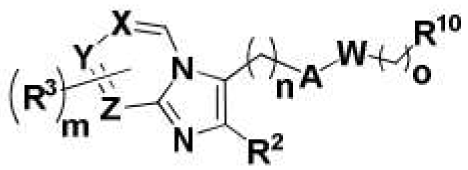
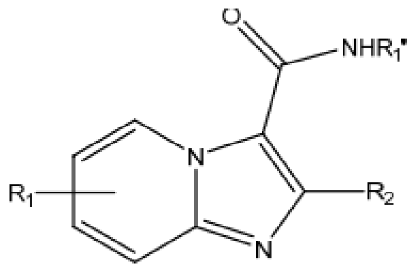
	Priority data	Publication date
8533/DELNP/2012	61/315,113 US (18.03.2010) and 61/440,937 US (09.02.2011)	22/01/2016
4917/DELNP/2012	61/258,549 US (05.11.2009)	25/09/2015

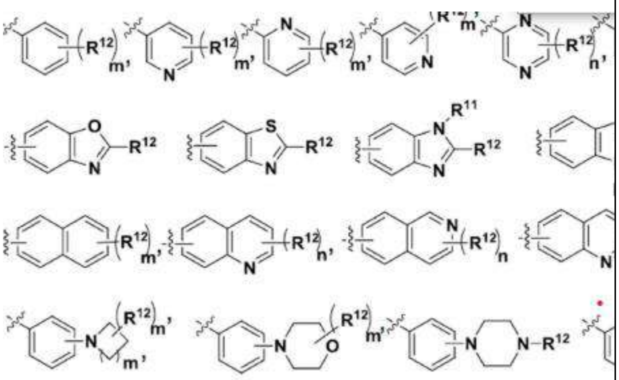
3. From the table above, it is clear that IN ‘4917 –

    a) Has earlier priority date (05.11.2009) as compared to Impugned Patent Application No. 8533/DELNP/2012 (whose priority is 18.03.2010)

    b) Has been published after the priority date of impugned patent application i.e. published on 25/09/2015i.e. after 18.03.2010.

Further, a comparison of the claims of the impugned patent application with IN '4917 (Prior art) it can be clearly seen that imidazopyridine amide which is claimed in the impugned patent application is also covered and claimed by Claim 1 of (IN'4917)as illustrated here below.

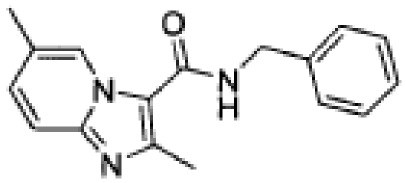
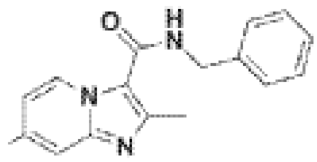
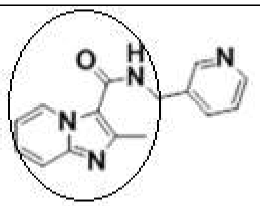
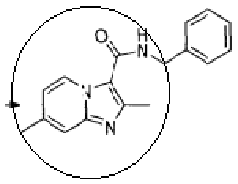
Impugned Patent Application No. 8533/DELNP/2012	**Prior art** 4917/DELNP/2012 **(IN'4917)**
Claim 1: 1. A compound having the general formula Ib:  **Ib** wherein X, Y and Z are **CH;** o is**1**; n is 0; m is 0, 1, 2, 3 or 4; A is **C=O W is NH**; R2 is, at each occurrence, independently selected from the group consisting of hydrogen, halogen, **C1-C10 alkyl,** C3-C10 cycloalkyl, C2-C10 alkenyl, C3-C10 cycloalkenyl, C2-C10 alkynyl, C1-C10 haloalkyl, -OH, -OR5 , C1-C10 alkoxy, C3-C10 cycloalkoxy, C3-C15 cycloalkylalkoxy, C3-C15 cycloalkylalkyl, -CN, -NO2, -NH2, -N(R5)2, -C(O)R5 , -C(O)OR5 , -C(O)N(R5)2, -SR5 , - S(O)R5 , -S(O)2R 5 , -S(O)2N(R5)2, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl; R3 is, at each occurrence, independently selected from the group consisting of hydrogen, **halogen,** C1-C10 alkyl, C3-C10 cycloalkyl, hydroxyl, -OR6 , -CN, -NO2, -NH2, -N(R6)C(O)R6 , - C(O)R6 , -C(O)OR6	1. A compound, having the following formula or a pharmaceutically acceptable salt thereof:  wherein R1' is independently alkyl, **substituted alkyl,** cycloalkyl, cycloheteroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or heterocycle, or halogen; and wherein R1 is halogen or methyl, and **R2 is methyl or ethyl.** **In dependent claims it further discloses** R1' is methyl, and the heterocycle, heteroaryl, and aryl are substituted with 1-4 substituents selected from the group consisting of halogen and Q15; wherein said Q15 is independently selected from the group consisting of H, alkyl, cycloalkyl, heteroaryl, phenyl, or naphthyl, each optionally substituted with 1-4 substituents independently selected from the group

, -C(O)N(R6)2, -S(O)R6 , -S(O)2R 6 , -S(O)2N(R6)2, aryl, e.g. phenyl, benzyl, heteroaryl, heterocyclyl, any of which is optionally substituted, or two groups of R 3 are connected to each other to make five or six membered cyclic and heterocyclic rings; R 5 and R 6 are, at each occurrence, independently selected from the group consisting of hydrogen, C1-C10 alkyl, C3-C10 cycloalkyl, C2-C10 alkenyl, C3-C10 cycloalkenyl, C2-C10 alkynyl, C1-C10 haloalkyl, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl; R 10 is a moiety selected from the group consisting of 	consisting of F, Cl, Br, I, -OQ16, - SQ16, -S(O)2Q16, -S(O)Q16, -OS(O)2Q16, -C(=NQ16)Q16, -S(O)2-N=S(O)(Q16)2, -S(O)2- N=S(Q16)2, -SC(O)Q16, -NQ16Q16, -C(O)Q16, -C(S)Q16, -C(O)OQ16, -OC(O)Q16, - C(S)NQ 16Q16, -C(O)C(Q16)2OC(O)Q16, -CN, -…………z

4. A comparison of IN’4917 and the markush claims of impugned patent application would reveal that the compound claimed in the impugned patent application (claim 1) are encompassed and embraced by the Markush formula of claim 1 of IN’4917. The compound claimed in claim 1 of the impugned patent application is fully disclosed by the claim 1 of IN’4917. Hence, the claims of IN’4917 and impugned patent application are overlapping.

5. Further, below is the comparison of one of the specific compound disclosed in D1 and impugned patent application

Compound of impugned application	D1

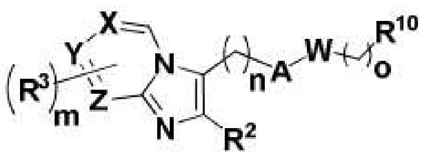
 Compound 32 (specification)	
 Compound 13 (Claim 2)	

6. Both, the compound have same pharmacophore Further, compound 32 of impugned application and compound disclosed in IN‘4917 is same compound 13 of impugned application and compound disclosed in IN‘4917 have same pharmacophore.

7. In view of the above, case of prior claiming is fully made out. Hence, the impugned patent application ought to be refused on this ground alone

GROUND 2: LACK OF INVENTIVE STEP

8. Claim 1 is drawn towards identifying the compounds effective against bacterial infections, imidazopyridine amide compounds with the below general formula Ib



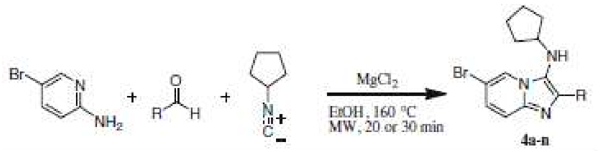
Ib

wherein X, Y and Z are **CH;** o is **1**; n is 0; m is 0, 1, 2, 3 or 4; A is **C=O W is NH**;

9. D2 relates to 3-amino-imidazo[1,2-a]pyridines have been identified as a novel class of Mycobacterium tuberculosis glutamine synthetase inhibitors. Moreover, these compounds represent the first drug-like inhibitors of this enzyme. A series of compounds exploring structural diversity in the pyridine and phenyl rings have been synthesized and biologically evaluated. Compound 4n was found to be the most potent inhibitor (IC50 =

0.38 ± 0.02 lM). This compound was significantly more potent than the known inhibitors, Lmethionine- SR-sulfoximine and phosphinothricin.

10. Table 3 Synthesis and biological evaluation of 3-amino-imidazo[1,2-a]pyridines (4a–n)

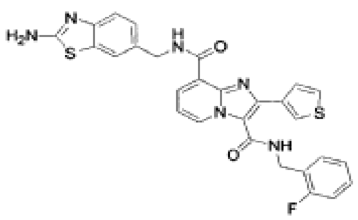
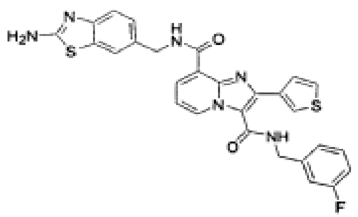


ntry	Product[a]	R	IC_{50}[b] (μM)
1	**4a**	H	>50
2	**4b**	3′-OMe,4′-OHC_6H_3	>50
3	**4c**	C_6H_5	>50
4	**4d**	4′-OHC_6H_4	nd[c]
5	**4e**	3′-OHC_6H_4	3.3 ± 0.6
6	**4f**	2′-OHC_6H_4	>50
7	**4g**	3′-$OMeC_6H_4$	>50
8	**4h**	2′,3′-$DiOMeC_6H_3$	>50
9	**4i**	2′-Cl,3′-OHC_6H_3	>50
10	**4j**	3′-OH,4′-$NO_2C_6H_3$	>50
1	**4k**	3′-$NO_2C_6H_4$	>50
2	**4l**	3′-$NH_2C_6H_4$	10.1 ± 1.1
3	**4m**	3′-$(CH_2OH)C_6H_4$	13.2 ± 1.5
4	**4n**	3′-$(COOH)C_6H_4$	0.38 ± 0.02

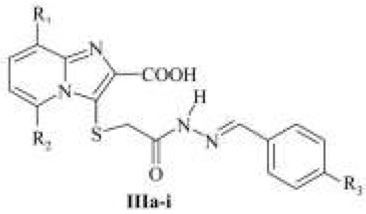
11. It further discloses three small series of trisubstituted 3-amino imidazo[1,2-a]pyridines have been investigated as MtGS inhibitors.

12. Moreover, it discloses that “Given their drug-like nature, we anticipate they will serve as important lead compounds in the search for new anti-tuberculosis”. Hence, D2discloses the imidazole pyridine as new anti-tuberculosis agent.

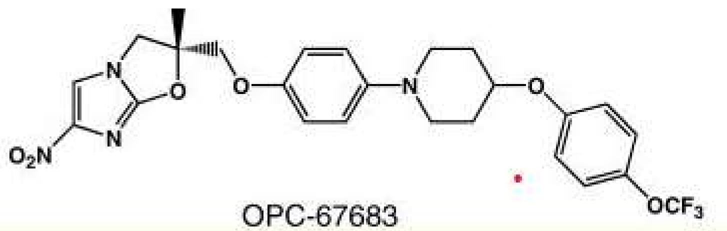
13. D3 discloses substituted imidazo[1,2-a]pyridines, specifically discloses Compound 33, 34 and 35 with amide linkage.

33	
34	

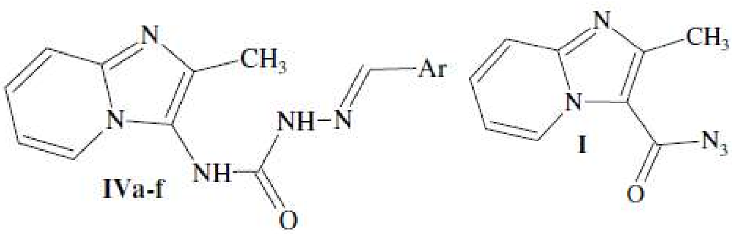
14. D4 discloses new hydrazide derivatives of imidazo[1,2- a]pyridine were synthesized and evaluated for antituberculosis activity. Further, it discloses that the inventors have chosen imidazo[1,2-a]pyridines, which have emerged as potentially interesting drugs, particularly with regard to their antituberculosis activityamong the various heterocycles that have attracted the attention as potential antitubercular agents as the basic heterocyclic moiety. It specifically discloses the below compound



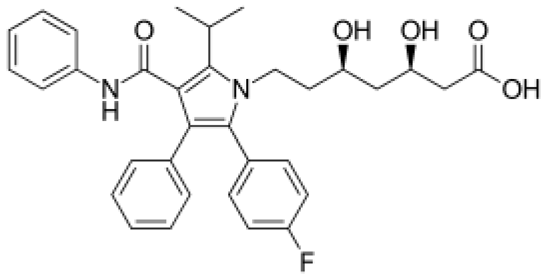
15. D5 discloses new nitro-dihydro-imidazooxazoles with anti-tubercular activity that had no mutagenicity by performing the bacterial reverse mutation (BRM) test. About 95% of the compounds we screened earlier that had mono- or di-alkyl substituents at 2-position were mutagenic. However, after introducing heteroatoms to the substituent, mutagenicity rate was successfully decreased to 16%. Among the non-mutagenic derivatives, OPC-67683 was found to have potent anti-TB activity. OPC-67683 was further evaluated to determine as potential candidate for TB treatment.



16. D6 discloses new anti-tubercular agents with new semicarbazones (IVa-f) and 4-thiazolidinones (Va-d) incorporating an imidazo[1,2-a] pyridine moiety. It specifically discloses following compounds



17. D7 discloses amide bond are present in huge array of molecules such as atorvastatin wherein phenyl ring and heterocyclic ring is linked through amide linkage



18. At the effective date, a skilled person would have envisagedimidazole pyridine which have emerged as potentially interesting drugs, particularly about their antituberculosis activity among the various heterocycles that have attracted the attention as potential antitubercular agents as the basic heterocyclic moiety. Various linkages were explored in between the heterocycle rings (IP) and phenyl group such asamine, hydrazine. Therefore, the person skilled in the art would have retained imidazole pyridine in view of D2, D4 and D6. D3 discloses the amide linkage between the imidazole pyridine and phenyl ring. Also as disclosed in D7 that amide linkage is used in huge number of molecules. Hence, it is obvious for the person skilled to retain the imidazole pyridine pharmacophore and combine it with aromatic ring through amide linkage to get an alternate drug moiety.

GROUND 2: INSUFFICIENCY OF DISCLOSUR

19. The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed. Claim 1discloses huge number of arbitrary compound. None of the compound claimed in claim 1have not been tested for efficacy. Few compounds were tested for *in vivo* activity only. Hence, these compounds are therefore prophetic. The person skilled in the art will have to do undue experimentation to reach at the claimed invention.

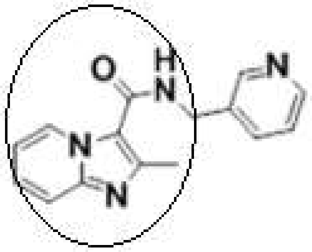
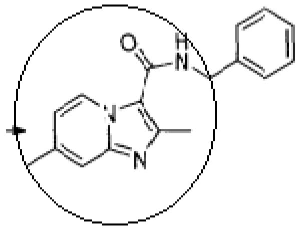
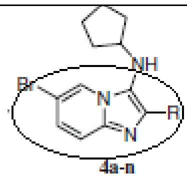
The invention claimed by the impugned patent application is not sufficiently disclosed and does not provide enough motivation to a person skilled in the art to understand the invention and reproduce it.

GROUND 3: Claims not patentable under Section 25(1)(f)

20. The Opponent states that the claimed invention clearly falls under the section 3 (d) which clearly states that the mere discovery of a new form of a known substance which does not result in the enhancement of known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the

mere use of a known process results in a new product or employs at least one new reactant is not patentable under this Act.

21. The Opponent states that the compounds claimed in claim 1impugned application is the new form of the known compound disclosed in D1and D2which does not result in the enhancement of known efficacy and thus not patentable under section 3 (d). The pharmacophore of D1 and D2 are similar. Further, D1 has the similar linkage between heterocyclic ring and aromatic ring. Also, the specific compounds disclosed in D1 are overlapping with impugned patent application.

Compound of impugned application	D1	D2
		

22. Complete specification of the impugned application does not provide any comparative data to demonstrate enhancement in the therapeutic efficacy with respect to the known efficacy of compound as disclosed in D1 and D2. The Opponent states that the applicant miserably failed to provide data demonstrating enhanced 'therapeutic' efficacy as there is no comparative data disclosed in the impugned application showing improved efficacy of pharmaceutical composition of impugned application over compound as disclosed in D1and D2. The Opponent thus sates that alleged invention claimed in the impugned application is a mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of 'substances' disclosed in D1 and D2and thus falls under section 3 (d) and ought to be rejected in to under this ground alone.

CONCLUSION

23. In view of the above, the claims are prior claimed, not inventive, insufficient and not patentable. The pre-grant opposition as filed may be allowed and the subject patent application may be refused. The pre-grant opposition as filed may be allowed and the subject patent application may be refused.

PRAYER

In the fact and circumstances of the case, the Opponent prays as follows:

i. that the Controller take the present Opposition on record;
ii. that the Indian application 8533/DELNP/2012, be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;
iii. that the Opponent may be allowed to file further documents as evidence if necessary to support their averments;
iv. that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;
v. that the Opponent may be allowed to make further submissions in case the Patentee makes any amendments in the claims;
vi. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this the 29th day of June, 2020

Rajeshwari.

RAJESHWARI H.
AGENT FOR THE OPPONENT,
RAJESHWARI AND ASSOCIATE

To
The Controller of Patents,
Patent Office, New Delhi

Annexure - 1

Pulse

DR-TB patients need access to new drugs

Leena Menghaney | Updated on March 14, 2020 | Published on March 14, 2020

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Till now the
pharmaceu

But India's TB Programme faces patent barriers

Globally, out of the half-a-million people who develop DR-TB (drug-resistant-tuberculosis) each year, India currently contributes over 25 per cent of the burden. On an annual basis, there are at over 1,00,000 new cases of DR-TB in India.

After a gap of 50 years, new antibiotics, bedaquiline and delamanid, now provide opportunities to high-burden countries like India to improve the efficacy of their DR-TB treatment.

Looking at the extraordinary need for these new drugs to reduce treatment failure and death, India's National Drug Regulatory Authority allowed the Central TB Division (CTD) to progressively include bedaquiline and delamanid in treatment regimens to improve treatment outcomes for adults, adolescents and children with multi-drug resistant (MDR) and extensively drug resistant (XDR) TB.

The introduction of these two new drugs in the country's TB programme could be a game changer in the fight against this public health emergency. In the last two years, it has spurred CTD to scale up testing for drug resistance across the country as the drugs cannot be prescribed, as per WHO recommendations, without diagnosis of the resistant strain and pattern. Pharmacovigilance and monitoring of adverse effects of DR-TB drugs have been strengthened.

These drugs are also the backbone of India's announcement in September 2019 that it will scale up injection free DR-TB treatment, improving not just treatment outcomes but also preventing permanent disabilities in patients, such as hearing loss.

Benefits to children

Perhaps the greatest benefits could be in children with DR-TB who can now potentially be treated with injectable-free regimens as safety data on different age groups becomes available. Hearing loss, a frequent severe adverse event caused by injectables, has a profound impact on children's development.

Despite the benefits to the TB programme, till now CTD has acquired the new TB drugs, patented in India till 2023, as donations from pharmaceutical corporations and the United States Agency for International Development. In particular, the quantity of delamanid under the donation has been severely limited to just 400 six-month treatments, leaving children with DR-TB without access to the drug in many parts of the country alongside reports that the drug is in short supply and stocked out in many States.

Donations of medical products are not sustainable for ensuring long-term access to treatment for patients and therefore the CTD has embarked on negotiations with the patent holders on the price at which the new drugs will be supplied to the programme.

There is no doubt that prices of the new drugs are a consideration for the CTD as it seeks to provide an injection-free regimen to all patients with DR-TB, who are registered with it. A six-month course of bedaquiline is available to the TB programme at approximately $30,000 per patient and delamanid prices are more than double that.

The negotiations launched, in the absence of competition and multiple suppliers, have been long and protracted.

India failed to achieve significant reduction in prices over what South Africa had already achieved in 2019. Tenders in the case of bedaquiline had to be re-issued, and in the case of delamanid, finalisation of the bid only came after the programme was facing shortages.

The experience of dealing with single-source supply due to patent monopolies is new to the Indian Ministry of Health, with tenders not receiving any competitive bids. The absence of any credible threat from the Health Ministry and the TB Programme that generic sources will be roped in under government use licensing could see prices remain stagnant globally, despite scale-up of volumes till 2023, when the patents on these drugs expire and generic suppliers enter the market.

If alternative sources are to be encouraged before the patents expire in 2023, the government, across all ministries, must give a clear signal to the domestic industry to manufacture and register the new TB drugs for domestic and global supply. For that to happen, the government needs to figure out how compulsory licensing provisions can be applied in public health emergencies.

The writer is a lawyer and South Asia Head of Médecins Sans Frontières' (MSF - Doctors without Borders) Access Campaign.

Views are personal

Published on March 14, 2020

healthcare industry tuberculosis

Annexure - 2

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)
&
THE PATENTS RULES, 2003

COMPLETE SPECIFICATION
(See section 10, rule 13)

"ANTI-INFECTIVE COMPOUNDS"

1) INSTITUT PASTEUR KOREA of 696 Sampyeong-dong, Bundang-gu, 463-400 Sungnam-si, Gyeonggi-do, Republic of Korea

2) INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) of 101, rue de Tolbiac, F-75013 Paris, France

The following specification particularly describes the invention and the manner in which it is to be performed.

Anti-infective compounds

The present invention relates to small molecule compounds and their use in the treatment of bacterial infections, in particular Tuberculosis.

Background of the Invention

Tuberculosis (TB) as a disease continues to result in millions of deaths each year. Inadequate use of chemotherapy has led to an increasing number of drug resistant cases. This situation is likely to worsen with the emergence of extremely resistant strains to all currently known drugs (Van Rie and Enarson, 2006). The internationally recommended TB control strategy, also referred to as directly observed short-course chemotherapy (DOTS), relies on a combination of five antibacterial agents to be taken for a protracted period of more than six months (http://www.who.int/tb/dots/en/). With the use of a mathematical model, taking into consideration treatment duration and TB dynamics, benefits of reduced treatment length were predicted to be substantial and likely to greatly contribute to a reduced global TB burden (Salomon *et al.*, 2006).

Current chemotherapy consists of compounds that directly target *Mycobacterium tuberculosis* bacillus, either by neutralizing general information pathways and critical processes such as RNA polymerization and protein synthesis inhibition or by interfering with mycobacterial specific cell envelope synthesis. The most widely used dedicated anti-tubercular drugs isoniazid, ethionamide and pyrazinamide are pro-drugs that first require activation. As active forms, they demonstrate inhibitory activity on a wide range of mycobacterial targets, which have not yet been fully characterized. As for other chronic infectious diseases like human immunodeficiency virus, a multi-therapy approach, including drugs that target a wide range of critical features of *M. tuberculosis*, proved to be the most successful strategy to date. It is, thus, likely that a combination of current drug inhibitors, having different mechanisms of action against *M. tuberculosis*, will be the solution for the control of the disease.

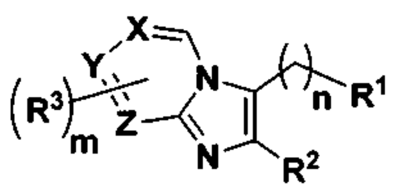
The most challenging approaches for discovering new anti-TB drugs rely on screening for active compounds that target critical features essential for the survival of the bacillus. Although there is still a lack of understanding of the biological mechanisms behind tubercle bacillus persistence, i.e. the location and state of latent bacteria, in humans, *M. tuberculosis* is thought to reside in primary granulomas under hypoxic conditions (Lenaerts *et al.*, 2007) as well as to hide within various types of cells (Houben *et al.*, 2006; Neyrolles *et al.*, 2006). The bacillus mainly localizes inside phagocytic cells, such as macrophages and dendritic cells, and it has clearly been established that the tubercle bacillus adopts a different phenotype in the host macrophage's phagosome compared to growth in extracellular conditions (Rohde *et al.*, 2007; Schnappinger *et al.*, 2003). Upon infection, an inflammatory response is induced, thereby initiating recruitment of T lymphocytes that release interleukins and cytokines, which in turn activate the infected macrophages to enable the destruction of the pathogen. Upon the appropriate trigger, the host macrophage is, thus, able to eliminate the invading bacillus. This is further supported by the fact that of the people that inhale *M. tuberculosis*, more than 95% percent do not develop the disease, suggesting that the human host response is sufficient in most cases to thwart *M. tuberculosis* induced pathogenesis. This gives rise to the hypothesis that small molecular compounds could mimic the immune cell response signals and induce the host cells to clear the mycobacteria.

Accordingly, a phenotypic cell-based assay, suitable for high throughput screening, which allows for the search of compounds that would prevent *M. tuberculosis* multiplication inside the host macrophage was utilized (WO2010003533A2), overcoming many of the numerous and burdensome steps involved in previous methodologies (Arain *et al.*, 1996).

It was an object of the present invention to identify compounds effective against bacterial infections, in particular compounds that would prevent *M. tuberculosis* multiplication inside the host macrophage.

Description of the Invention

In one aspect, the present invention relates to compounds having the general formula Ia:



Ia

wherein
m is 0, 1, 2, 3 or 4;
n is 0, 1, 2, or 3;

X, Y and Z are CH, N or N-oxide;

R^1 is, at each occurence, independently selected from the group consisting of hydrogen, halogen, C_1-C_{10} alkyl, C_1-C_3 haloalkyl, C_3-C_7 cycloalkyl, hydroxyl, oxo, $-OR^4$, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, -CN, $-NO_2$, $-NH_2$, $-N(R^4)_2$, $-OR^4HetA$, $-OR^4N(R^4)_2$, $-C(O)N(R^4)R^4HetA$, $-C(O)N(R^4)HetA$, -C(O)HetA, $-C(O)N(R^4)R^4S(O)_2R_4$; $-S(O)_2N(R^4)_2$, $-S(O)_2R^4$, $-N(R^4)C(O)R^4SR^4$, $-N(R^4)R^4S(O)_2R^4$, or $-N(R^4)S(O)_2R^4$, $-C(S)R^4$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl, any of which is optionally substituted;

R^2 is, at each occurence, independently, selected from the group consisting of hydrogen, halogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, -OH, $-OR^5$, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkoxy, C_3-C_{15} cycloalkylalkoxy, C_3-C_{15} cycloalkylalkyl, -CN, $-NO_2$, $-NH_2$, $-N(R^5)_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-SR^5$, $-S(O)R^5$, $-S(O)_2R^5$, $-S(O)_2N(R^5)_2$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl, any of which is optionally substituted;

R^3 is, at each ocurence, independently selected from the group consisting of hydrogen, halogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-C_3 haloalkyl, hydroxyl, $-OR^6$, -CN, $-NO_2$, $-NH_2$, $-N(R^6)C(O)R^6$, $-C(O)R^6$, $-C(O)OR^6$, $-C(O)N(R^6)_2$, $-S(O)R^6$, $-S(O)_2R^6$, $-S(O)_2N(R^6)_2$, aryl, e.g. phenyl, benzyl, heteroaryl, heterocyclyl, any of which is optionally substituted, or two groups of R^3 are connected to each other to make five or six membered cyclic and heterocyclic rings, any of which is optionally substituted;

R^4 is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, $-C(O)R^7$, $-R^7(R^7)C(O)R^7$, $-C(O)OR^7$, $-R^7(R^7)C(O)OR^7$, $-C(O)N(R^7)_2$, $-R^7(R^7)C(O)N(R^7)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^7)_2$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl, any of which is optionally substituted; and

R^5, R^6 and R^7 are, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl, any of which is optionally substituted.

The term "optionally substituted" as used herein is meant to indicate that a hydrogen atom attached to a member atom within a group, or several such hydrogen atoms, is replaced by a group, such as halogen including fluorine, C_1-C_{10} alkyl, C_1-C_3 haloalkyl, C_3-C_7 cycloalkyl, oxo, -OH, -OR^8, -$OC(O)R^8$, -CN, NO_2, -$N(R^8)_2$, -$N(R^8)C(O)R^8$, -$R^8N(R^8)C(O)R^8$, -$C(O)R^8$, -$R^8C(O)R^8$, -$C(O)OR^8$, -$R^8C(O)OR^8$, -$C(O)N(R^8)_2$, -$R^8C(O)N(R^8)_2$, -$S(O)R^8$, -$S(O)_2R^8$, -$S(O)_2N(R^8)_2$, phenyl, benzyl, aryl, heteroaryl or heterocyclyl, any of which itself is "optionally substituted"; i.e. one or several of the hydrogen atoms may be replaced by one of the aforementioned groups.

R^8 is, at each occurence, independently selected from the group consisting of hydrogen, halogen, C_1-C_{10} alkyl, C_1-C_3 haloalkyl, C_3-C_7 cycloalkyl, hydroxyl, oxo, -OR^9, -$C(O)OR^9$, -$C(O)R^9$, -$C(O)N(R^9)_2$, -CN, -NO_2, -NH_2, -$N(R^9)_2$, -OR^4HetA, -$OR^4N(R^9)_2$, -$C(O)N(R^9)$HetA, -C(O)HetA, -$C(O)N(R^9)R^4S(O)_2R^9$; -$S(O)_2N(R^9)_2$, -$S(O)_2R^9$, -$N(R^9)C(O)R^4SR^9$, -$N(R^9)R^4S(O)_2R^9$, or –$N(R^9)S(O)_2R^9$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl, any of which is optionally substituted.

R^9 is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_8 alkyl optionally substituted with at least one hydroxyl or halogen; C_3-C_7 cycloalkyl, aryl, e.g. phenyl, benzyl, and heterocyclyl, any of which is optionally substituted.

In one embodiment, the present invention also relates to pharmeceutically acceptable salts of the compounds according to the present invention.

The term "alkyl" refers to a monovalent straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range. Thus, for example, "C_1-C_6 alkyl" refers to any of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec-, and t-butyl, n- and isopropyl, ethyl and methyl.

The term "alkoxy" means a group having the formula –O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (*i.e.*, C_1-C_{20} alkoxy), 1 to 12 carbon atoms (*i.e.*, C_1-C_{12} alkoxy), or 1 to 6 carbon atoms (*i.e.*, C_1-C_6 alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-O-CH_3 or OMe), ethoxy (-OCH_2CH_3 or –OEt), t-butoxy (-O-$C(CH_3)_3$ or -OtBu) and the like.

The term "alkenyl" refers to a monovalent straight or branched chain aliphatic hydrocarbon radical containing one carbon-carbon double bond and having a number of carbon atoms in the specified range. Thus, for example, "C_2-C_6 alkenyl" refers to all of the hexenyl and pentenyl isomers as well as 1-butenyl, 2-butenyl, 3-butenyl, isobutenyl, 1-propenyl, 2-propenyl, and ethenyl (or vinyl).

The term "alkynyl" refers to a monovalent straight or branched chain aliphatic hydrocarbon radical containing one carbon-carbon triple bond and having a number of carbon atoms in the specified range. Thus, for example, "C_2-C_6 alkynyl" refers to all of the hexynyl and pentynyl isomers as well as 1-butynyl, 2-butynyl, 3-butynyl, 1-propynyl, 2-propynyl, and ethynyl.

The term "alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene ($-CH_2-$), 1,1-ethyl ($-CH(CH_3)-$), 1,2-ethyl ($-CH_2CH_2-$), 1,1-propyl ($-CH(CH_2CH_3)-$), 1,2-propyl ($-CH_2CH(CH_3)-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), and the like.

The term "alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of parent alkene. For example, an alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethenyl ($-CH=CH-$).

The term "alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of parent alkyne. For example, an alkynylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene ($-C\equiv C-$), propargyl ($-CH_2C\equiv C-$), and 4-pentynyl ($-CH_2CH_2CH_2C\equiv CH-$).

The term "cycloalkyl", alone or in combination with any other term, refers to a group, such as optionally substituted or non-substituted cyclic hydrocarbon, having from three to eight carbon atoms, unless otherwise defined. Thus, for example, "C_3-C_8 cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term "haloalkyl" refers to an alkyl group, as defined herein that is substituted with at least one halogen. Examples of straight or branched chained "haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, and *t*-butyl substituted independently with one or more halogens. The term "haloalkyl" should be interpreted to include such substituents such as $-CHF_2$, $-CF_3$, $-CH_2-CH_2-F$, $-CH_2-CF_3$, and the like.

The term "heteroalkyl" refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of alkyl group which is attached to the parent molecule is replaced with a heteroatom (*e.g.*, O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (*e.g.*, $-OCH_3$, etc.), an amine (*e.g.*, $-NHCH_3$, $-N(CH_3)_2$, etc.), or thioalkyl group (*e.g.*, $-SCH_3$, etc.). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (*e.g.*, O, N, or S) and the resulting heteroalkyl groups are, respectively, an alkyl ether (*e.g.*, $-CH_2CH_2-O-CH_3$, etc.), alkyl amine (*e.g.*, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, etc.), or thioalkyl ether (e.g., $-CH_2-S-CH_3$).

The term "halogen" refers to fluorine, chlorine, bromine, or iodine.

The term "aryl" refers to (i) optionally substituted phenyl, (ii) optionally substituted 9- or 10 membered bicyclic, fused carbocyclic ring systems in which at least one ring is aromatic, and (iii) optionally substituted 11- to 14-membered tricyclic, fused carbocyclic ring systems in which at least one ring is aromatic. Suitable aryls include, for example, phenyl, biphenyl, naphthyl, tetrahydronaphthyl (tetralinyl), indenyl, anthracenyl, and fluorenyl.

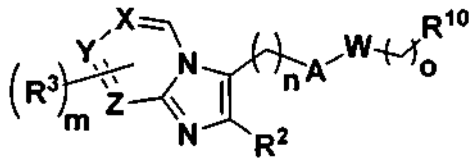
The term "phenyl" as used herein is meant to indicate that optionally substituted or non-substituted phenyl group.

The term "benzyl" as used herein is meant to indicate that optionally substituted or non-substituted benzyl group.

The term "heteroaryl" refers to (i) optionally substituted 5- and 6-membered heteroaromatic rings and (ii) optionally substituted 9- and 10-membered bicyclic, fused ring systems in which at least one ring is aromatic, wherein the heteroaromatic ring or the bicyclic, fused ring system contains from 1 to 4 heteroatoms independently selected from N, O, and S, where each N is optionally in the form of an oxide and each S in a ring which is not aromatic is optionally S(O) or $S(O)_2$. Suitable 5- and 6-membered heteroaromatic rings include, for example, pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. Suitable 9-and 10-membered heterobicyclic, fused ring systems include, for example, benzofuranyl, indolyl, indazolyl, naphthyridinyl, isobenzofuranyl, benzopiperidinyl, benzisoxazolyl, benzoxazolyl, chromenyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, isoindolyl, benzodioxolyl, benzofuranyl, imidazo[1,2-a]pyridinyl, benzotriazolyl, dihydroindolyl, dihydroisoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, 2,3-dihydrobenzofuranyl, and 2,3-dihydrobenzo-1,4-dioxinyl.

The term "heterocyclyl" refers to (i) optionally substituted 4- to 8-membered, saturated and unsaturated but non-aromatic monocyclic rings containing at least one carbon atom and from 1 to 4 heteroatoms, (ii) optionally substituted bicyclic ring systems containing from 1 to 6 heteroatoms, and (iii) optionally substituted tricyclic ring systems, wherein each ring in (ii) or (iii) is independent of fused to, or bridged with the other ring or rings and each ring is saturated or unsaturated but nonaromatic, and wherein each heteroatom in (i), (ii), and (iii) is independently selected from N, O, and S, wherein each N is optionally in the form of an oxide and each S is optionally oxidized to S(O) or $S(O)_2$. Suitable 4- to 8-membered saturated heterocyclyls include, for example, azetidinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl, thiazepanyl, azepanyl, diazepanyl, tetrahydropyranyl, tetrahydrothiopyranyl, dioxanyl, and azacyclooctyl. Suitable unsaturated heterocyclic rings include those corresponding to the saturated heterocyclic rings listed in the above sentence in which a single bond is replaced with a double bond. It is understood that the specific rings and ring systems suitable for use in the present invention are not limited to those listed in this and the preceding paragraphs. These rings and ring systems are merely representative.

In one embodiment, the compound has the general formula Ib:

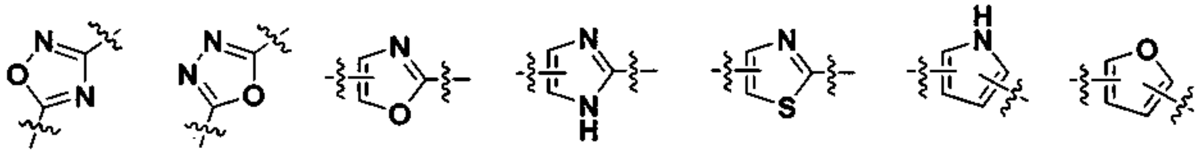


Ib

wherein

o is 0, 1, 2, or 3; n is 0, 1, 2 or 3; m is 0, 1, 2, 3 or 4;

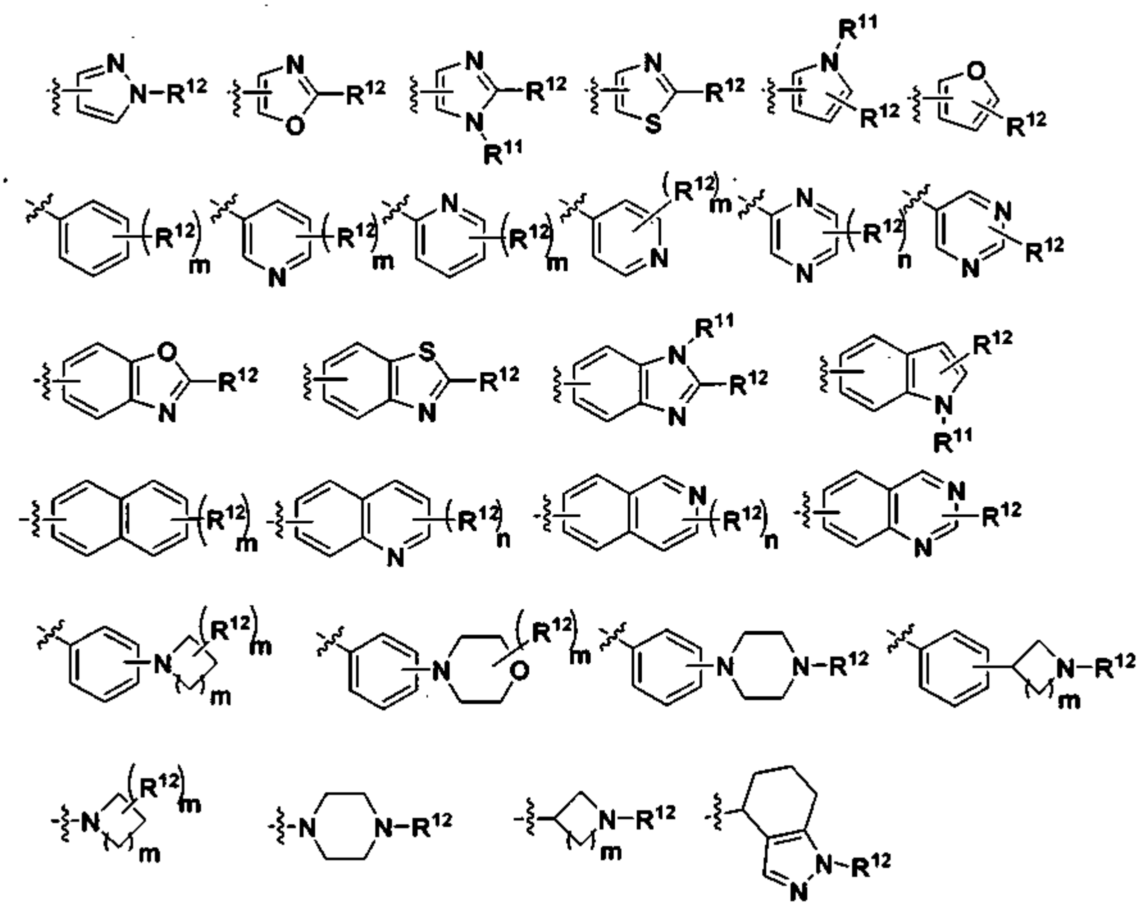
A is is NR^{11}, C=O, C=S, OP(O), P=O, CH_2, or a heteroaryl selected from the group consisting of



;

W is C=O, O, S, CH_2 or NR^{11};

R^{10} is a moiety selected from the group consisting of



R^{11} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, -OH, -OR^{13}, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkoxy, C_3-C_{15} cycloalkylalkoxy, C_3-C_{15} cycloalkylalkyl, -NH_2, -$N(R^{13})_2$, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$C(O)N(R^{13})_2$, -$S(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{13})_2$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl, any of which is optionally substituted;

R^{12} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, hydroxyl, -OR^{14}, -$C(O)R^{14}$, -$R^{14}(R^{14})C(O)R^{14}$, -$C(O)OR^{14}$, -$R^{14}(R^{14})C(O)OR^{14}$, -CN, -$NO_2$, -$NH_2$, -$N(R^{14})_2$, -$C(O)N(R^{14})_2$, -$R^{14}(R^{14})C(O)N(R^{14})_2$, -$S(O)R^{14}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})_2$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl, any of which is optionally substituted;

R^{13} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl, any of which is optionally substituted; and

R^{14} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_8 alkyl optionally substituted with at least one hydroxyl or halogen; C_3-C_7 cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, aryl, e.g. phenyl, benzyl, heteroaryl and heterocyclyl, any of which is optionally substituted.

In another aspect, the present invention relates to compounds having one of the formulae 1-352, as shown in Table 1 and/or Example 2, preferably 15, 16, 31, 32, 44, 45, 47, 49, 54-57, 60-87, 89-103, 106, 107, 110, 111, 113, 116-135, 137-141, 143, 144, 147, 148, 152, 154, 157-159, 161-167, 171-182, 184-193, 196, 198, 199-202, 209-218, 221-227, 231, 248-260, 262-264, 267-269, 271-274, 280-293, 295-315, 317-318, 320-321, 324, and 330 as shown in Table 1, and pharmaceutically acceptable salts thereof. Particularly preferred compounds are compounds having one of the formulae 47, 54, 177 and 185 as shown in Table 1. Their pharmaceutical acitivity is also shown in Figure 2.

Preferably, the compounds as defined above have an inhibitory activity on bacterial growth, preferably on the growth of *M. tuberculosis*, inside a host cell, preferably a macrophage, at a concentration between 1-20 μM, preferably less than 1 μM.

In one aspect, the present invention relates to compounds as defined above for use in the treatment of a bacterial infection, e.g. tuberculosis.

In one aspect, the present invention relates to compounds as defined above for use in the treatment of Tuberculosis.

In one aspect, the present invention relates to a pharmaceutical composition comprising a compound as defined above, and a pharmaceutically acceptable carrier.

In one aspect, the present invention relates to a method of treatment of Tuberculosis, comprising the application of a suitable amount of a compound as defined above or of a pharmaceutical composition as defined above to a person in need thereof.

In one embodiment, a "suitable amount", as used herein, is meant to refer to an amount in the range of from 0.01 mg/kg body weight to 1 g/kg body weight.

The objects of the present invention are also solved by a compound that competitively inhibits the specific binding of a compound according to the present invention. Preferably, such specific binding is with respect to a target protein of said compound according to the present invention.

The objects of the present invention are also solved by a method of treatment of a bacterial infection, in particular tuberculosis comprising the application of a suitable amount of a compound which compound is characterized by an ability to competitively inhibit the specific binding of a compound according to the present invention or a pharmaceutical composition according to the present invention, to a target protein, to a person in need thereof.

Pharmaceutical compositions

Pharmaceutically acceptable salts

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulfonate derived from benzensulfonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the formate derived from formic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulfonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the sulphate derived from sulphuric acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

In another embodiment, the compounds of the invention are used in their respective free base form according to the present invention.

Metal salts of a chemical compound of the invention include alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

The chemical compounds of the invention may be provided in unsolvated or solvated forms together with a pharmaceutically acceptable solvent(s) such as water, ethanol, and the like. Solvated forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, solvated forms are considered equivalent to unsolvated forms for the purposes of this invention.

Administration and Formulation

The production of medicaments containing the compounds of the invention, its active metabolites or isomers and salts according to the invention and their application can be performed according to well-known pharmaceutical methods.

While the compounds of the invention, useable according to the invention for use in therapy, may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries. Such salts of the compounds of the invention may be anhydrous or solvated.

In a preferred embodiment, the invention provides medicaments comprising a compound useable according to the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor, and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

A medicament of the invention may be those suitable for oral, rectal, bronchial, nasal, topical, buccal, sub-lingual, transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The compounds useable according to the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of medicament and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such medicament and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The compounds useable according to the invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound(s) useable according to the invention or a pharmaceutically acceptable salt of a compound(s) useable according to the invention.

For preparing a medicament from a compound useable according to the invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify. Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate. Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The chemical compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

In one embodiment of the present invention, the medicament is applied topically or systemically or via a combination of the two routes.

For administration, the compounds of the present invention may, in one embodiment, be administered in a formulation containing 0,001% to 70% per weight of the compound, preferably between 0,01% to 70% per weight of the compound, even more preferred between

0,1% and 70% per weight of the compound. In one embodiment, a suitable amount of compound administered is in the range of from 0.01 mg/kg body weight to 1 g/kg body weight.

Compositions suitable for administration also include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerol or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co. Easton, Pa.).

Figures and Tables

Reference is now made to the figures and tables, wherein

Figure 1 shows the dose response results on compound 8 (A) from the *in vitro* growth fluorescence assay (QUM) (B) and the intracellular growth assay (QIM) (C). Each curve represents a separate replicate experiment, [Cpd] refers to compound concentration, (M) refers to molar;

Figure 2 illustrates the kinetics of inhibition and bactericidal activity of imidazopyridine compounds 47 and 54 compared to the reference compound PA-824 represented in terms of CFU reduction (A) and as a time course (B) . Chemical structure of positive control PA-824 (C);

Figure 3 shows the in vivo efficacy of compounds 177 and 185 in a murine model of acute tuberculosis infection.

Table 1 summarizes imidazopyridine derivatives (general scaffolds Ia and Ib) with their respective inhibitory activities, wherein the numbers in bold print refer to the compounds listed in Example 2;

Table 2 shows anti-bacterial activity for compound 47 and compound 54 on several multi-drug resistant (MDR) strains.

Examples

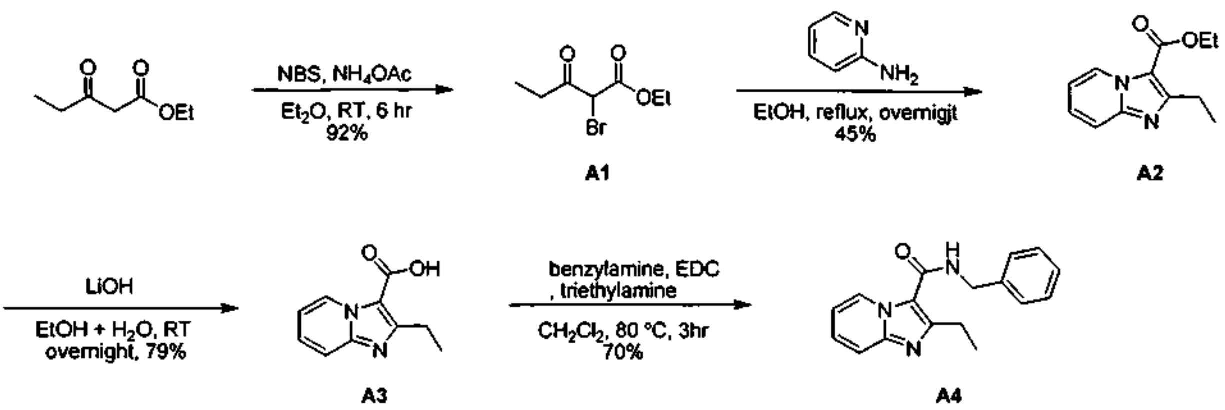
The invention is now further described by reference to the following examples which are intended to illustrate, not to limit the scope of the invention.

Example 1: Primary screening of a large library of small synthetic compounds using the phenotypic cell-based assay

A 120,000 small molecule compound library was screened using a validated phenotypic cell-based assay (WO2010003533A2). Active compounds from the primary screen were confirmed via dose response in the intracellular (QIM) assay and an *in vitro* (QUM) assay, wherein the abbreviation "QIM" stands for Quantification of Intracellular Mycobacteria and the abbreviation "QUM" stands for Quantification of *in vitro* grown Mycobacteria. Compound 8 (Figure 1A) demonstrated activity in both the QUM and QIM assay (Figure 1B and 1C respectively) and is the basis of the imidazopyridine general scaffolds Ia and Ib. Compound 8, from the dose response confirmation experiments demonstrated a minimum inhibitory concentration (MIC) or 5 μM and 2.5 μM in the QUM and QIM assays respectively. The MIC is the minimum concentration of compound required to obtain 80% bacterial growth inhibition. Compound 8 demonstrated potent antibacterial activity and consequently is the focus of the present invention.

Example 2: Derivatization of the imidazopyridine general scaffold

The imidazopyridine compounds (scaffolds Ia and Ib; see **Table 1**) underwent derivatization according to the methods outlined below (**Schemes 1-13**). Resulting derivatives were examined for inhibitory activity (MIC) using the assays described above (Example 1) and the results are summarized in **Table 1**.



Scheme 1

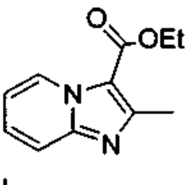
<u>**General procedure for the synthesis of A1**</u>

To a solution of Ethyl propionylacetate (6.9 mmol) in Et_2O (30 mL) was added Ammonium acetate (2.07 mmol) and *N*-Bromosuccinimide (7.6 mmol). The mixture was stirred at room temperature for 6 hour. After reaction was completed, the reaction mixture was filtered off and washed with H_2O (30 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give **A1.**

<u>**General procedure for the synthesis of A2**</u>

To a solution of **A1** (0.89 mmol) in EtOH (4 mL) was added 2-aminopyridine (0.89 mmol). The mixture was stirred and refluxed for overnight. After cooling, the dark residue was diluted with EtOAc (20 mL) and saturated $NaHCO_3$ solution (30 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography to give **A2**.

<u>**Ethyl 2-methylimidazo[1,2-a]pyridine-3-carboxylate (A2)**</u>



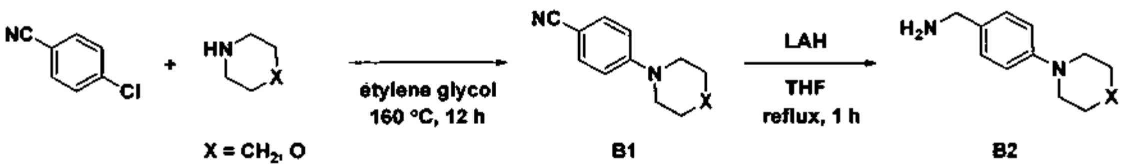
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 2.56 (s, 3H), 4.27 (q, J = 7.2 Hz, 2H), 6.78 (dd, J = 7.2 Hz, 7.2 Hz, 1H), 7.19 (dd, J = 6.8Hz, 6.8 Hz, 1H), 7.42 (dd, J = 8.8 Hz, 8.8 Hz, 1H), 9.12 (dd, J = 6.8 Hz, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 16.7, 60.3, 112.6, 113.6, 116.9, 127.5, 127.9, 146.9, 152.8, 161.4.

<u>**General procedure for the synthesis of A3**</u>

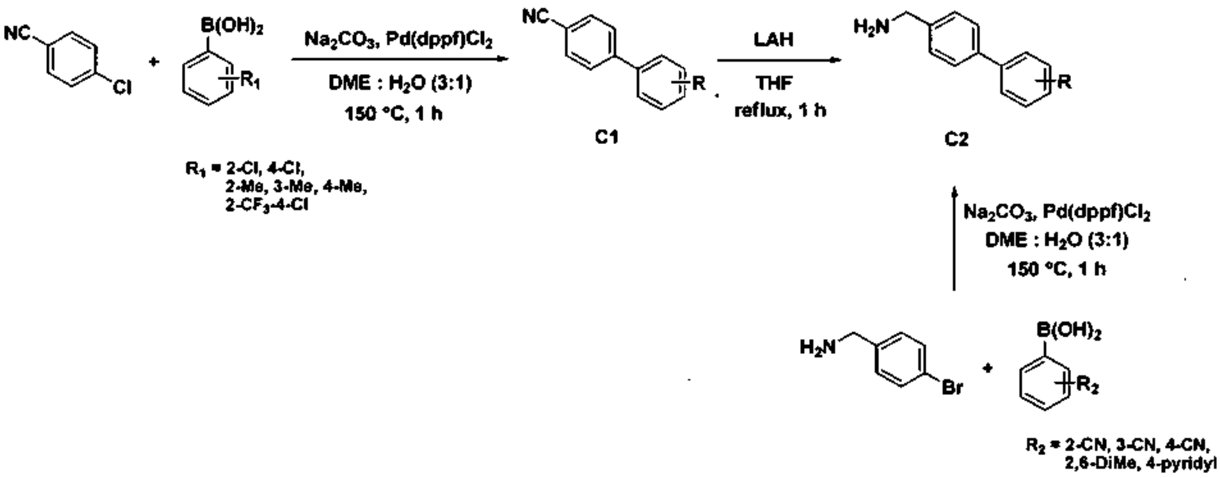
To a solution of **A2** (0.31 mmol) in H_2O (1.0 mL) and EtOH (3.0 mL) was added Lithium hydroxide (0.93 mmol). The mixture was stirred at room temperature for overnight. After reaction was completed, the mixture was evaporated and 1 N HCl (10 ml) was added until pH was 4. The residual pale solid was collected by filtration and washed with H_2O to give **A3.**

General procedure for the synthesis of A4

To a solution of **A3** (0.56 mmol) in CH_2Cl_2 (3 mL) was added triethylamine (1.7 mmol), benzylamine (0.56 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.84 mmol). The reaction mixture was stirred at room temperature for overnight. After reaction was completed, the reaction mixture was diluted with CH_2Cl_2 (10 mL) washed with 1N HCl (10 ml) and saturated $NaHCO_3$ solution (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography to give **A4**.



Scheme 2

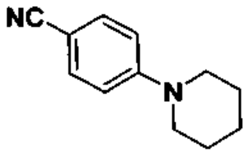


Scheme 3

General Procedure of B1

A solution of 4-chlorobenzonitrile (1.0 mmol) in ethylene glycol (2 mL) was added the appropriate amine (5.0 mmol). The reaction mixture was heated to 160 °C for 12 h and then cooled to room temperature, poured into ice water, and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified *via* flash column chromatography to give B1.

4-(Piperidin-1-yl)benzonitrile

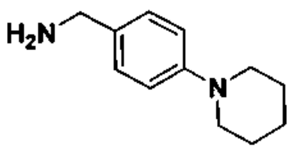


^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 – 1.68 (m, 5H), 3.30 – 3.40 (m, 4H), 6.83 (d, J = 9.2 Hz 2H), 7.46 (d, J = 8.8 Hz, 2H).

General Procedure of B2 and C2

Method I: A solution of **B1**(1.0 mmol) in THF (10 mL) was added LAH at 0 °C. The mixture was refluxed for 1 h and then cooled to room temperature. The reaction mixture was quenched by the addition of saturated aq. $NaHCO_3$ (10 mL) and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified *via* flash column chromatography to give **B2.**

(4-(Piperidin-1-yl)phenyl)methanamine



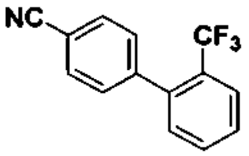
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 – 1.59 (m, 2H), 1.68 – 1.74 (m, 4H), 3.13 (t, J = 5.6 Hz, 4H), 3.77 (s, 2H), 6.92 (d, J = 8.4 Hz 2H), 7.19 (d, J = 8.8 Hz, 2H).

Method II: A solution of 4-bromobenzylamine (1.0 mmol) in DME (3 mL) were added the appropriate arylboronic acid (1.0 mmol), 1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.03 mmol), Na_2CO_3 (aq. 2.0 mmol). The mixture was stirred and heated at reflux under N_2 atmosphere. After 1 h, the mixture was cooled to room temperature, then the mixture was extracted with EtOAc, washed with sat. $NaHCO_3$ (aq.) brine and dried over $MgSO_4$ and filtered. After removal of the solvent, the amines were obtained, which were used without purification.

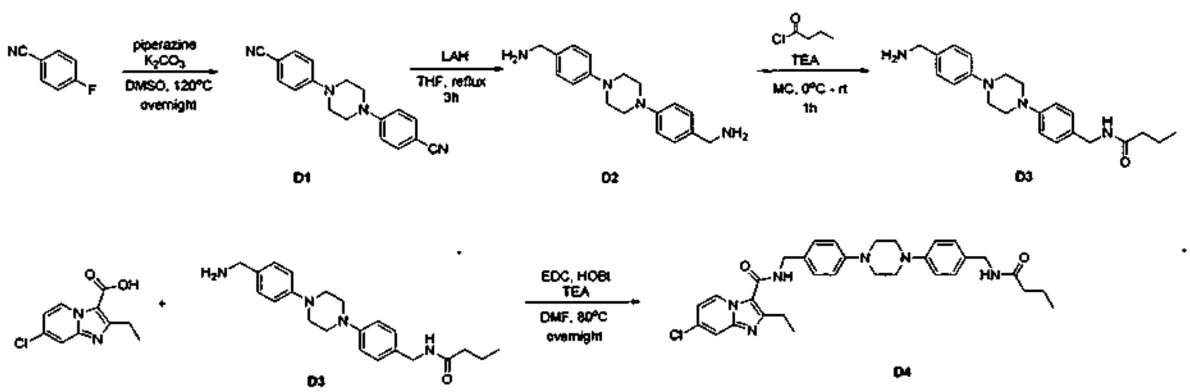
General Procedure of C1

A solution of 4-chlorobenzonitrile (1.0 mmol) in DME (3 mL) were added the appropriate arylboronic acid (1.0 mmol), 1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II) (0.03 mmol), Na_2CO_3 (aq. 2.0 mmol). The mixture was stirred and heated at reflux under N_2 atmosphere. After 1 h, the mixture was cooled to room temperature, then filtered and evaporated in vacuo. The residue was extracted with EtOAc, washed with sat. $NaHCO_3$ (aq.) brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified *via* flash column chromatography to give **C1**.

2'-(Trifluoromethyl)biphenyl-4-carbonitrile



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J – 7.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.54 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.61 (dd, *J* = 7.2, 7.6 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 1H).



Scheme 4

Procedure for the synthesis of D1

A mixture of 4-fluorobenzonitrile (4.2 g, 35 mmol), piperazine (1.0 g, 12 mmol) and K_2CO_3 (4.8 g, 35 mmol) in DMSO (30 mL) was stirred for overnight at 120°C. The reaction mixture was poured to the ice and resulting solid was filtered, washed with methanol and dried *in vacuo* to give **D1** as a white solid; ^{1}H NMR (400 MHz, DMSO) δ 3.49 (s, 8H), 7.01 (d, *J* = 9.2 Hz, 4H), 7.57 (d, *J* = 9.2 Hz, 4H); LCMS (electrospray) m/z $(M+H)^+$ 289.

Procedure for the synthesis of D2

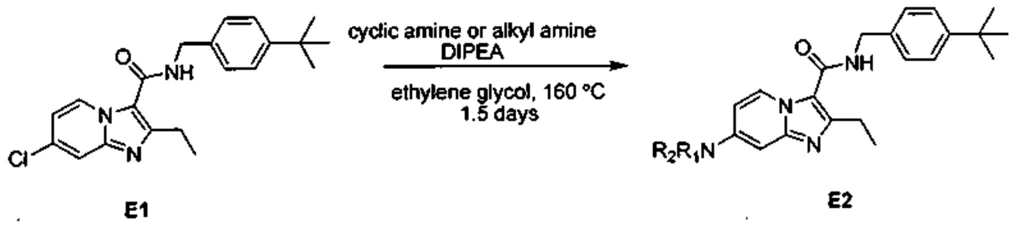
To a stirred solution of **D1** (0.30 g, 1.00 mmol) in THF (5 mL) was added LAH (0.24 g, 6.20 mmol) and the resulting mixture was heated to reflux temperature for 3h. The reaction mixture was quenched with water and the solid was filtered off. The filtrate was extracted with MC (30 mL x 2), the organic layer was washed with saturated aqueous Na_2CO_3 (20 mL) and concentrated *in vacuo* to give **D2**; ^1H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 8H), 3.80 (s, 4H), 6.95 (d, J = 8.4 Hz, 4H), 7.25 (d, J = 8.4 Hz, 4H); LCMS (electrospray) m/z $(M)^+$ 296.

Procedure for the synthesis of D3

To a stirred solution of **D2** (0.70 g, 2.36 mmol) in MC (25 mL) was added butyryl chloride (25 uL, 0.23 mmol) and the resulting mixture was stirred for 30 min under ice bath. After removal of the ice bath, the reaction mixture was stirred for another 30 min. The reaction mixture was diluted with MC (20 mL), washed with saturated aqueous Na_2CO_3 (20 mL) and the organic layer was concentrated under reduced pressure. The crude residue was purified by column chromatography (20 % MeOH in MC) to give **D3**; ^1H NMR (400 MHz, $CDCl_3$) δ 0.41(t, J = 7.2 Hz, 3H), 1.00 (brs, 2H), 1.12 – 1.21 (m, 2H), 1.63 (t, J = 7.2 Hz, 2H), 2.80 (s, 8H), 3.27 (s, 2H), 3.84 (d, J = 5.2 Hz, 2H), 5.16 (brs, 1H), 6.38 – 6.45 (m, 4H), 6.67 – 6.74 (m, 4H); LCMS (electrospray) m/z $(M+H)^+$ 367.

Procedure for the synthesis of D4

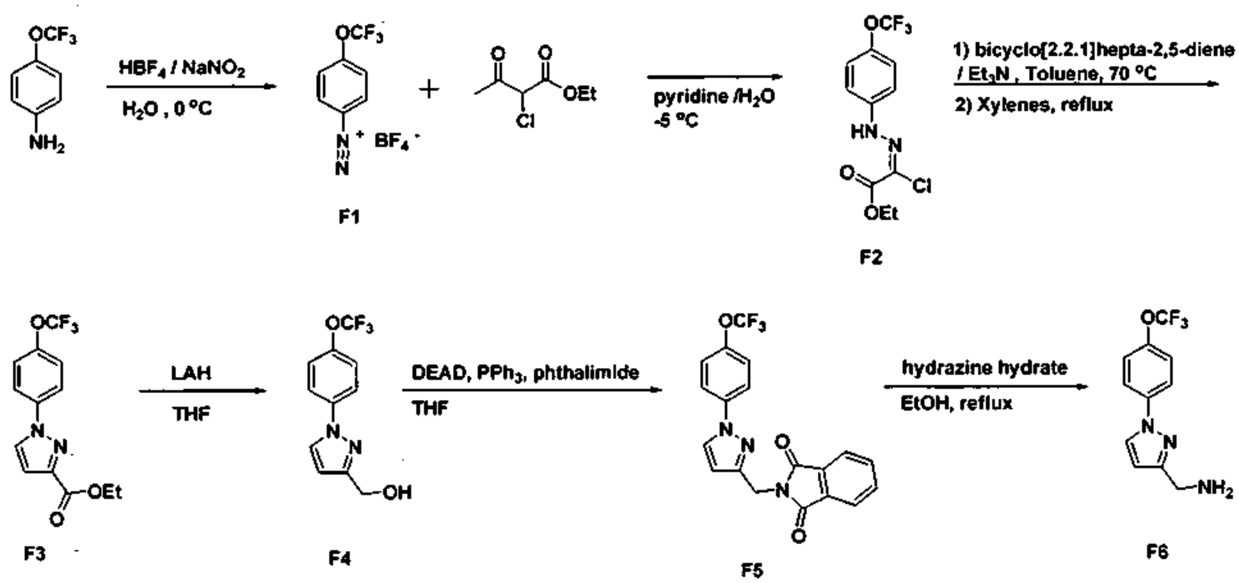
To a solution of acid (0.012 g, 0.054 mmol) in DMF (1 mL) was added triethylamine (15uL, 0.11 mmol), **D3** (0.020 g, 0.055 mmol), hydroxybenzotriazole (3.7 mg, 0.027 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.016 g, 0.082 mmol) and the reaction mixture was stirred at 80°C for overnight. The reaction mixture was cooled to -10°C , the resulting solid was filtered, washed with MC and dried *in vacuo* to give **D4**;



Scheme 5

Procedure for the synthesis of E2

A mixture of **E1** (0.32 g, 0.86 mmol), an amine (excess) and DIPEA (0.75 mL, 4.32 mmol) in ethylene glycol (4 mL) was heated to 160°C for 1.5 days. After reaction completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20 % MeOH in MC) and then precipitated with acetonitrile to give **E2** as a white solid.



Scheme 6

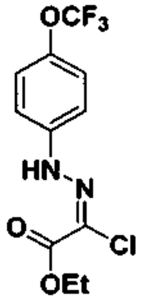
General procedure for the synthesis of F1

To an ice-salt-cooled solution of the 4-(trifluoromethoxy)aniline (11.29 mmol) in HBF_4 (50%, 22.58 mmol) and water (2 mL) was dropwise added a precooled solution of $NaNO_2$ (12.42 mmol) in water (2 mL). During the addition, the temperature was carefully kept below 5 °C and the resulting mixture was left to stir at 0 °C for 30 min. The diazonium salt (**F1**) was collected by filtration, washed with Et_2O, and extensively dried *in vacuo*.

General procedure for the synthesis of F2

F1 (11.30 mmol) was added to a solution of 2-chloroacetoacetate (11.30 mmol) in pyridine (4 mL) and water (4 mL) at -5 °C. The mixture was stirred at -5 °C for 30 min, and the resulting precipitate was filtered and washed with ice cold water. Recrystallization from EtOH/water gave **F2**.

(E)-Ethyl 2-chloro-2-(2-(4-(trifluoromethoxy)phenyl)hydrazono)acetate (F2)

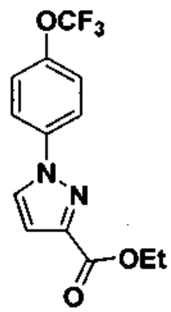


^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 7.20 (d, *J* = 9.6 Hz, 2H), 7.24 (d, *J* = 9.2 Hz, 2H), 8.32 (brs, 1H)

General procedure for the synthesis of F3

A mixture of **F2** (9.33 mmol), bicyclo[2.2.1]hepta-2,5-diene (46.67 mmol) and Et_3N (28.00 mmol) in toluene (10 mL) was stirred at 70 °C for 1 h. The resulting mixture was cooled and filtered, the filter cake was washed with toluene, and the organic fractions were combined and evaporated. The residue was refluxed in xylenes (10 mL) for 2 h. Column chromatography of the cooled reaction mixture, eluting with hexanes, first gave xylenes, and then further elution with ethyl acetate gave **F3**.

Ethyl 1-(4-(trifluoromethoxy)phenyl)-1H-pyrazole-3-carboxylate (F3)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.2 Hz, 3H), 4.44 (q, *J* = 7.2 Hz, 2H), 7.00 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 9.2 Hz, 2H), 7.91 (d, *J* = 2.4 Hz, 1H)

General procedure for the synthesis of F4

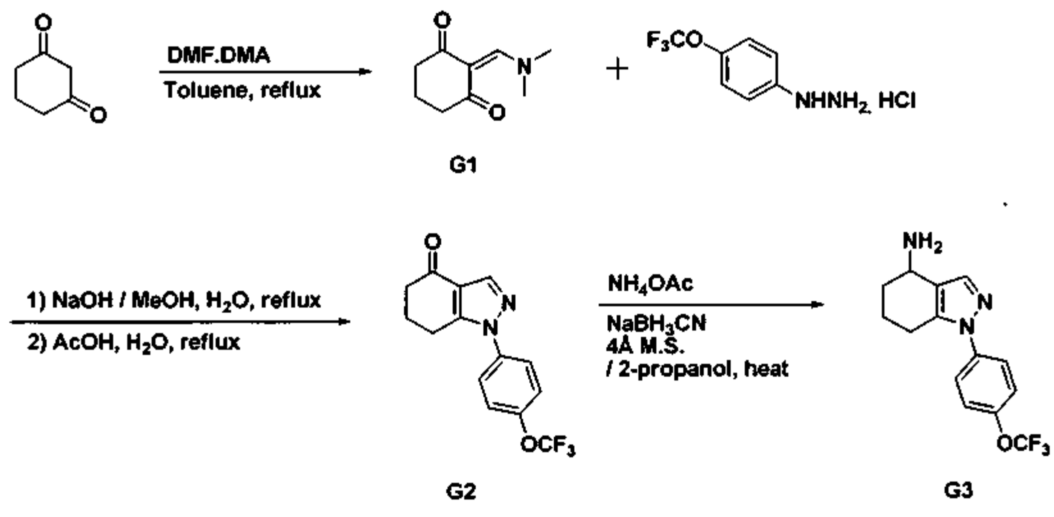
$LiAlH_4$ (0.67 mmol) was added to a stirred solution of **F3** (0.67 mmol) in THF (5 mL) at 0 °C, and the mixture was warmed to room temperature for 1 hr, then cooled to 0 °C and quenched with ice. The resulting mixture was diluted with ethyl acetate (10 mL) washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography to give **F4**.

General procedure for the synthesis of F5

DEAD (0.84 mmol) was added dropwise to a stirred and cooled (0 °C) solution of phthalimide (0.83 mmol), Ph_3P (0.84 mmol) and **F4** (0.69 mmol) in dry THF. The cooling bath removed and stirring was continued at room temperature for 4 hr, then water (1 mL) was added the reaction mixture was filtered through a column of silica, eluting with CH_2Cl_2. The eluate was concentrated *in vacuo* and the residue was purified by flash column chromatography to give **F5**.

General procedure for the synthesis of F6

To a solution of **F5** (0.69 mmol) in EtOH (5 mL) was added hydrazine hydrate (1.38 mmol). The reaction mixture was stirred and refluxed for 4 hr. After cooling, the reaction mixture was evaporated and diluted with EtOAc (10 mL) and saturated $NaHCO_3$ solution (10 mL), then washed with brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product **F6** was used for next step without further purification.



Scheme 7

General procedure for the synthesis of G1

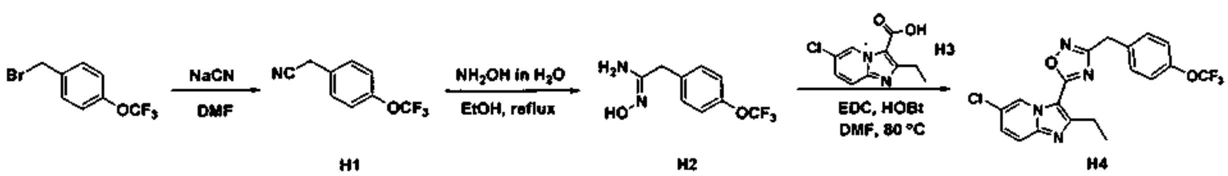
To a solution of cyclohexane-1,3-dione (17.84 mmol) in toluene (20 mL) was added DMF.DMA (26.75 mmol). The reaction mixture was stirred and refluxed for overnight. After cooling, the reaction mixture was concentrated *in vacuo*. The crude product **G1** was used for next step without further purification.

General procedure for the synthesis of G2

To a solution of **G1** (8.98 mmol) in methanol (20 mL) and water (3 mL) was added (4-(trifluoromethoxy)phenyl)hydrazine hydrochloride (8.98 mmol) and sodium hydroxide (8.98 mmol). The reaction mixture heated at reflux for 2 h and concentrated *in vacuo*. Then to the residue were added AcOH (20 mL) and water (10 mL), and the reaction mixture was heated to 110 °C for 2 h. On completion of the reaction, the solution was concentrated *in vacuo*, the residue was diluted with EtOAc (20 mL) and saturated $NaHCO_3$ solution (20 mL), then washed with brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography to give **G2**.

General procedure for the synthesis of G3

To a solution of **G2** (2.36 mmol) in 2-propanol (5 mL) was added ammonium acetate (23.65 mmol). After complete dissolution, molecular sieves (4Å , 1.0 g) and $NaBH_3CN$ (11.82 mmol) were added and the reaction mixture was stirred and refluxed for overnight. After cooling, the reaction mixture was evaporated and diluted with EtOAc (10 mL) and saturated $NaHCO_3$ solution (10 mL), then washed with brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product **G3** was used for next step without further purification.



Scheme 8

General procedure for the synthesis of H1

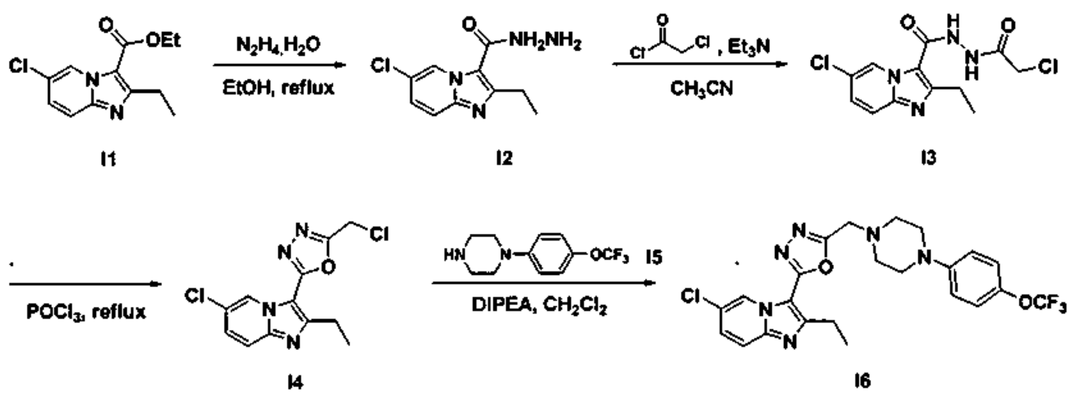
To a solution of 4-trifluoromethoxybenzyl bromide (1.05 g, 4.09 mmol) in 5 mL dry DMF was added sodium cyanide (220 mg, 4.50 mmol). The reaction was stirred for 1 h at room temperature, poured into water and extracted with of ethyl acetate (2 x 20 mL). The combined layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product **H1** was used in the next reaction without further purification.

General procedure for the synthesis of H2

To a solution of **H1** (93 mg, 0.46 mmol) in EtOH was added a solution of hydroxylamine 50 wt% in water (0.12 mL, 1.84 mmol). The reaction mixture was refluxed for overnight. After cooling, the mixture was concentrated *in vacuo*. The crude product **H2** was used in the next reaction without further purification.

General procedure for the synthesis of H4

To a solution of **H3** (114 mg, 0.506 mmol) in dry DMF were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (97 mg, 0.506 mmol), 1-hydroxybenzotriazole (68 mg, 0.506 mmol). The mixture was stirred for 30 min at room temperature. Then to the reaction mixture was added a solution of C2 (108 mg, 0.46 mmol) in dry DMF. The reaction mixture was stirred at 140 °C for 2 h. After cooling, the reaction mixture was diluted with ethyl acetate (10 mL), washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography to give **H4**.



Scheme 9

General procedure for the synthesis of I2

To a solution of **I1** (253 mg, 1.0 mmol) in EtOH was added hydrazine hydrate (0.75 mL, mmol). The reaction mixture was refluxed for 12 h. After cooling, the resulting precipitate (**D2**) was filtered, washed with EtOH and dried.

General procedure for the synthesis of I3

To a solution of **I2** (96 mg, 0.402 mmol) in CH_2Cl_2 was added Et_3N (0.057 mL, 0.406 mmol). The reaction mixture was cooled to 0 °C and to the mixture was added dropwise a solution of chloroacetyl chloride (0.035 mL, 0.442 mmol) in CH_2Cl_2. The reaction mixture was stirred at

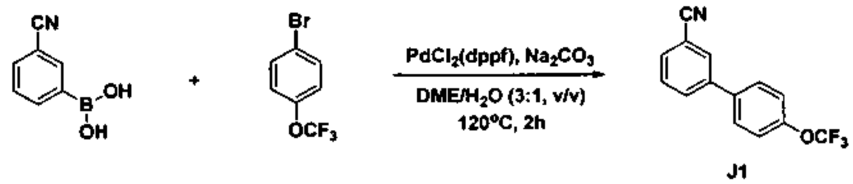
0 °C, the reaction temperature was raised to room temperature and the resultant mixture is further stirred for 30 min. To the mixture was added water, the solution was extracted with CH_2Cl_2, washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product (**I3**) was used in the next reaction without further purification.

General procedure for the synthesis of I4

I3 (0.402 mmol) was placed under nitrogen and $POCl_3$ (2 mL) was added. The reaction mixture was refluxed for 2 h. The mixture was cooled to room temperature, poured into water and extracted with ethylacetate (x 2). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography to give **I4**.

General procedure for the synthesis of I6

To a solution of **I4** (50 mg, 0.17 mmol) in CH_2Cl_2 were added **I5** (50 mg, 0.20 mmol) and DIPEA (0.035 mL, 0.20 mmol). The reaction mixture was stirred for overnight. the mixture was extracted with CH_2Cl_2 and water, washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography to give **I6**.

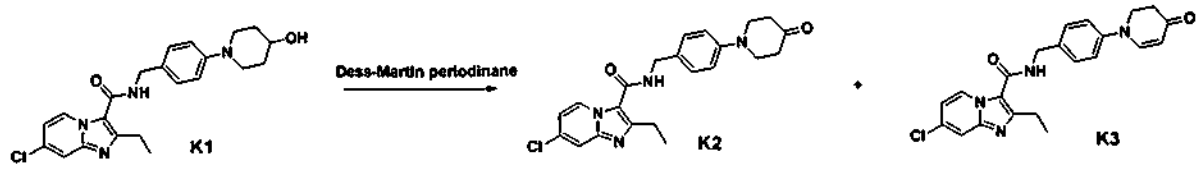


Scheme 10

General procedure for the synthesis of J1

To a solution of 1-bromo-4-(trifluoromethoxy)benzene (0.50 g, 2.07 mmol) in DME (6 mL) were added 3-cyanophenyl boronic acid (0.37 g, 2.49 mmol), 1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.046 g, 0.062 mmol) and Na_2CO_3 (2 mL of aqueous solution, 0.44 g, 4.14 mmol). The resulting mixture was stirred at 120 °C for 2h. After removal of organic solvent, the resulting residue was dilited with water (10 mL) and extracted with methylene chloride (10 mL x 2). The organic layer was dried over $MgSO_4$

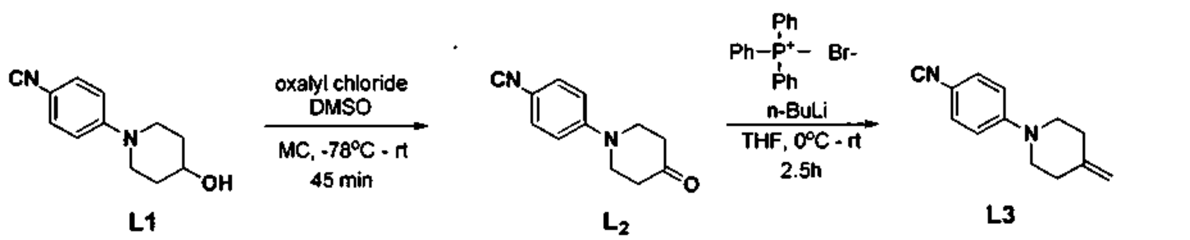
and concentrated in *vacuo*. The resulting crude residue was purified by flash column chromatography (n-hexane : ethyl acetate = 10 : 1 ratio) to give a **J1**.



Scheme 11

General procedure for the synthesis of K2 and K3

To a stirred suspension of **K1** (0.050 g, 0.12 mmol) and $NaHCO_3$ (0.051 g, 0.60 mmol) in methylene chloride (2.0 mL) was added dess-martin periodinane (0.10 g, 0.24 mmol) under ice-bath. After 5-minutes, the reaction temperature was raise to room temperature and the resulting solution was stirred for 2h. The reaction mixture was diluted with methylene chloride (10 mL) and washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The resulting crude residue was purified by flash column chromatography (methylene chloride : methanol = 50 : 1 ratio) to give **K2** and **K3**.



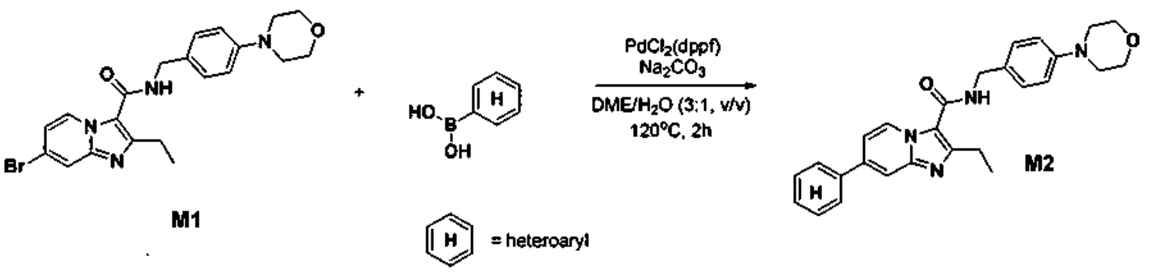
Scheme 52

General procedure for the synthesis of L2

A solution of oxalyl chloride (0.43 mL, 4.94 mmol) in methylene chloride (5 mL) was cooled to -78°C and DMSO (0.70 mL, 9.88 mmol) was added slowly. After 10 minutes, a solution of alcohol (0.50 g, 2.47 mmol) in methylene chloride (3mL) was added over 10 min, and the mixture was further stirred for 15min at -78°C. Triethylamine (1.4 mL, 9.88 mmol)was added to the solution and the mixture was stirred for 15 min and allowed to warm up to 0 °C. After reaction completion, the reaction mixture was diluted with methylene chloride (15 mL) and washed with aqueous Na_2CO_3 (15mL). The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The resulting crude residue was purified by flash column chromatography (n-hexane : ethyl acetate = 5 : 1 ratio) to give **L2**.

General procedure for the synthesis of L3

To a suspension of methyltriphenylphosphonium bromide (0.43 g, 1.20 mmol) in THF (5 mL) was added nBuLi (2.5 M in n-hexane, 0.48 mL, 1.20 mmol) under ice-bath and the mixture was stirred for 30min. A solution of ketone compound in THF (3 mL) was added dropwise and the resulting mixture was allowed to warm up to room temperature over 2h. After reaction completion, solution was diluted with methylene chloride (10 mL) and washed with aqueous $NaHCO_3$ (15 mL). The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The resulting crude residue was purified by flash column chromatography (n-hexane : ethyl acetate = 15 : 1 ratio) to give a target compound **L3**.

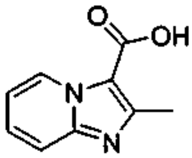


Scheme 13

General procedure for the synthesis of M2

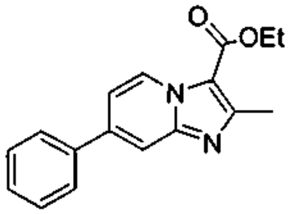
To a solution of **M1** (0.050 g, 0.13 mmol) in DME (2 mL) were added pyridine boronic acid (0.017 g, 0.13 mmol), 1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (1.5 mg, 3.38 umol) and Na_2CO_3 (0.5 mL of aqueous solution, 0.024 g, 0.22 mmol). The resulting mixture was stirred at 120 °C for 2h. After removal of organic solvent, the resulting residue was dilited with water (10 mL) and extracted with methylene chloride (10 mL x 2). The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The resulting crude residue was purified by flash column chromatography (methylene chloride : methanol = 20 : 1 ratio) to give a target compound **M2**.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (1)



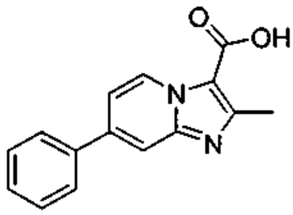
^{1}H NMR (400 MHz, CD_3OD) δ 2.84 (s, 3H), 7.04 (dd, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 8.07 (dd, *J* = 1.2 Hz, 7.2 Hz, 1H), 9.65 (d, *J* = 7.2 Hz, 1H).

Ethyl 2-methyl-7-phenylimidazo[1,2-a]pyridine-3-carboxylate (2)



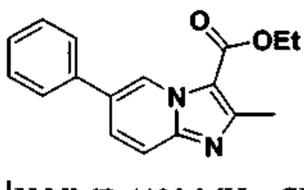
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, *J* = 7.2 Hz, 3H), 2.73 (s, 3H), 4.44 (q, *J* = 7.2 Hz, 2H), 7.25 (dd, *J* = 1.6 Hz, 7.2 Hz, 1H), 7.42 – 7.51 (m, 3H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.80 (s, 1H), 9.32 (d, *J* = 7.2 Hz, 1H).

2-Methyl-7-phenylimidazo[1,2-a]pyridine-3-carboxylic acid (3)



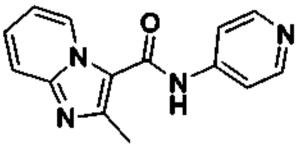
^{1}H NMR (400 MHz, DMSO *d*-6) δ 2.60 (s, 3H), 7.43 – 7.52 (m, 5H), 7.83 (s, 1H), 7.85 (s, 1H), 7.94 (s, 1H), 9.26 (d, *J* = 7.6 Hz, 1H)

Ethyl 2-methyl-6-phenylimidazo[1,2-a]pyridine-3-carboxylate(4)



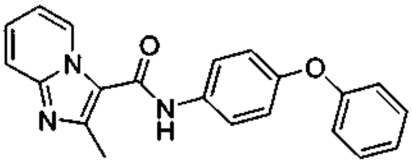
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3H), 2.70 (s, 3H), 4.40 (q, *J* = 7.2 Hz, 2H), 7.33 – 7.36 (m, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.60 – 7.61 (m, 1H), 9.52 (s, 1H).

2-Methyl-N-(pyridin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (5)



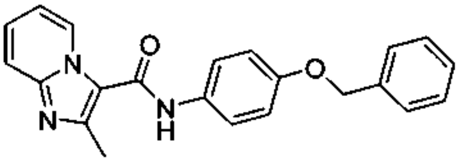
^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 2.72 (s, 3H), 6.89 (dd, J = 1.2, 7.2 Hz, 1H), 7.28 – 7.33 (m, 1H), 7.52 (d, J = 9.2 Hz, 1H), 7.57 (dd, J = 1.6, 4.8 Hz, 2H), 8.43 (dd, J = 1.6, 4.8 Hz, 1H), 8.92 (br s, 1H), 9.11 (d, J = 6.8 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 253.18

2-Methyl-N-(4-phenoxyphenyl)imidazo[1,2-a]pyridine-3-carboxamide (6)



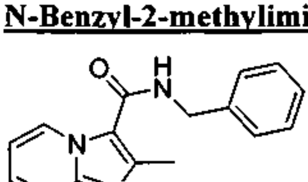
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60(s, 3H), 6.89(t, J=8.0Hz, 3H), 6.96(d, J=6.8Hz, 2H), 7.02(t, J=7.6Hz, 1H), 7.27(t, J=7.6Hz, 2H), 7.38(t, J=6.8Hz, 1H), 7.47(d, J=8.8Hz, 1H), 7.57(d, J=6.8Hz, 2H), 8.89(d, J=6.8Hz, 1H).

N-(4-(Benzyloxy)phenyl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide (7)



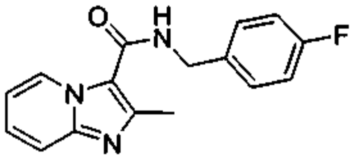
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57(s, 3H), 4.97(s, 2H), 6.88 - 6.91(m, 3H), 7.19(t, J=7.2Hz, 1H), 7.28(t, J=8.4Hz, 2H), 7.32(t, J=6.8Hz, 3H), 7.43 – 7.46(m, 3H), 8.85(d, J=5.6Hz, 1H).

N-Benzyl-2-methylimidazo[1,2-a]pyridine-3-carboxamide (8)



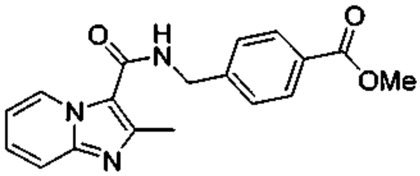
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 4.70 (d, J = 5.6 Hz, 2H), 6.13 (brs, 1H), 6.91 (dd, J = 1.2 Hz, 7.2 Hz, 1H), 7.29 – 7.39 (m, 6H), 7.56 (d, J = 9.2 Hz, 1H), 9.42 (d, J = 7.2 Hz, 1H).

N-(4-Fluorobenzyl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide (9)



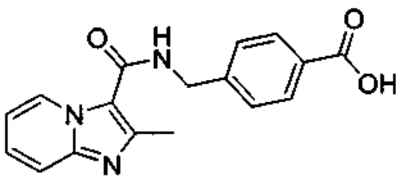
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 3H), 4.66 (d, *J* = 6.0 Hz, 2H), 6.11 (brs, 1H), 6.91 (d, *J* = 6.8 Hz, 1H), 7.02 – 7.06 (m, 2H), 7.30 – 7.36 (m, 3H), 7.56 (d, *J* = 8.8 Hz, 1H), 9.41 (d, *J* = 6.8 Hz, 1H).

Methyl 4-((2-me3thylimidazo[1,2-a]pyridine-3-carboxamido)methyl)benzoate (10)



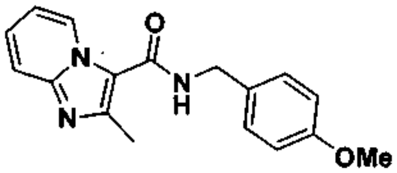
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 3.90 (s, 3H), 4.76 (d, *J* = 6.0 Hz, 2H), 6.24 (brs, 1H), 6.91 – 6.95 (m, 1H), 7.32 – 7.36 (m, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 9.2 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 9.41 (d, *J* = 6.8 Hz, 1H).

4-((2-Methylimidazo[1,2-a]pyridine-3-carboxamido)methyl)benzoic acid (11)



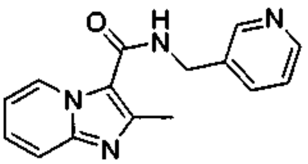
^{1}H NMR (400 MHz, CD_3OD) δ 2.64 (s, 3H), 4.69 (s, 2H), 7.03 (dd, *J* = 6.8 Hz, 6.8 Hz, 1H), 7.43 – 7.47 (m, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.55 (m, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 9.04 (d, *J* = 7.2 Hz, 1H).

N-(4-Methoxybenzyl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide (12)



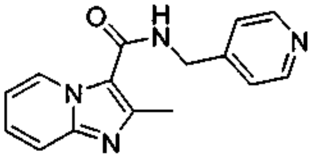
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 3H), 3.810 (s, 3H), 4.63 (d, *J* = 5.2 Hz, 2H), 6.01 (m, 1H), 6.89 – 6.94 (m, 3H), 7.30 – 7.35 (m, 3H), 7.56 – 7.58 (m, 1H), 9.43 (dd, *J* = 0.8, 6.8 Hz, 1H).

2-Methyl-N-(pyridin-3-ylmethyl)imidazo[1,2-a]pyridine-3-carboxamide (13)



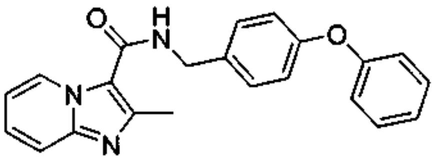
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 4.70 (d, J = 6.0 Hz, 2H), 6.30 (brs, 1H), 6.89 – 6.93 (m, 1H), 7.26 – 7.35 (m, 2H), 7.55 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 8.53 (d, J = 3.6 Hz, 1H), 8.62 (s, 1H), 9.38 (d, J = 7.2 Hz, 1H).

2-Methyl-N-(pyridin-4-ylmethyl)imidazo[1,2-a]pyridine-3-carboxamide (14)



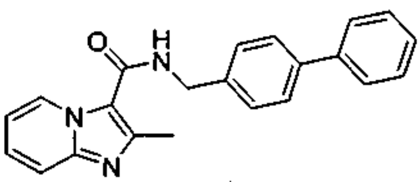
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 4.68 (d, J = 6.0 Hz, 2H), 6.41 (brs, 1H), 6.88 – 6.92 (m, 1H), 7.25 (d, J = 4.4 Hz, 2H), 7.30 – 7.34 (m, 1H), 7.53 (d, J = 8.8 Hz, 1H), 8.53 (d, J = 4.4 Hz, 2H), 9.35 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 42.4, 113.6, 115.2, 116.7, 122.3, 127.5, 128.3, 145.9, 146.4, 147.7, 150.3, 161.9.

2-Methyl-N-(4-phenoxybenzyl)imidazo[1,2-a]pyridine-3-carboxamide (15)



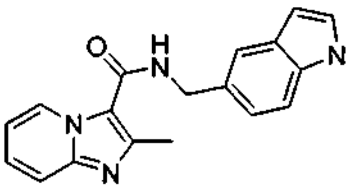
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 4.67 (d, J = 5.6 Hz, 2H), 6.14 (brs, 1H), 6.92 – 6.96 (m, 1H), 6.99 – 7.08 (m, 4H), 7.12 (dd, J = 6.4 Hz, 6.4 Hz, 1H), 7.31 – 7.37 (m, 5H), 7.59 (d, J = 8.8 Hz, 1H), 9.43 (d, J = 6.8 Hz, 1H).

N-(Biphenyl-4-ylmethyl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide (16)



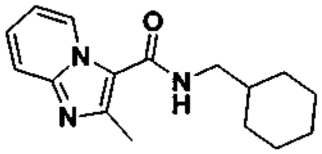
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 4.74 (d, J = 4.0 Hz, 2H), 6.19 (brs, 1H), 6.91 (dd, J = 6.0 Hz, 6.0 Hz, 1H), 7.30 – 7.36 (m, 2H), 7.41 – 7.45 (m, 5H), 7.58 (m, 4H), 9.43 (d, J = 6.8 Hz, 1H).

N-((1H-Indol-5-yl)methyl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide (17)



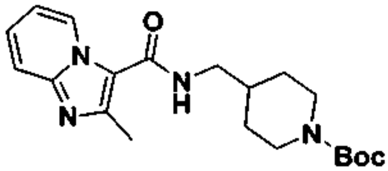
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 4.78 (d, J = 5.2 Hz, 2H), 6.18 (brs, 1H), 6.55 (s, 1H), 6.98 – 7.02 (m, 1H), 7.22 – 7.24 (m, 2H), 7.40 (s, 1H), 7.42 (s, 1H), 7.66 – 7.68 (m, 2H), 8.24 (brs, 1H), 9.47 (d, J = 7.2 Hz, 1H).

N-(Cyclohexylmethyl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide (18)



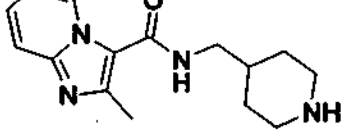
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 – 1.27 (m, 5H), 1.54 – 1.78 (m, 6H), 2.67 (s, 3H), 3.31 (t, J = 6.2 Hz, 2H), 5.91 (m 1H), 6.64 (t, J = 6.8 Hz, 1H), 7.24 – 7.28 (m, 1H), 7.50 (d, J = 9.2 Hz, 1H), 9.32 (d, J = 6.8 Hz, 1H).

tert-Butyl 4-((2-methylimidazo[1,2-a]pyridine-3-carboxamido)methyl)piperidine-1-carboxylate (19)



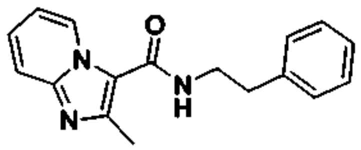
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 – 1.25 (m, 2H), 1.44 (s, 9H), 1.73 – 1.82 (m, 3H), 1.97 (m, 2H), 2.70 (s, 3H), 3.40 (m, 2H), 5.92 (t, J = 5.6 Hz, 1H), 6.90 (t, J = 6.8 Hz, 1H), 7.29 – 7.33 (m, 1H), 7.55 (d, J = 8.8 Hz, 1H), 9.36 (d, J = 6.8 Hz, 1H).

2-Methyl-N-(piperidin-4-ylmethyl)imidazo[1,2-a]pyridine-3-carboxamide (20)



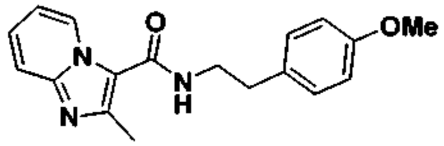
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 – 1.77 (m, 6H), 2.58 – 2.64 (m, 1H), 2.65 (s, 3H), 3.13 (d, J = 11.6 Hz, 2H), 3.34 (t, J = 12.0 Hz, 2H), 3.68 (br s, 1H), 6.71 (m, 1H), 6.84 (t, J = 6.8 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 9.28 (d, J = 6.8 Hz, 1H).

2-Methyl-N-phenethylimidazo[1,2-a]pyridine-3-carboxamide (21)



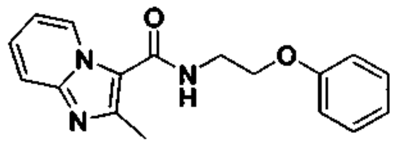
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28(s, 3H), 2.82(t, *J*=7.2Hz, 2H), 3.56(t, *J*=6.8Hz, 2H), 6.79(t, *J*=6.8Hz, 1H), 7.06(t, *J* =6.8Hz, 1H), 7.14(d, *J* =7.2Hz, 3H), 7.30(t, *J*=7.2Hz, 2H), 7.33(d, *J*=6.8Hz, 1H), 8.74(d, *J* =5.6Hz, 1H).

N-(4-Methoxyphenethyl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide (22)



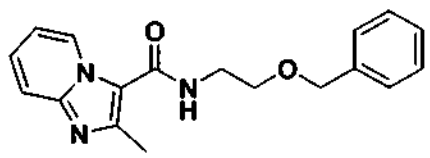
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.92 (t, *J* = 6.6 Hz, 2H), 3.74 (q, *J* = 6.4 Hz, 2H), 3.80 (s, 3H), 6.87 – 6.92 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.33 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 9.41 (d, *J* = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 310.25

2-Methyl-N-(2-phenoxyethyl)imidazo[1,2-a]pyridine-3-carboxamide (23)



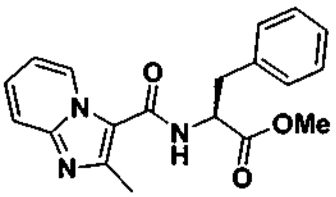
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (s, 3H), 3.93 (q, *J* = 4.8 Hz, 2H), 4.19 (t, *J* = 5.0 Hz, 2H), 6.33 (m, 1H), 6.90 – 9.94 (m, 3H), 6.98 (d, *J* = 7.4 Hz, 1H), 7.28 – 7.34 (m, 3H), 7.57 (d, *J* = 9.2 Hz, 1H), 9.40 (d, *J* = 7.2 Hz, 1H).

N-(2-(Benzyloxy)ethyl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide (24)



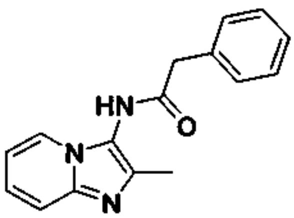
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.68 – 3.75 (m, 4H), 4.57 (s, 2H), 6.90 (dd, *J* = 1.2, 6.8 Hz, 1H), 7.27 – 7.34 (m, 6H), 7.57 (dd, *J* = 1.2, 9.2 Hz, 1H), 9.37 (dd, *J* = 2.0, 6.8 Hz, 1H).

(S)-Methyl 2-(2-methylimidazo[1,2-a]pyridine-3-carboxamido)-3-phenylpropanoate (25)



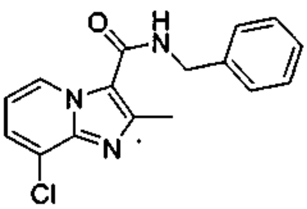
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.25 (dd, J = 5.6, 14.0 Hz, 1H), 3.33 (dd, J = 5.6, 14.0 Hz, 1H), 5.08 – 5.13 (m, 1H), 6.23 (d, J = 7.2 Hz, 1H), 6.91 (dd, J = 1.2 , 6.8 Hz, 1H), 7.14 – 7.16 (m, 2H), 7.27 – 7.35 (m, 4H), 7.57 (d, J = 8.8 Hz, 1H), 9.39 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 338.28

N-(2-Methylimidazo[1,2-a]pyridin-3-yl)-2-phenylacetamide (26)



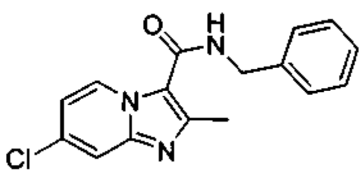
^{1}H NMR (400 MHz, CD_3OD) δ 2.26 (s, 3H), 3.82 (s, 2H), 7.24 – 7.31 (m, 2H), 7.36 – 7.41 (m, 2H), 7.43 – 7.44 (m, 3H), 7.76 (d, J = 6.8 Hz, 1H).

N-Benzyl-8-chloro-2-methylimidazo[1,2-a]pyridine-3-carboxamide (27)



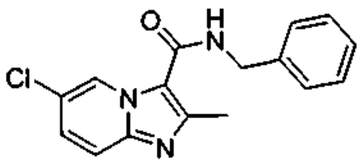
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (s, 3H), 4.71 (d, J = 6.0 Hz, 2H), 6.14 (brs, 1H), 6.87 (dd, J = 7.2 Hz, 7.2 Hz, 1H), 7.32 (dd, J = 4.4 Hz, 4.4 Hz, 1H), 7.34 – 7.42 (m, 5H), 9.38 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) □16.9, 29.9, 43.8, 113.1, 122.4, 126.2, 127.1, 127.9, 128.0, 129.1, 138.1, 141.8, 145.9, 161.3.

N-Benzyl-7-chloro-2-methylimidazo[1,2-a]pyridine-3-carboxamide (28)



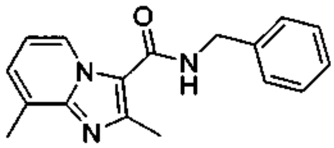
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 4.69 (d, J = 5.6 Hz, 2H), 6.13 (brs, 1H), 6.89 – 6.91 (m, 1H), 7.29 – 7.37 (m, 5H), 7.55 (d, J = 1.6 Hz, 1H), 9.37 (d, J = 7.6 Hz, 1H).

N-Benzyl-6-chloro-2-methylimidazo[1,2-a]pyridine-3-carboxamide (29)



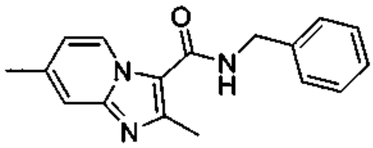
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 4.70 (d, J = 5.6 Hz, 2H), 6.16 (brs, 1H), 7.30 – 7.35 (m, 3H), 7.37 – 7.38 (m, 3H), 7.53 (d, J = 9.2 Hz, 1H), 9.56 (d, J = 1.6 Hz, 1H).

N-Benzyl-2,8-dimethylimidazo[1,2-a]pyridine-3-carboxamide (30)



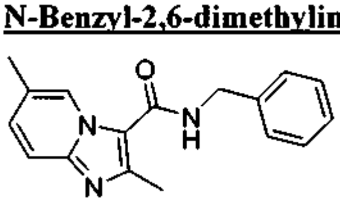
^{1}H NMR (400 MHz, MeOH-d_4) δ 2.55(s, 3H), 2.63(s, 3H), 4.63(s, 2H), 6.95(t, J=6.8Hz, 1H), 7.25(d, J=6.8Hz, 1H), 7.28(d, J=7.2Hz, 1H), 7.37(t, J=7.2Hz, 2H), 7.42(d, J=7.6Hz, 2H), 8.87(d, J=6.8Hz, 1H).

N-Benzyl-2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamide (31)



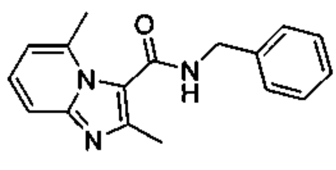
^{1}H NMR (400 MHz, MeOH-d_4) δ 2.44(s, 3H), 2.59(s, 3H), 4.63(s, 2H), 6.91(d, J=7.2Hz, 1H), 7.28(t, J=7.2Hz, 1H), 7.33(d, J=6.4Hz, 2H), 7.37(t, J=7.2Hz, 1H), 7.42(d, J=7.6Hz, 2H), 8.92(d, J=7.2Hz, 1H).

N-Benzyl-2,6-dimethylimidazo[1,2-a]pyridine-3-carboxamide (32)



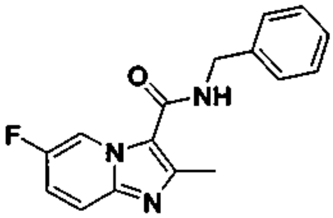
^{1}H NMR (400 MHz, MeOH-d_4) δ 2.36(s, 3H), 2.59(s, 3H), 4.63(s, 2H), 7.29(d, J=7.6Hz, 1H), 7.31(d, J=1.6Hz, 1H), 7.37(t, J=7.2Hz, 3H), 7.43(t, J=4.8Hz, 2H), 7.46(s, 1H), 8.83(s, 1H).

N-Benzyl-2,5-dimethylimidazo[1,2-a]pyridine-3-carboxamide (33)



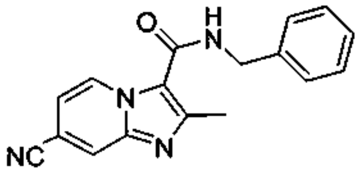
^{1}H NMR (400 MHz, MeOH-d_4) δ 2.44(s, 3H), 2.59(s, 3H), 4.29(s, 2H), 6.75(d, J=7.2Hz, 1H), 7.21 - 7.27(m, 3H), 7.33(t, J=6.4Hz, 2H), 7.41(t, J=8.8Hz, 1H), 7.49(s, 1H).

N-Benzyl-6-fluoro-2-methylimidazo[1,2-a]pyridine-3-carboxamide (34)



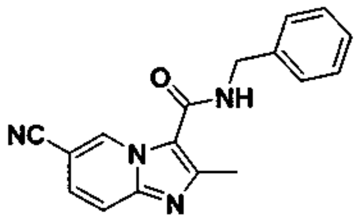
^{1}H NMR (400 MHz, CD_3OD) δ 2.68 (s, 3H), 4.71 (d, J = 6.0 Hz, 2H), 7.24 – 7.39 (m 6H), 7.52 – 7.56 (m, 1H), 9.48 – 9.49 (m, 1H); LCMS (electrospray) m/z $(M+H)^+$ 284.27

N-Benzyl-7-cyano-2-methylimidazo[1,2-a]pyridine-3-carboxamide (35)



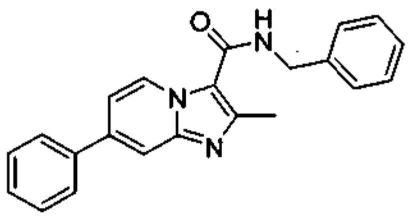
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (s, 3H), 4.61 (d, J = 6.0 Hz, 2H), 6.39 (brs, 1H), 6.85 (dd, J = 1.2 Hz, 5.2 Hz, 1H), 6.89 (s, 1H), 7.29 – 7.38 (m, 5H), 8.13 (d, J = 5.6 Hz, 1H)

N-Benzyl-6-cyano-2-methylimidazo[1,2-a]pyridine-3-carboxamide (36)



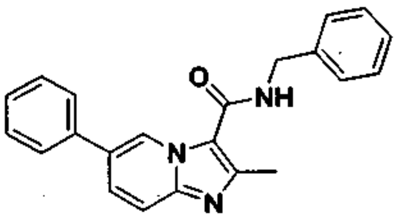
^{1}H NMR (400 MHz, CD_3OD) δ 2.63 (s, 3H), 4.65 (s, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H), 7.57 (dd, J = 0.8, 9.2 Hz, 1H), 7.85 (dd, J = 1.6, 9.2 Hz, 1H), 9.58 (m, 1H).

N-Benzyl-2-methyl-7-phenylimidazo[1,2-a]pyridine-3-carboxamide (37)



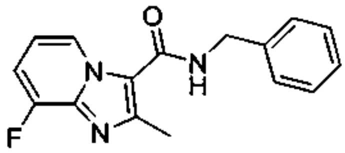
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 4.71 (d, *J* = 5.6 Hz, 2H), 6.15 (brs, 1H), 7.22 (dd, *J* = 2.0 Hz, 7.2 Hz, 1H), 7.29 – 7.33 (m, 1H), 7.36 – 7.44 (m, 5H), 7.47 – 7.51 (m, 2H), 7.66 (s, 1H), 7.68 (d, *J* = 1.2 Hz, 1H), 7.78 (s, 1H), 9.47 (d, *J* = 7.2 Hz, 1H).

N-Benzyl-2-methyl-6-phenylimidazo[1,2-a]pyridine-3-carboxamide (38)



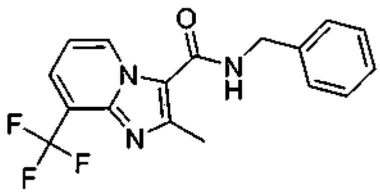
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 4.73 (d, *J* = 5.6 Hz, 2H), 6.12 (m, 1H), 7.30 – 7.34 (m, 1H), 7.36 – 7.40 (m, 7H), 7.60 – 7.66 (m, 4H), 9.71 (s, 1H).

N-Benzyl-8-fluoro-2-methylimidazo[1,2-a]pyridine-3-carboxamide (39)



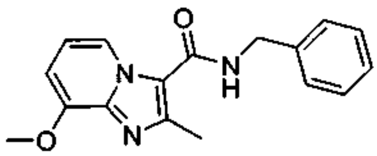
^{1}H NMR (400 MHz, MeOH-d_4) δ 2.63(s, 3H), 4.64(s, 2H), 6.96–7.01(m, 1H), 7.21(t, *J* =6.8Hz, 1H), 7.25 – 7.29(m, 2H), 7.37(t, *J*=7.2Hz, 2H), 7.41(t, *J* =7.6Hz, 2H), 8.84(d, *J* =6.8Hz, 1H).

N-Benzyl-2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamide (40)



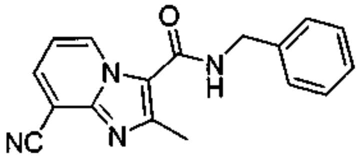
^{1}H NMR (400 MHz, MeOH-d_4) δ 2.66(s, 3H), 4.63(s, 2H), 7.15(t, *J*=6.8Hz, 1H), 7.25-7.28(m, 1H), 7.37(t, *J*=8.0Hz, 2H), 7.43(d, *J* =7.6Hz, 2H), 7.82(d, *J* =7.2Hz, 1H), 9.21(d, *J* =6.8Hz, 1H).

N-Benzyl-8-methoxy-2-methylimidazo[1,2-a]pyridine-3-carboxamide (41)



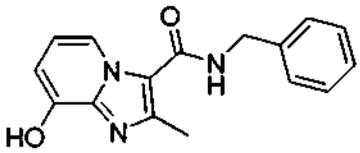
^{1}H NMR (400 MHz, MeOH-d_4) δ 2.65(s, 3H), 3.95(s, 2H), 4.02(s, 3H), 6.96(d, J=8.0Hz, 1H), 7.03(t, J=6.8Hz, 1H), 7.23-7.26(m, 1H), 7.29(d, J=5.6Hz, 2H), 7.34(t, J=6.0Hz, 2H), 7.39(t, J=6.4Hz, 1H), 8.93(d, J=7.2Hz, 1H).

N-Benzyl-8-cyano-2-methylimidazo[1,2-a]pyridine-3-carboxamide (42)



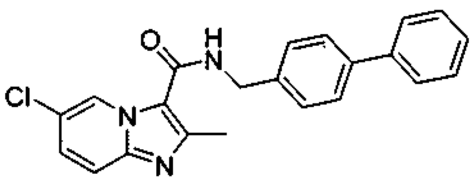
^{1}H NMR (400 MHz, MeOH-d_4) δ 2.67(s, 3H), 4.65(s, 2H), 7.17(t, J=7.2Hz, 1H), 7.26-7.31(m, 2H), 7.38(t, J=7.2Hz, 2H), 7.44(d, J=8.0Hz, 2H), 8.21(d, J=7.2Hz, 1H), 9.19(d, J=6.8Hz, 1H).

N-Benzyl-8-hydroxy-2-methylimidazo[1,2-a]pyridine-3-carboxamide (43)



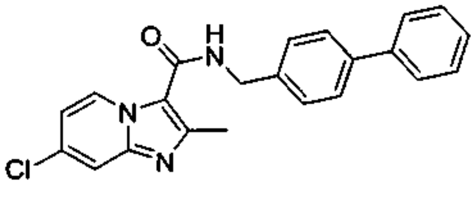
^{1}H NMR (400 MHz, MeOH-d_4) δ 2.60(s, 3H), 4.63(s, 2H), 6.70(d, J=7.6Hz, 1H), 6.83(t, J=6.8Hz, 1H), 7.28(t, J=7.2Hz, 1H), 7.40(t, J=8.0Hz, 3H), 7.42(d, J=7.2Hz, 2H), 8.53(d, J=6.0Hz, 1H).

N-(Biphenyl-4-ylmethyl)-6-chloro-2-methylimidazo[1,2-a]pyridine-3-carboxamide (44)



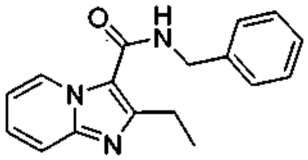
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 4.73 (d, J = 5.2 Hz, 2H), 6.18 (brs, 1H), 6.92 (d, J = 6.4 Hz, 1H), 7.36 (d, J = 7.2 Hz, 1H), 7.44 – 7.45 (m, 4H), 7.57 – 7.60 (m, 5H), 9.39 (d, J = 7.6 Hz, 1H).

N-(Biphenyl-4-ylmethyl)-7-chloro-2-methylimidazo[1,2-a]pyridine-3-carboxamide (45)



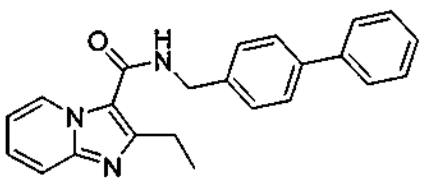
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 4.73 (d, *J* = 5.2 Hz, 2H), 6.20 (brs, 1H), 7.29 – 7.36 (m, 4H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 9.6 Hz, 1H), 7.57 (m, 5H), 9.56 (s, 1H)

N-Benzyl-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (46)



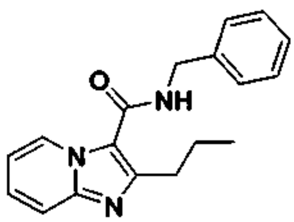
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.6 Hz, 3H), 1.63 (s, 3H), 2.99 (q, *J* = 7.6 Hz, 2H), 4.71 (d, *J* = 6.0 Hz, 2H), 6.09 (brs, 1H), 6.92 (dd, *J* = 5.6 Hz, 1H), 7.30 – 7.38 (m, 6H), 7.60 (d, *J* = 9.2 Hz, 1H), 9.40 (d, *J* = 7.2 Hz, 1H).

N-(Biphenyl-4-ylmethyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (47)



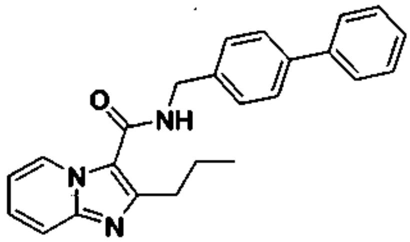
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.6 Hz, 3H), 3.02 (q, *J* = 7.6 Hz, 2H), 4.75 (d, *J* = 5.6 Hz, 2H), 6.19 (brs, 1H), 6.92 (dd, *J* = 6.4 Hz, 6.4 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 4H), 7.58 – 7.59 (m, 5H), 9.41 (d, *J* = 6.8 Hz, 1H).

N-Benzyl-2-propylimidazo[1,2-a]pyridine-3-carboxamide (48)



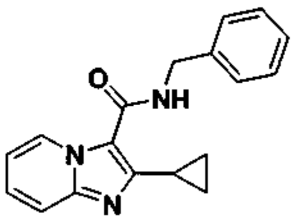
^{1}H NMR (400 MHz, CD_3OD) δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.75 – 1.85 (m, 2H), 2.89 (t, *J* = 7.8 Hz, 2H), 4.67 (d, *J* = 5.6 Hz, 2H), 6.24 (m, 1H), 6.86 (t, *J* = 6.8 Hz, 1H), 7.26 – 7.36 (m, 6H), 7.54 (d, *J* = 8.8 Hz, 1H), 9.31 (d, *J* = 6.8 Hz, 1H).

N-(Biphenyl-4-ylmethyl)-2-propylimidazo[1,2-a]pyridine-3-carboxamide (49)



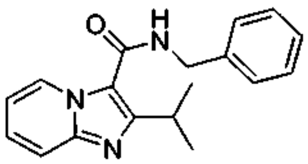
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3H), 1.80 – 1.89 (m, 2H), 2.93 (t, J = 7.8 Hz, 2H), 4.73 (d, J = 5.6 Hz, 2H), 6.29 (t, J = 5.2 Hz, 1H), 6.89 (dd, J = 1.2, 6.8 Hz, 1H), 7.27 – 7.37 (m, 2H), 7.42 – 7.46 (m, 4H), 7.56 – 7.61 (m, 5H), 9.35 (d, J = 6.8 Hz, 1H). ; LCMS (electrospray) m/z $(M+H)^+$ 370.32

N-Benzyl-2-cyclopropylimidazo[1,2-a]pyridine-3-carboxamide (50)



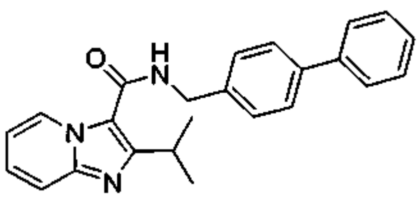
^{1}H NMR (400 MHz, CD_3OD) δ 1.00 – 1.03 (m, 2H), 1.14 – 1.18 (m, 2H), 2.11 – 2.15 (m, 1H), 6.91 (dd, J = 1.2, 6.8 Hz, 1H), 7.29 – 7.38 (m, 5H), 7.57 (dd, J = 0.8, 8.8 Hz, 1H), 9.49 – 9.51 (m, 1H); LCMS (electrospray) m/z $(M+H)^+$ 292.23

N-Benzyl-2-isopropylimidazo[1,2-a]pyridine-3-carboxamide (51)



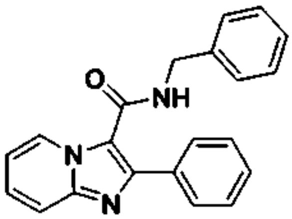
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, J = 6.8 Hz, 6H), 3.36 – 3.32 (m, 1H), 4.71 (d, J = 5.6 Hz, 2H), 6.11 (brs, 1H), 6.88 (dd, J = 6.8 Hz, 6.8 Hz, 1H), 7.29 (dd, J = 6.8 Hz, 6.8 Hz, 1H), 7.31 – 7.39 (m, 5H), 7.62 (d, J = 9.2 Hz, 1H), 9.31 (d, J = 7.2 Hz, 1H).

N-(Biphenyl-4-ylmethyl)-2-isopropylimidazo[1,2-a]pyridine-3-carboxamide (52)



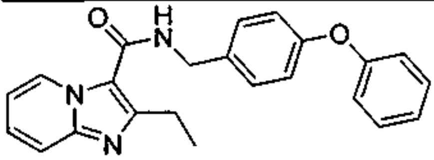
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (d, J = 6.4 Hz, 6H), 3.34 – 3.41 (m, 1H), 4.76 (d, J = 5.6 Hz, 2H), 6.16 (brs, 1H), 6.90 (dd, J = 7.2 Hz, 7.2 Hz, 1H), 7.29 – 7.37 (m, 2H), 7.42 – 7.47 (m, 4H), 7.60 – 7.64 (m, 5H), 9.32 (d, J = 7.2 Hz, 1H).

N-Benzyl-2-phenylimidazo[1,2-a]pyridine-3-carboxamide (53)



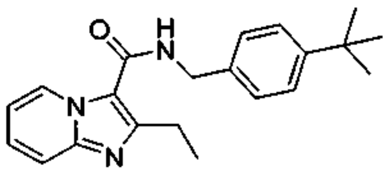
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (d, *J* = 5.6 Hz, 2H), 6.090 (m, 1H), 7.14 – 7.16 (m, 2H), 7.26 – 7.32 (m, 4H), 7.36 – 7.40 (m, 4H), 7.61 – 7.63 (m, 2H), 7.69 (d, *J* = 9.2 Hz, 1H),

2-Ethyl-N-(4-phenoxybenzyl)imidazo[1,2-a]pyridine-3-carboxamide (54)



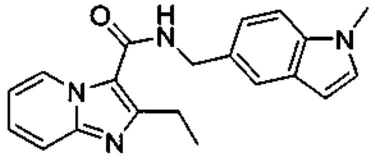
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.6 Hz, 3H), 2.99 (q, *J* = 7.6 Hz, 2H), 4.67 (d, *J* = 5.6 Hz, 2H), 6.08 (brs, 1H), 6.89 – 6.93 (m, 1H), 7.00 (dd, *J* = 2.0 Hz, 8.8 Hz, 4H), 7.08 – 7.12 (m, 1H), 7.30 – 7.35 (m, 5H), 7.60 (d, *J* = 9.2 Hz, 1H), 9.39 (d, *J* = 7.2 Hz, 1H).

N-(4-tert-Butylbenzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (55)



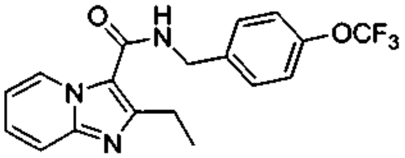
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.41 (t, *J* = 7.6 Hz, 3H), 2.99 (q, *J* = 7.6 Hz, 2H), 4.68 (d, *J* = 5.6 Hz, 2H), 6.12 (brs, 1H), 6.93 (dd, *J* = 6.8 Hz, 6.8 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.36 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.63 (d, J = 8.8 Hz, 1H), 9.40 (d, *J* = 7.2 Hz, 1H).

2-Ethyl-N-((1-methyl-1H-indol-5-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (56)



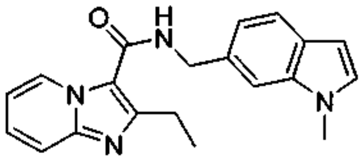
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, *J* = 7.6 Hz, 3H), 2.95 (q, *J* = 7.6 Hz, 2H), 3.81 (s, 3H), 4.79 (d, *J* = 5.6 Hz, 2H), 6.08 (brs, 1H), 6.48 (s, 1H), 6.92 (dd, *J* = 6.8 Hz, 6.8 Hz, 1H), 7.08 (s, 1H), 7.25 (s, 1H), 7.26 – 7.34 (m, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.63 (s, 1H), 9.43 (d, *J* = 7.2 Hz, 1H).

2-Ethyl-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (57)



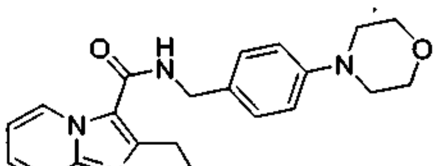
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 3.00 (q, J = 7.6 Hz, 2H), 4.69 (d, J = 6.0 Hz, 2H), 6.21 (brs, 1H), 6.91 (dd, J = 6.8 Hz, 6.8 Hz, 1H), 7.19 (s, 1H), 7.21 (s, 1H), 7.30 – 7.34 (m, 1H), 7.39 (s, 1H), 7.41 (s, 1H), 7.60 (d, J = 9.2 Hz, 1H), 9.37 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 23.7, 42.9, 113.5, 114.7, 119.3, 121.5, 121.9, 127.3, 128.3, 129.2, 137.3, 146.4, 148.8, 151.1, 161.7.

2-Ethyl-N-((1-methyl-1H-indol-6-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (58)



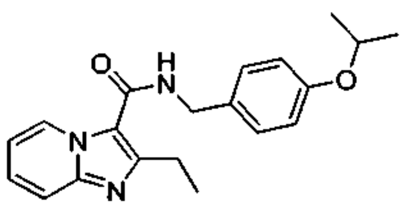
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 3.80 (s, 3H), 4.78 (d, J = 5.6 Hz, 2H), 6.09 (brs, 1H), 6.48 (d, J = 2.8 Hz, 1H), 6.89 – 6.93 (m, 1H), 7.08 (d, J = 3.2 Hz, 1H), 7.23 – 7.33 (m, 3H), 7.59 (s, 1H), 7.62(d, J = 5.6 Hz, 1H), 9.41 (d, J = 6.8 Hz, 1H).

2-Ethyl-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (59)



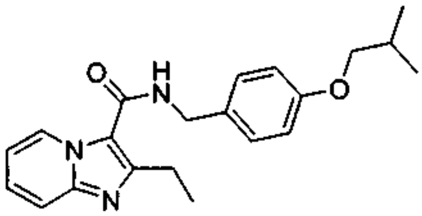
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.6 Hz, 3H), 2.96 (q, J = 7.6 Hz, 2H), 3.14 (t, J = 4.8 Hz, 4H), 3.85 (t, J = 4.8 Hz, 4H), 4.61 (d, J = 5.6 Hz, 2H), 6.05 (brs, 1H), 6.88 – 6.92 (m, 3H), 7.27 – 7.33 (m, 3H), 7.59 (d, J = 8.8 Hz, 1H), 9.39 (d, J = 7.2 Hz, 1H).

2-Ethyl-N-(4-isopropoxybenzyl)imidazo[1,2-a]pyridine-3-carboxamide (60)



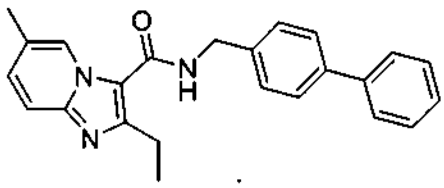
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 5.6 Hz, 6H), 1.38 (t, *J* = 7.6 Hz, 3H), 2.96 (q, *J* = 7.6 Hz, 2H), 4.52 – 4.56 (m, 1H), 4.61 (d, *J* = 4.8 Hz, 2H), 6.05 (brs, 1H), 6.86 – 6.92 (m, 3H), 7.26 – 7.33 (m, 3H), 7.59 (d, *J* = 8.8 Hz, 1H), 9.38 (d, *J* = 6.4 Hz, 1H).

2-Ethyl-N-(4-isobutoxybenzyl)imidazo[1,2-a]pyridine-3-carboxamide (61)



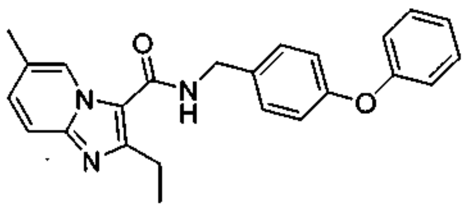
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.8 Hz, 6H), 1.37 (t, *J* = 7.6 Hz, 3H), 2.05 – 2.09 (m, 1H), 2.96 (q, *J* = 7.6 Hz, 2H), 3.71 (d, *J* = 6.8 Hz, 2H), 4.62 (d, *J* = 5.2 Hz, 2H), 6.06 (brs, 1H), 6.89 (dd, *J* = 2.4 Hz, 2H), 6.92 (dd, *J* = 1.2 Hz, 6.8 Hz, 1H), 7.27 – 7.34 (m, 3H), 7.59 (d, *J* = 8.0 Hz, 1H), 9.37 (dd, *J* = 2.4 Hz, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.4, 23.5, 28.4, 43.3, 53.1, 74.7, 113.4, 115.0, 116.7, 124.2, 127.2, 128.3, 129.2, 130.0, 146.2, 150.7, 159.0, 161.5.

N-(Biphenyl-4-ylmethyl)-2-ethyl-6-methylimidazo[1,2-a]pyridine-3-carboxamide (62)



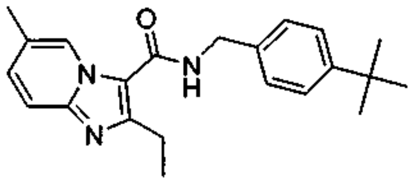
^{1}H NMR (400 MHz, MeOH-d_4) δ 1.34(t, *J* =7.6Hz, 3H), 2.37(s, 3H), 3.02(q, *J*=7.6Hz, 2H), 4.68(s, 2H), 7.31-7.34(m, 2H), 7.43(d, *J*=8.0Hz, 2H), 7.46(d, *J* =4.8Hz, 1H), 7.51(d, *J* =8.8Hz, 3H), 7.64(t, *J* =4.4Hz, 4H), 8.78(s, 1H).

2-Ethyl-6-methyl-N-(4-phenoxybenzyl)imidazo[1,2-a]pyridine-3-carboxamide (63)



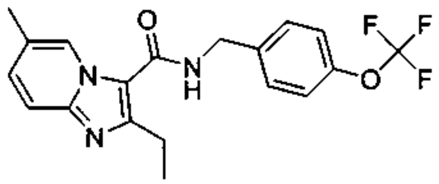
^{1}H NMR (400 MHz, MeOH-d_4) δ 1.35(t, *J* =8.0Hz, 3H), 2.37(s, 3H), 2.99(q, *J*=7.2Hz, 2H), 4.61(s, 2H), 6.99(d, *J*=8.8Hz, 4H), 7.12(t, *J* =7.2Hz, 1H), 7.31-7.36(m, 3H), 7.42(d, *J* =8.8Hz, 2H), 7.48(d, *J* =9.2Hz, 1H), 8.76(s, 1H).

N-(4-tert-Butylbenzyl)-2-ethyl-6-methylimidazo[1,2-a]pyridine-3-carboxamide (64)



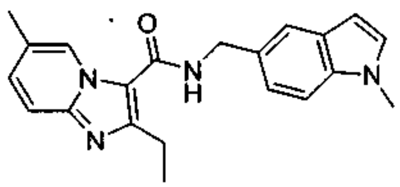
[1]H NMR (400 MHz, MeOH-d_4) δ 1.30(t, J=7.2Hz, 3H), 1.32(s, 9H), 2.37(s, 3H), 2.98(q, J=8.0Hz, 2H), 4.59(s, 2H), 7.30(d, J=1.6Hz, 1H), 7.34(d, J=8.4Hz, 2H), 7.41(d, J=6.8Hz, 2H), 7.47(d, J=9.2Hz, 1H), 8.74(s, 1H).

2-Ethyl-6-methyl-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (65)



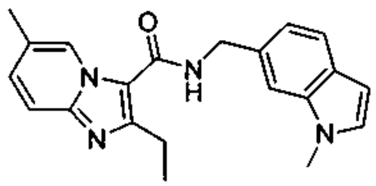
[1]H NMR (400 MHz, MeOH-d_4) δ 1.33(t, J=8.0Hz, 3H), 2.36(s, 3H), 3.00(q, J=7.6Hz, 2H), 4.65(s, 2H), 7.28(d, J=8.0Hz, 2H), 7.34(d, J=9.2Hz, 1H), 7.48(d, J=9.2Hz, 1H), 7.52(d, J=8.4Hz, 2H), 8.77(s, 1H).

2-Ethyl-6-methyl-N-((1-methyl-1H-indol-5-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (66)



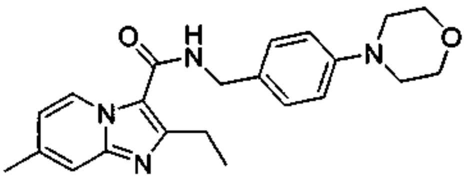
[1]H NMR (400 MHz, MeOH-d_4) δ 1.28(t, J=7.6Hz, 3H), 2.36(s, 3H), 2.95(q, J=7.2Hz, 2H), 3.80(s, 3H), 4.71(s, 2H), 6.42(d, J=2.8Hz, 1H), 7.16(d, J=3.2Hz, 1H), 7.26(d, J=8.4Hz, 1H), 7.32(d, J=9.2Hz, 1H), 7.38(d, J=8.4Hz, 1H), 7.46(d, J=9.2Hz, 2H), 7.59(s, 1H), 8.73(s, 1H).

2-Ethyl-6-methyl-N-((1-methyl-1H-indol-6-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (67)



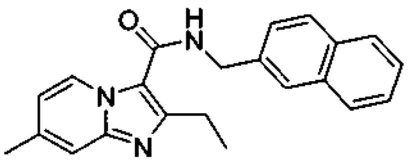
^{1}H NMR (400 MHz, MeOH-d_4) δ 1.30(t, *J* =7.6Hz, 3H), 2.35(s, 3H), 3.0(q, *J*=7.6Hz, 2H), 3.80(s, 3H), 4.75(s, 2H), 6.41(d, *J*=3.2Hz, 1H), 7.11-7.14(m, 2H), 7.32(d, *J* =9.2Hz, 1H), 7.46(d, *J* =9.2Hz, 2H), 7.55(d, *J* =8.0Hz, 1H), 8.74(s, 1H).

2-Ethyl-7-methyl-N-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (68)



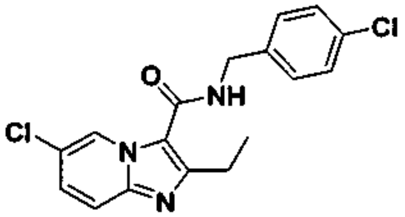
White solid, mp 190°C ; ^{1}H NMR(400 MHz, MeOH-*d4*) δ 1.31 (t, *J* = 7.6 Hz, 3H), 2.43 (s, 3H), 2.98 (q, *J* = 7.6 Hz, 2H), 3.14 (t, *J* = 4.8 Hz, 4H), 3.35 (s, 1H), 3.85 (t, *J* = 4.8 Hz, 4H), 4.53 (s, 2H), 6.90 (d, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 3H), 8.83 (d, *J* = 7.2 Hz, 1H).

2-Ethyl-7-methyl-N-(naphthalen-2-ylmethyl)imidazo[1,2-a]pyridine-3-carboxamide (69)



White solid, mp 192°C ; ^{1}H NMR(400 MHz, MeOH-*d4*) δ 1.33 (t, *J* = 7.6 Hz, 3H), 2.45 (s, 3H), 3.02 (q, *J* = 7.6 Hz, 2H), 4.79 (s, 2H), 6.9 (d, *J* = 7.2 Hz, 1H), 7.33(s, 1H), 7.45-7.48(m, 2H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.82-7.88 (m, 4H), 8.87 (d, *J* = 7.2 Hz, 1H).

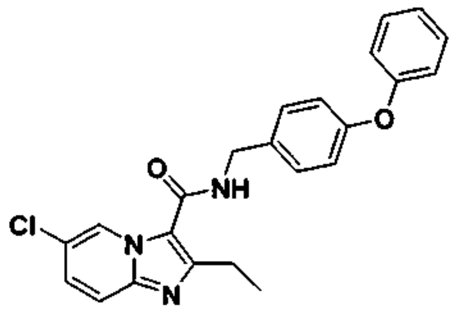
6-Chloro-N-(4-chlorobenzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (70)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.6 Hz, 3H), 2.98 (q, *J* = 7.6 Hz, 2H), 4.66 (d, *J* = 5.6 Hz, 2H), 6.14 (m, 1H), 7.29 – 7.35 (m, 5H), 7.54 (dd, *J* = 0.8, 9.6 Hz, 1H), 9.51 (dd, *J* = 0.8, 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 348.14

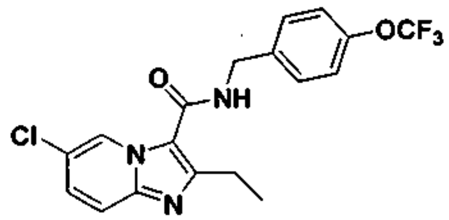
6-Chloro-2-methyl-N-(4-phenoxybenzyl)imidazo[1,2-a]pyridine-3-carboxamide

(71)



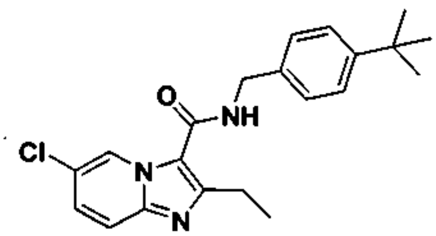
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.6 Hz, 3H), 2.99 (q, *J* = 7.6 Hz, 2H), 4.67 (d, *J* = 5.6 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 4H), 7.09 – 7.13 (m, 1H), 7.30 (dd, *J* = 2.0, 9.6 Hz, 1H), 7.32 – 7.36 (m, 4H), 7.54 (d, *J* = 9.6 Hz, 1H), 9.54 (d, *J* = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 406.23

6-Chloro-2-methyl-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (72)



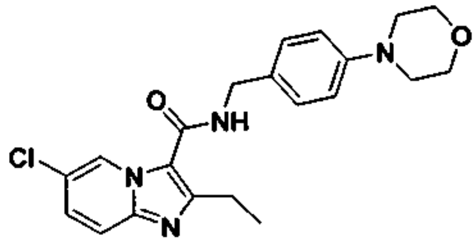
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, *J* = 7.6 Hz, 3H), 3.00 (q, *J* = 7.6 Hz, 2H), 4.71 (d, *J* = 6.0 Hz, 2H), 6.15 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.31 (dd, *J* = 2.0, 9.6 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 9.6 Hz, 1H), 9.54 (d, *J* = 2.0 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 398.21

N-(4-tert-Butylbenzyl)-6-chloro-2-methylimidazo[1,2-a]pyridine-3-carboxamide (73)



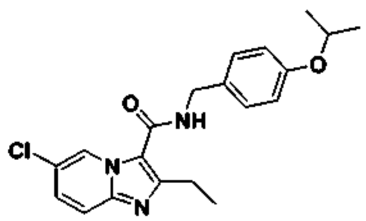
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.6 Hz, 3H), 2.98 (q, *J* = 7.6 Hz, 2H), 4.68 (d, *J* = 6.0 Hz, 2H), 6.09 (m, 1H), 7.28 – 7.31 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 9.6 Hz, 1H), 9.54 (d, *J* = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 370.25

6-Chloro-2-methyl-N-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (74)



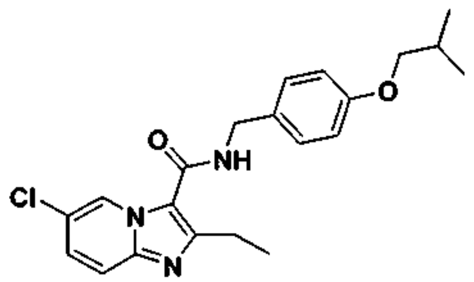
[1]H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 3.16 (t, J = 4.8 Hz, 4H), 3.96 (t, J = 4.8 Hz, 4H), 4.61 (d, J = 5.6 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 7.26 – 7.30 (m, 3H), 7.54 (d, J = 9.6 Hz, 1H), 9.52 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 399.30

6-Chloro-N-(4-isopropoxybenzyl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide (75)



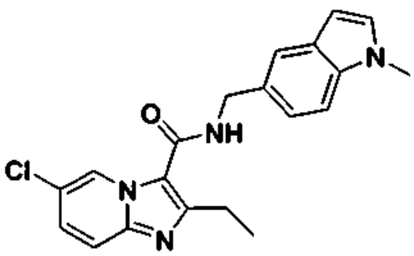
[1]H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.0 Hz, 6H), 1.39 (t, J = 7.6 Hz, 3H), 2.96 (q, J = 7.6 Hz, 2H), 4.52 – 4.58 (m, 1H), 4.62 (d, J = 5.6 Hz, 2H), 6.03 (m, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.27 – 7.31 (m, 3H), 7.54 (d, J = 9.6 Hz, 1H), 9.53 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 372.22

6-Chloro-N-(4-isobutoxybenzyl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide (76)



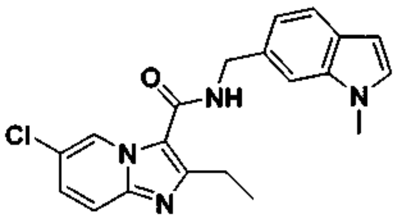
[1]H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J = 6.8 Hz, 6H), 1.36 (t, J = 7.6 Hz, 3H), 2.03 – 2.09 (m, 1H), 2.93 (q, J = 7.6 Hz, 2H), 3.69 (d, J = 6.8 Hz, 2H), 4.59 (d, J = 5.6 Hz, 2H), 6.13 (t, J = 4.8 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.24 – 7.27 (m, 3H), 7.49 (d, J = 9.6 Hz, 1H), 9.47 (d, J = 1.2 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 386.30

6-Chloro-2-methyl-N-((1-methyl-1H-indol-5-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (77)



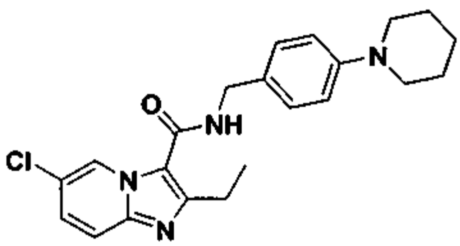
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.6 Hz, 3H), 2.94 (q, J = 7.6 Hz, 2H), 3.81 (s, 3H), 4.78 (d, J = 5.6 Hz, 2H), 6.07 (m, 1H), 6.48 (d, J = 3.2 Hz, 1H), 7.09 (d, J = 2.8 Hz, 1H), 7.24 – 7.26 (m, 1H), 7.29 (dd, J = 2.0, 9.6 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 9.6 Hz, 1H), 7.63 (s, 1H), 9.54 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 367.19

6-Chloro-2-methyl-N-((1-methyl-1H-indol-6-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (78)



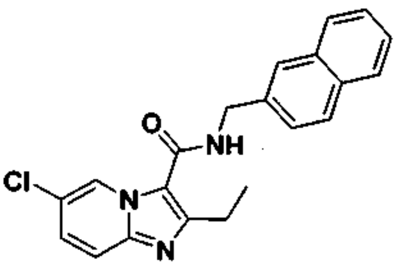
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 3.80 (s, 3H), 4.82 (d, J = 5.6 Hz, 2H), 6.13 (m, 1H), 6.49 (d, J = 3.2 Hz, 1H), 7.08 (d, J = 2.8 Hz, 1H), 7.12 (dd, J = 1.2, 8.0 Hz, 1H), 7.30 (dd, J = 2.0, 9.6 Hz, 1H), 7.34 (s, 1H), 7.55 (d, J = 9.6 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 9.54 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 367.26

6-Chloro-2-ethyl-N-(4-(piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (79)



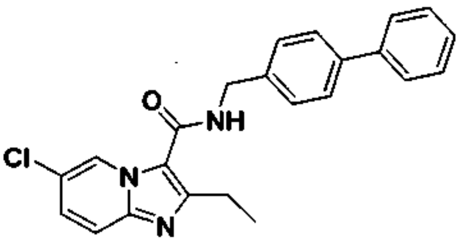
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 1.54 – 1.60 (m, 2H), 1.69 – 1.73 (m, 4H), 2.94 (q, J = 7.6 Hz, 2H), 3.16 (t, J = 5.14 Hz, 4H), 4.59 (d, J = 5.6 Hz, 2H), 6.00 (m, 1H), 6.93 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.29 (dd, J = 2.0, 9.6 Hz, 1H), 7.53 (d, J = 9.6 Hz, 1H), 9.52 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 397.32

6-Chloro-2-ethyl-N-(naphthalen-2-ylmethyl)imidazo[1,2-a]pyridine-3-carboxamide (80)



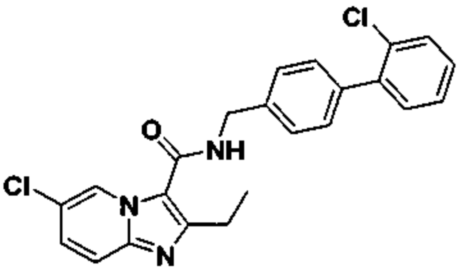
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.4 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 4.87 (q, J = 5.6 Hz, 2H), 6.19 (m, 1H), 7.31 (dd, J = 2.0, 9.6 Hz, 1H), 7.47 – 7.51 (m, 3H), 7.55 (d, J = 9.6 Hz, 1H), 7.82 – 7.85 (m, 3H), 7.87 (d, J = 8.4 Hz, 1H), 9.57 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 364.20

N-(Biphenyl-4-ylmethyl)-6-chloro-2-methylimidazo[1,2-a]pyridine-3-carboxamide (81)



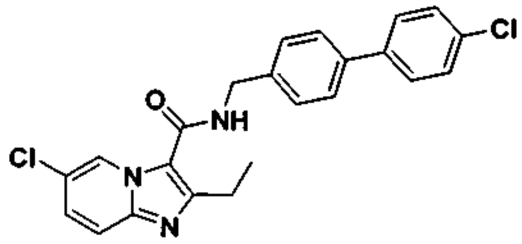
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.6 Hz, 3H), 3.01 (q, J = 7.6 Hz, 2H), 4.75 (d, J = 5.6 Hz, 2H), 6.15 (m, 1H), 7.31 (dd, J = 2.0, 9.6 Hz, 1H), 7.43 – 7.47 (m, 4H), 7.55 (d, J = 9.2 Hz, 1H), 7.58 – 7.62 (m, 4H), 9.56 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 390.25

6-Chloro-N-((2'-chlorobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (82)



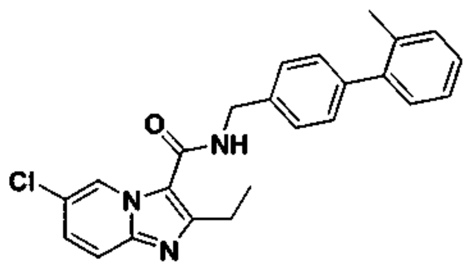
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.6 Hz, 3H), 3.02 (q, J = 7.6 Hz, 2H), 4.77 (d, J = 6.0 Hz, 2H), 6.18 (m, 1H), 7.27 – 7.35 (m, 4H), 7.43 – 7.48 (m, 5H), 7.56 (d, J = 9.6 Hz, 1H), 9.56 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 404.26

6-Chloro-N-((4'-chlorobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (83)



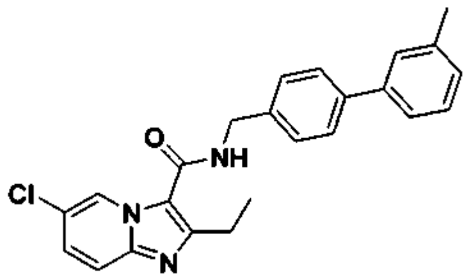
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.6 Hz, 3H), 3.01 (q, J = 7.6 Hz, 2H), 4.71 (d, J = 6.0 Hz, 2H), 6.13 (m, 1H), 7.31 (dd, J = 2.0, 9.6 Hz, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.54 – 7.58 (m, 3H), 9.55 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 424.26

6-Chloro-2-ethyl-N-((2'-methylbiphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (84)



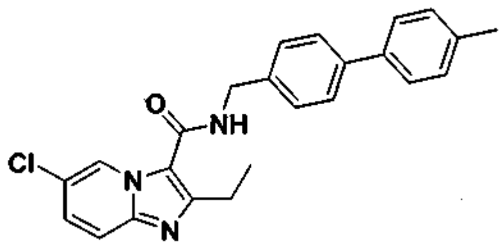
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.6 Hz, 3H), 2.27 (s, 3H), 3.02 (q, J = 7.6 Hz, 2H), 4.76 (d, J = 5.6 Hz, 2H), 6.21 (t, J = 5.2 Hz, 1H), 7.20 – 7.28 (m, 4H), 7.30 (dd, J = 2.0, 9.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 9.6 Hz, 1H), 9.55 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 404.26

6-Chloro-2-ethyl-N-((3'-methylbiphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (85)



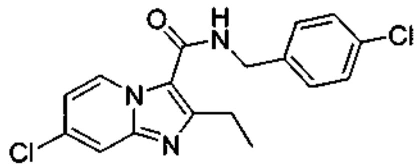
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.6 Hz, 3H), 2.42 (s, 3H), 3.00 (q, J = 7.6 Hz, 2H), 4.75 (d, J = 5.6 Hz, 2H), 6.14 (m, 1H), 7.18 (d, J = 7.2 Hz, 1H), 7.31 (dd, J = 2.0, 9.6 Hz, 1H), 7.34 (d, J = 7.2 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 9.6 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 9.56 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 404.26

6-Chloro-2-ethyl-N-((4'-methylbiphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (86)



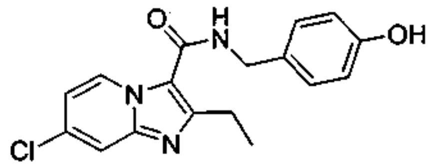
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 3.00 (q, J = 7.6 Hz, 2H), 2.40 (s, 3H), 4.74 (d, J = 5.6 Hz, 2H), 6.16 (m, 1H), 7.25 (d, J = 7.2 Hz, 2H), 7.30 (dd, J = 2.0, 9.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 9.6 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 9.55 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 404.26

7-Chloro-N-(4-chlorobenzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (87)



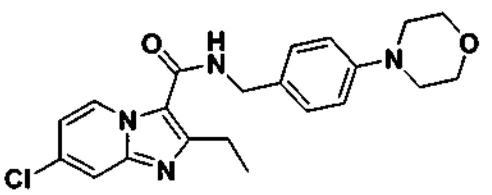
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.96 (q, J = 7.6 Hz, 2H), 4.65 (d, J = 5.6 Hz, 2H), 6.12 (brs, 1H), 6.90 (dd, J = 7.6, 2.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.58 (d, 1H), 9.34 (d, J = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 348.21

7-Chloro-2-ethyl-N-(4-hydroxybenzyl)imidazo[1,2-a]pyridine-3-carboxamide (88)



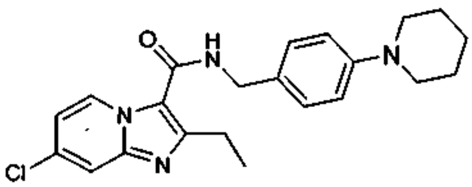
^{1}H NMR (400 MHz, MeOH-d_4) δ 1.29 (t, J = 7.6 Hz, 3H), 2.96 (q, J = 7.6 Hz, 2H), 3.12 – 3.15 (m, 4H), 4.52 (s, 2H), 6.76 (d, J = 8.4 Hz, 2H), 7.06 (dd, J = 7.6, 2.0 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 1.6 Hz, 1H), 8.91 (d, J = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 330.25

7-Chloro-2-ethyl-N-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (89)



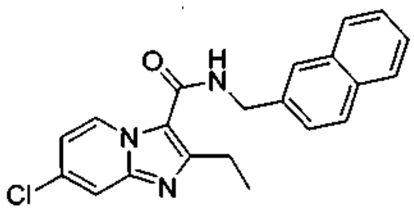
White solid, mp 195°C ; ^{1}H NMR(400 MHz, MeOH-*d4*) δ 1.31 (t, *J* = 7.6 Hz, 3H), 3.00 (q, *J* = 7.6 Hz, 2H), 3.14 (t, *J* = 4.8 Hz, 4H), 3.84 (t, *J* = 4.8 Hz, 4H), 4.54 (s, 2H), 6.97 (d, *J* = 6.8 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.59 (s, 1H), 8.93 (d, *J* = 7.2 Hz, 1H).

7-Chloro-2-ethyl-N-(4-(piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (90)



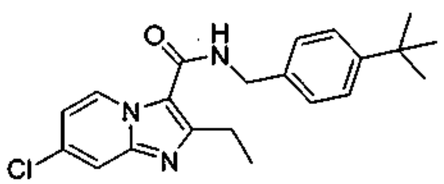
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.6 Hz, 3H), 1.55 – 1.57 (m, 2H), 1.66 – 1.70 (m, 4H), 2.91 (q, *J* = 7.6 Hz, 2H), 3.12 – 3.15 (m, 4H), 4.56 (d, *J* = 5.6 Hz, 2H), 6.07 (brs, 1H), 6.86 (dd, *J* = 7.6, 2.0 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 2.0 Hz, 1H), 9.30 (d, *J* = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 397.32

7-Chloro-2-ethyl-N-(naphthalen-2-ylmethyl)imidazo[1,2-a]pyridine-3-carboxamide (91)



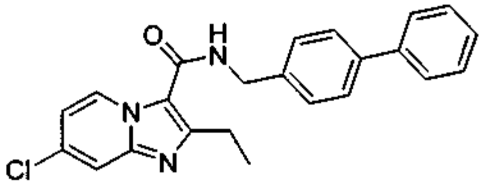
^{1}H NMR (400 MHz, MeOH-d_4) δ 1.32 (t, *J* = 7.6 Hz, 3H), 3.02 (q, *J* = 7.6 Hz, 2H), 4.79 (s, 2H), 7.06 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.45 – 7.48 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.82 – 7.88 (m, 4H), 8.96 (d, *J* = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 364.20

N-(4-tert-Butylbenzyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (92)



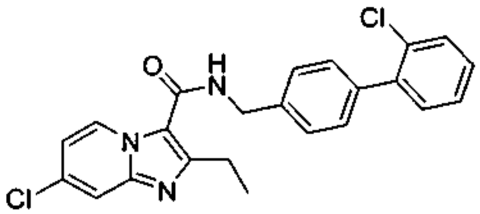
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.40 (t, J = 7.6 Hz, 3H), 2.96 (q, J = 7.6 Hz, 2H), 4.67 (d, J = 5.6 Hz, 2H), 6.13 (brs, 1H), 6.90 (dd, J = 7.2, 2.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 1.6 Hz, 1H), 9.36 (d, J = 7.2 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 370.25

<u>N-(Biphenyl-4-ylmethyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (93)</u>



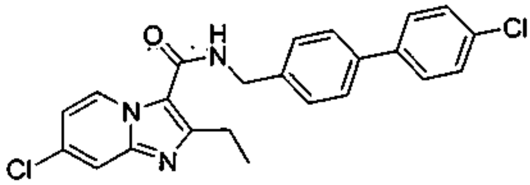
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 3.00 (q, J = 7.6 Hz, 2H), 4.74 (d, J = 5.6 Hz, 2H), 6.14 (brs, 1H), 6.91 (dd, J = 7.6, 2.4 Hz, 1H), 7.35 (m, 1H), 7.42 – 7.46 (m, 4H), 7.57 – 7.62 (m, 5H), 9.38 (d, J = 7.6 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.6, 31.5, 34.7, 43.4, 114.7, 115.8, 126.0, 127.5, 128.6, 133.6, 135.0, 146.2, 150.9, 151.6, 161.3. ; LCMS (electrospray) m/z $(M+H)^+$ 390.25

<u>7-Chloro-N-((2'-chlorobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (94)</u>



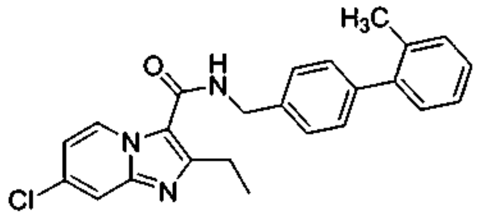
^{1}H NMR (400 MHz, MeOH-d_4) δ 1.32 (t, J = 7.6 Hz, 3H), 3.01 (q, J = 7.6 Hz, 2H), 4.68 (s, 2H), 7.03 (dd, J = 7.6, 2.0 Hz, 1H), 7.29 – 7.57 (m, 9H), 8.94 (d, J = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 424.26

<u>7-Chloro-N-((4'-chlorobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (95)</u>



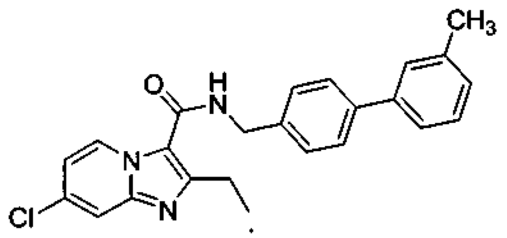
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.73 (s, 2H), 6.15 (brs, 1H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 1.6 Hz, 1H), 9.38 (d, J = 7.2 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 424.26

7-Chloro-2-ethyl-N-((2'-methylbiphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (96)



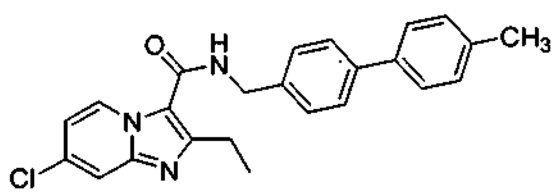
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, J = 7.6 Hz, 3H), 2.31 (s, 3H), 3.05 (q, J = 7.6 Hz, 2H), 4.79 (d, J = 5.6 Hz, 2H), 6.22 (brs, 1H), 6.95 (dd, J = 7.6, 1.6 Hz, 1H), 7.24 -7.36 (m, 4H), 7.39 (d, J = 7.6 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.63 (d, 1H), 9.42 (d, J = 7.2 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 404.26

7-Chloro-2-ethyl-N-((3'-methylbiphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (97)



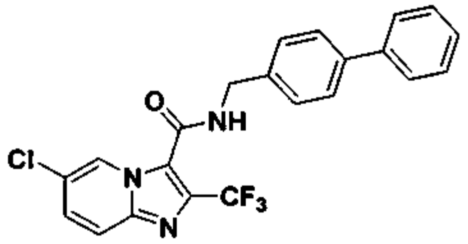
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 2.42 (s, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.74 (d, J = 5.6 Hz, 2H), 6.13 (brs, 1H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.33 – 7.40 (m, 3H), 7.43 (d, J = 8.4 Hz, 2H), 7.58 – 7.61 (m, 3H), 9.38 (d, J = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 404.33

7-Chloro-2-ethyl-N-((4'-methylbiphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (98)



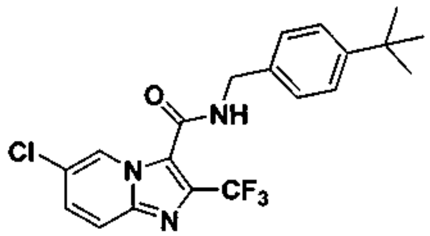
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 2.40 (s, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.73 (s, 2H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.58 – 7.60 (m, 3H), 9.38 (d, J = 7.2 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 404.26

N-(Biphenyl-4-ylmethyl)-6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamide (99)



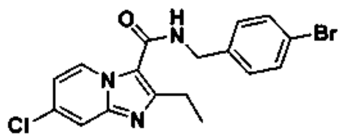
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (d, J = 5.6 Hz, 2H), 6.69 (m, 1H), 7.36 (dd, J = 7.2, 7.2 Hz, 1H), 7.43 – 7.47 (m, 5H), 7.56 (dd, J = 8.0, 8.4 Hz, 4H), 7.71 (d, J = 9.6 Hz, 1H), 9.45 (s, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 430.18

N-(4-tert-Butylbenzyl)-6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamide (100)



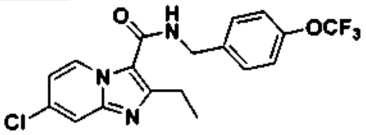
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 4.67 (d, J = 6.0 Hz, 2H), 6.63 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.41 – 7.45 (m, 1H), 7.69 (d, J = 9.6 Hz, 1H), 9.42 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 410.25

N-(4-Bromobenzyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (101)



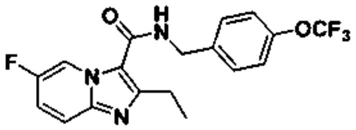
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 2.97 (q, J = 7.6 Hz, 2H), 4.65 (d, J = 5.6 Hz, 2H), 6.09 (brs, 1H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 2.0 Hz, 1H), 9.35 (d, J = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 394.13

7-Chloro-2-ethyl-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (102)



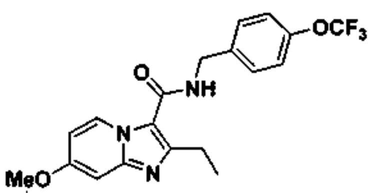
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 4.70 (d, J = 5.6 Hz, 2H), 6.09 (brs, 1H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 2.0 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 398.28

2-Ethyl-6-fluoro-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (103)



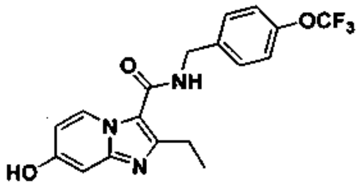
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 3.00 (q, J = 7.6 Hz, 2H), 4.71 (d, J = 6.0 Hz, 2H), 6.14 (brs, 1H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.26 (m, 1H), 7.57 (d, J = 5.2 Hz, 1H), 7.59 (d, J = 5.2 Hz, 1H), 9.45 (dd, J = 5.2, 2.4 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 382.15

2-Ethyl-7-methoxy-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (104)



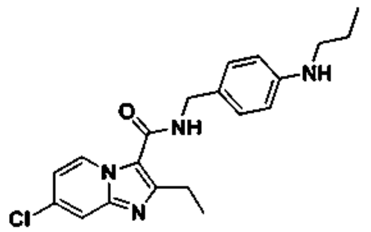
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 3.87 (s, 3H), 6.06 (m, 1H), 6.61 (dd, J = 2.8, 7.6, 1H), 6.89 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 9.24 (d, J = 7.6 Hz, 1H).

2-Ethyl-7-hydroxy-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (105)



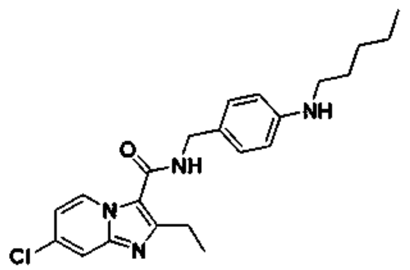
^{1}H NMR (400 MHz, $CDCl_3 + CD_3OD$) δ 1.21 (t, J = 7.6 Hz, 3H), 2.79 (q, J = 7.6 Hz, 2H), 4.51 (q, J = 4.0 Hz, 2H), 4.74 (brs, 1H), 6.49 (dd, J = 2.4, 7.6, 1H), 6.89 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 8.86 (d, J = 7.6 Hz, 1H).

7-Chloro-2-ethyl-N-(4-(propylamino)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (106)



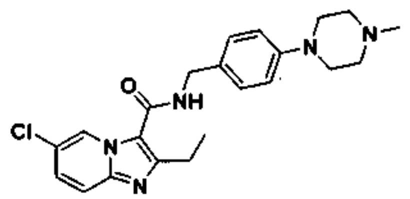
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J = 7.4 Hz, 3H), 1.37 (t, J = 7.6 Hz, 3H), 1.60 – 1.69 (m, 2H), 2.93 (q, J = 8.0 Hz, 2H), 3.08 (t, J = 7.2 Hz, 2H), 3.69 (brs, 1H), 4.55 (d, J = 5.2 Hz, 2H), 5.96 (m, 1H), 6.60 (d, J = 8.4, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 1.2 Hz, 1H), 9.35 (d, J = 7.6 Hz, 1H).

7-Chloro-2-ethyl-N-(4-(pentylamino)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (107)



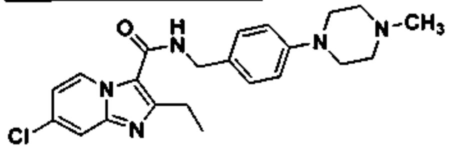
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.0 Hz, 3H), 1.25 – 1.42 (m, 8H), 1.58 – 1.66 (m, 2H), 2.93 (q, J = 7.6 Hz, 2H), 3.10 (t, J = 7.2 Hz, 2H), 3.66 (brs, 1H), 4.55 (d, J = 5.2 Hz, 2H), 5.95 (m, 1H), 6.60 (d, J = 8.4, 2H), 6.89 (dd, J = 2.0, 7.2 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 1.2 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H).

6-Chloro-2-ethyl-N-(4-(4-methylpiperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (108)



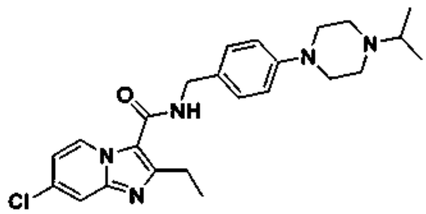
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.6 Hz, 3H), 2.36 (s, 3H), 2.58 (t, J = 5.0 Hz, 4H), 2.95(q, J = 7.6 Hz, 2H), 3.22 (t, J = 4.8 Hz, 4H), 4.60 (d, J = 5.6 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.26 – 7.30 (m, 3H), 7.53 (d, J = 5.6 Hz, 1H), 9.53 (d, J = 1.6 Hz, 1H).

7-Chloro-2-ethyl-N-(4-(4-methylpiperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (109)



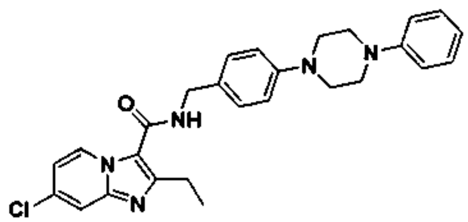
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.6 Hz, 3H), 2.35 (s, 3H), 2.57 – 2.59 (m, 4H), 2.94 (q, J = 7.6 Hz, 2H), 3.20 – 3.23 (m, 4H), 4.59 (d, J = 5.2 Hz, 2H), 6.00 (brs, 1H), 6.88 – 6.94 (m, 3H), 7.27 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 2.0 Hz, 1H), 9.35 (d, J = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 412.29

7-Chloro-2-ethyl-N-(4-(4-isopropylpiperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (110)



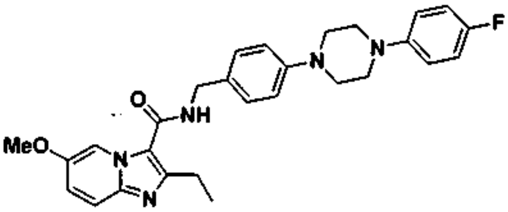
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, J = 6.0 Hz, 6H), 1.38 (t, J = 7.6 Hz, 3H), 2.69 (m, 4H), 2.94 (q, J = 7.6 Hz, 2H), 3.22 (m, 4H), 4.60 (d, J = 5.6 Hz, 2H), 5.99 (m, 1H), 6.90 (dd, J = 2.0, 7.6 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.26 – 7.38 (m, 5H), 7.58 (d, J = 1.6 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H).

7-Chloro-2-ethyl-N-(4-(4-phenylpiperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (111)



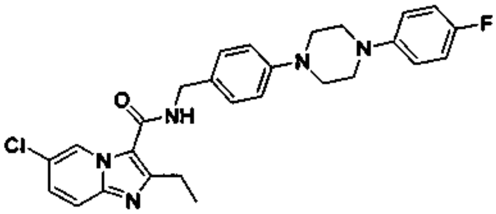
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (t, J = 7.6 Hz, 3H), 3.00 (q, J = 7.6 Hz, 2H), 3.30 (m, 8H), 4.48 (d, J = 6.0 Hz, 2H), 6.84 (t, J = 6.0 Hz, 1H), 7.01 – 7.05 (m, 4H), 7.13 (dd, J = 2.4, 7.6 Hz, 1H), 7.26 – 7.31 (m, 4H), 7.82 (d, J = 1.6 Hz, 1H), 8.45 (t, J = 6.0 Hz, 1H), 8.99 (d, J = 7.6 Hz, 1H).

2-Ethyl-N-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)-6-methoxyimidazo[1,2-a]pyridine-3-carboxamide (112)



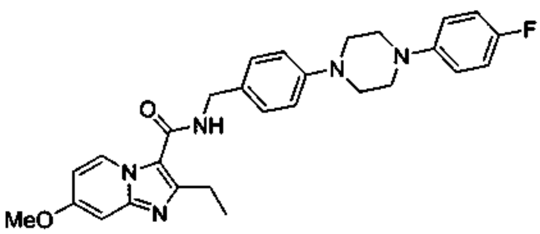
White solid; mp = 173.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.6 Hz, 3H), 2.95 (q, *J* = 7.2 Hz, 2H), 3.24 – 3.27 (m, 4H), 3.33 – 3.36 (m, 4H), 3.87 (s, 3H), 4.63 (d, *J* = 5.6 Hz, 2H), 6.03 (t, J = 5.0 Hz, 1H), 6.91 - 7.01 (m, 6H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 9.6 Hz, 1H), 9.11 (d, J = 2.4 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 488

6-Chloro-2-ethyl-N-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (113)



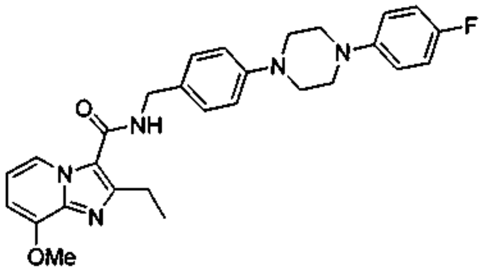
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.6 Hz, 3H), 2.96 (q, *J* = 7.6 Hz 2H), 3.25 – 3.27 (m, 4H), 3.34 – 3.36 (m, 4H), 4.62 (d, *J* = 5.6 Hz, 2H), 6.02 – 6.64 (m, 1H), 6.92 – 6.95 (m, 3H), 6.97 – 7.01 (m, 3H), 7.29 (dd, *J* = 2.4, 9.6 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 9.6 Hz, 2H), 9.54 (d, *J* = 1.2 Hz, 2H); LCMS (electrospray) m/z $(M+H)^+$ 492.28

2-Ethyl-*N*-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)-7-methoxyimidazo[1,2-a]pyridine-3-carboxamide(114)



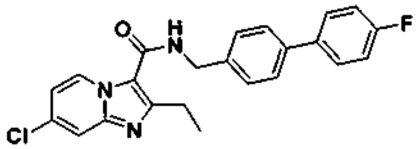
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.30 (t, *J* = 7.6 Hz, 3H), 2.84 (q, *J* = 7.6 Hz, 2H), 3.18 – 3.19 (m, 4H), 3.26 – 3.27 (m, 4H), 3.78 (s, 3H), 4.54 (d, *J* = 5.6 Hz, 2H), 6.15 (brs, 1H), 6.51 – 6.53 (m, 1H), 6.79 (s, 1H), 6.85 – 6.95 (m, 6H), 7.24 (d, *J* = 8.0 Hz, 2H), 9.12 (d, *J* = 8.0 Hz, 1H).

2-Ethyl-*N*-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)-8-methoxyimidazo[1,2-a]pyridine-3-carboxamide(115)



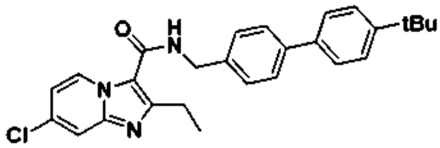
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.34 (t, J = 7.6 Hz, 3H), 2.93 (q, J = 7.6 Hz, 2H), 3.22 – 3.27 (m, 4H), 3.29 – 3.34 (m, 4H), 3.99 (s, 3H), 4.60 (d, J = 5.6 Hz, 2H), 6.08 (brs, 1H), 6.58 (d, J = 7.6 Hz, 1H), 6.76 (dd, J = 7.2, 7.6 Hz, 1H), 6.89 – 6.99 (m, 6H), 7.28 (d, J = 8.4 Hz, 2H), 8.95 (d, J = 7.2 Hz, 1H).

7-Chloro-2-ethyl-N-((4'-fluorobiphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (116)



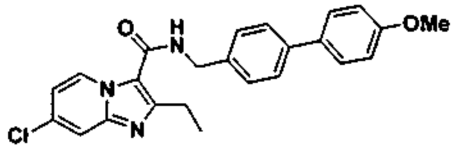
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.73 (d, J = 5.6 Hz, 2H), 6.14 (brs, 1H), 6.91 (dd, J = 7.2, 2.0 Hz, 1H), 7.13 (t, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.52 – 7.56 (m, 4H), 7.60 (d, J = 2.0 Hz, 1H), 9.38 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 408.21

N-((4'-tert-Butylbiphenyl-4-yl)methyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (117)



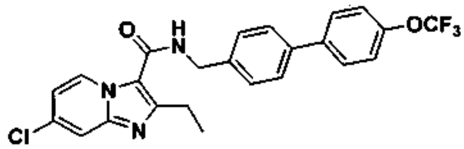
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.41 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.73 (d, J = 5.6 Hz, 2H), 6.13 (brs, 1H), 6.91 (dd, J = 7.2, 2.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.59 – 7.61 (m, 3H), 9.38 (d, J = 7.2 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 446.30

7-Chloro-2-ethyl-N-((4'-methoxybiphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (118)



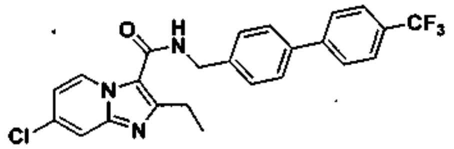
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 3.85 (s, 3H), 4.72 (d, J = 6.0 Hz, 2H), 6.12 (brs, 1H), 6.91 (dd, J = 7.2, 2.0 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 1.6 Hz, 1H), 9.38 (d, J = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 420.18

7-Chloro-2-ethyl-N-((4'-(trifluoromethoxy)biphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (119)



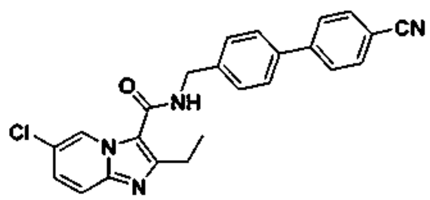
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 3.00 (q, J = 7.6 Hz, 2H), 4.75 (d, J = 6.0 Hz, 2H), 6.15 (brs, 1H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.54 – 7.60 (m, 5H), 9.38 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 474.18

7-Chloro-2-ethyl-N-((4'-(trifluoromethyl)biphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (120)



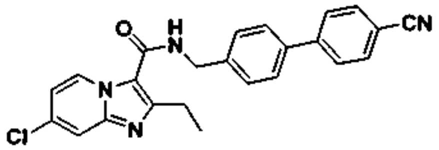
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 3.01 (q, J = 7.6 Hz, 2H), 4.76 (d, J = 6.0 Hz, 2H), 6.16 (brs, 1H), 6.92 (dd, J = 7.2, 2.0 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.60 (m, 3H), 7.70 (m, 3H), 9.38 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 458.20

6-Chloro-N-((4'-cyanobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (121)



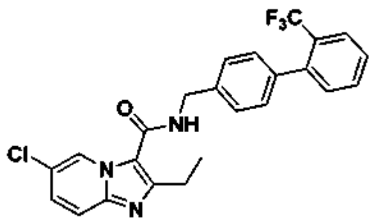
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.6 Hz, 3H), 3.02 (q, J = 7.2 Hz, 2H), 4.77 (d, J = 5.6 Hz, 2H), 6.19 (m, 1H), 7.32 (dd, J = 2.0, 9.6 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 9.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 9.55 (d, J = 2.0 Hz, 1H).

7-Chloro-N-((4'-cyanobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (122)



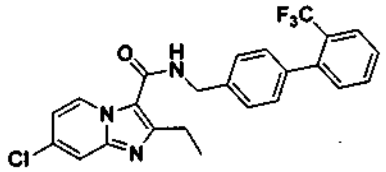
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 3.01 (q, J = 7.6 Hz, 2H), 4.76 (d, J = 6.0 Hz, 2H), 6.17 (brs, 1H), 6.92 (dd, J = 7.6, 2.4 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 2.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 9.38 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 415.21

6-Chloro-2-ethyl-N-((2'-(trifluoromethyl)biphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (123)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.6 Hz, 3H), 3.02 (q, J = 7.2 Hz, 2H), 4.78 (d, J = 5.6 Hz, 2H), 6.17 (m, 1H), 7.30 – 7.35 (m, 4H), 7.42 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 9.56 (d, J = 1.2 Hz, 1H).

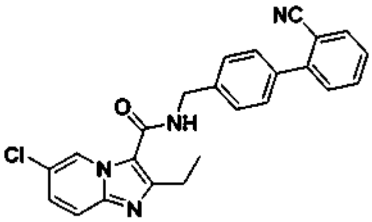
7-Chloro-2-ethyl-N-((2'-(trifluoromethyl)biphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (124)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 3.01 (q, J = 7.6 Hz, 2H), 4.77 (d, J = 5.6 Hz, 2H), 6.16 (brs, 1H), 6.92 (dd, J = 7.2, 2.4 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.60

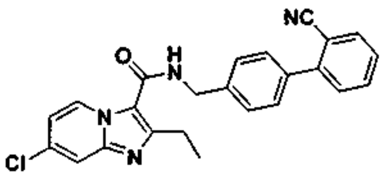
(d, J = 2.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 9.38 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 458.27

6-Chloro-N-((2'-cyanobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (125)



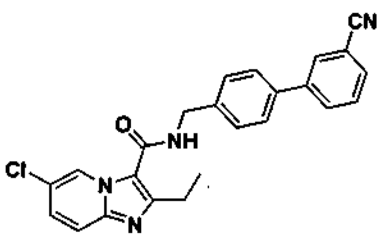
^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, J = 7.6 Hz, 3H), 3.03 (q, J = 7.6 Hz, 2H), 4.78 (d, J = 5.6 Hz, 2H), 6.18 – 6.20 (m, 1H), 7.32 (dd, J = 1.2, 7.6 Hz, 1H), 7.46 (dd, J = 7.6, 7.6 Hz, 1H), 7.50 – 7.55 (m, 3H), 7.57 (d, J = 8.4 Hz, 2H), 7.65 (dd, J = 7.6, 7.6 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 9.56 (d, J = 1.2 Hz, 1H).

7-Chloro-N-((2'-cyanobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (126)



^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.6 Hz, 3H), 3.02 (q, J = 7.6 Hz, 2H), 4.77 (d, J = 5.6 Hz, 2H), 6.18 (brs, 1H), 6.92 (dd, J = 7.6, 2.0 Hz, 1H), 7.47 – 7.60 (m, 4H), 7.63 – 7.65 (m, 4H), 7.77 (d, J = 7.6 Hz, 1H), 9.38 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 415.28

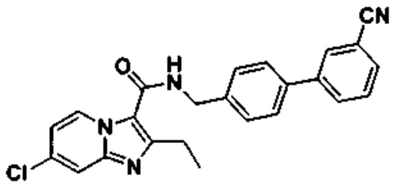
6-Chloro-N-((3'-cyanobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (127)



^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.6 Hz, 3H), 3.02 (q, J = 7.6 Hz, 2H), 4.77 (d, J = 5.6 Hz, 2H), 6.19 (m, 1H), 7.32 (dd, J = 2.0, 9.2 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.55 - 7.59

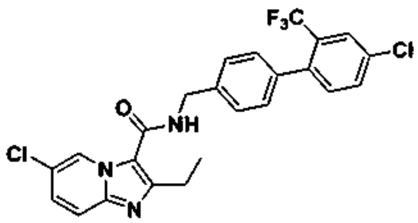
(m, 3H), 7.64 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 9.56 (d, J = 1.6 Hz, 1H).

7-Chloro-N-((3'-cyanobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (128)



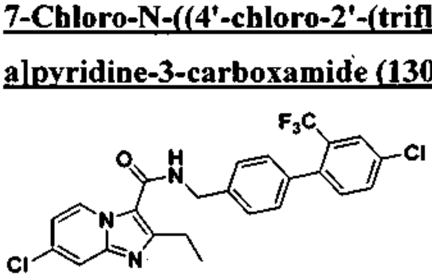
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 3.01 (q, J = 7.6 Hz, 2H), 4.76 (d, J = 6.0 Hz, 2H), 6.17 (brs, 1H), 6.92 (dd, J = 7.2, 2.0 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.55 – 7.63 (m, 5H), 7.80 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 1.6 Hz, 1H), 9.38 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 415.28

6-Chloro-N-((4'-chloro-2'-(trifluoromethyl)biphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (129)



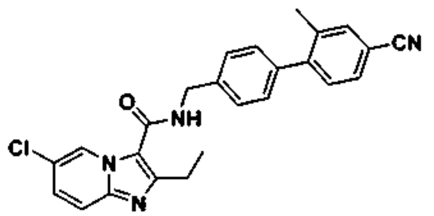
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.6 Hz, 3H), 3.02 (q, J = 7.6 Hz, 2H), 4.77 (d, J = 5.6 Hz, 2H), 6.18 (m, 1H), 7.27 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.52 – 7.56 (m, 2H), 7.73 (d, J = 2.0 Hz, 1H), 7.86 (s, 1H), 9.55 (d, J = 1.2 Hz, 1H).

7-Chloro-N-((4'-chloro-2'-(trifluoromethyl)biphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (130)



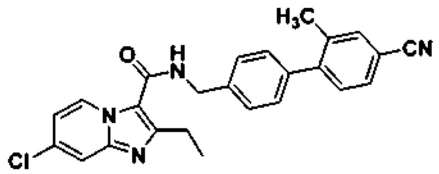
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 3.01 (q, J = 7.6 Hz, 2H), 4.76 (d, J = 6.0 Hz, 2H), 6.16 (brs, 1H), 6.92 (dd, J = 7.2, 2.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.53 (dd, J = 8.0, 1.6 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H), 9.38 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 492.21

6-Chloro-N-((4'-cyano-2'-methylbiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (131)



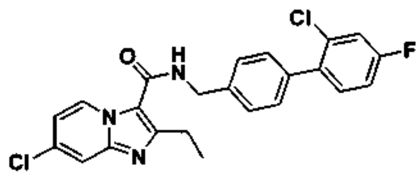
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.6 Hz, 3H), 2.30 (s, 3H), 3.03 (q, J = 7.6 Hz, 2H), 4.77 (d, J = 5.6 Hz, 2H), 6.21 (t, J = 5.2 Hz, 1H), 7.30 – 7.33 (m, 4H), 7.31 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.52 – 7.56 (m, 2H), 7.52 – 7.57 (m, 3H), 9.56 (d, J = 2.0 Hz, 1H).

7-Chloro-N-((4'-cyano-2'-methylbiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (132)



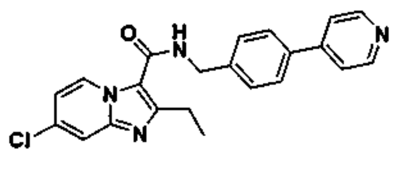
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.6 Hz, 3H), 2.29 (s, 3H), 3.02 (q, J = 7.6 Hz, 2H), 4.77 (d, J = 6.0 Hz, 2H), 6.18 (brs, 1H), 6.92 (dd, J = 7.6, 2.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 3H), 7.45 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.6 Hz, 1H), 7.56 (s, 1H), 7.60 (d, J = 2.4 Hz, 1H), 9.39 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 429.29

7-Chloro-N-((2'-chloro-4'-fluorobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (133)



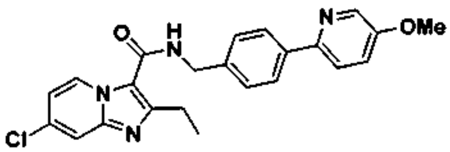
LCMS (electrospray) m/z $(M+H)^+$ 442.15

7-Chloro-2-ethyl-N-(4-(pyridin-4-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (134)



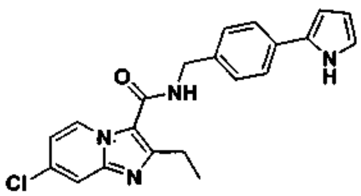
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 3.01 (q, J = 7.6 Hz, 2H), 4.76 (d, J = 5.6 Hz, 2H), 6.20 (brs, 1H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.26 – 7.51 (m, 4H), 7.61 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 8.65 (brs, 2H), 9.37 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 391.20

7-Chloro-2-ethyl-N-(4-(5-methoxypyridin-2-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (135)



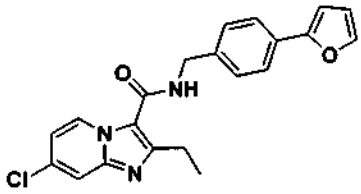
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.97 (q, J = 7.6 Hz, 2H), 3.91 (s, 3H), 4.74 (d, J = 5.6 Hz, 2H), 6.11 (brs, 1H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 2.0 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 8.39 (d, J = 2.8 Hz, 1H), 9.38 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 421.20

N-(4-(1H-Pyrrol-2-yl)benzyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (136)



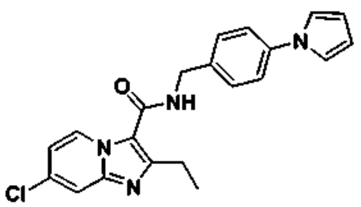
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.69 (m, 4H), 2.97 (q, J = 7.6 Hz, 2H), 4.68 (d, J = 6.0 Hz, 2H), 6.10 (m, 1H), 6.29 – 6.32 (m, 1H), 6.53 – 6.54 (m, 1H), 6.87 – 6.88 (m, 1H), 6.91 (dd, J = 2.0, 7.2 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 2.0 Hz, 1H), 8.51 (brs, 1H), 9.37 (d, J = 7.6 Hz, 1H).

7-Chloro-2-ethyl-N-(4-(furan-2-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (137)



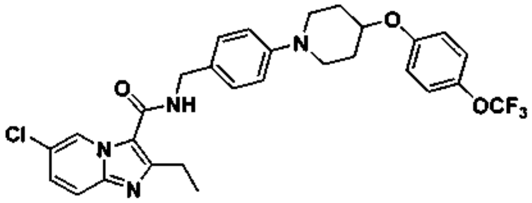
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 4.70 (d, J = 5.6 Hz, 2H), 6.47 – 6.48 (m, 1H), 6.53 – 6.54 (m, 1H), 6.66 (d, J = 3.2, 1H), 6.91 (dd, J = 2.0, 7.6 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 1.2 Hz, 1H), 7.60 (d, J = 1.6 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 9.37 (d, J = 7.2 Hz, 1H).

N-(4-(1H-Pyrrol-1-yl)benzyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (138)



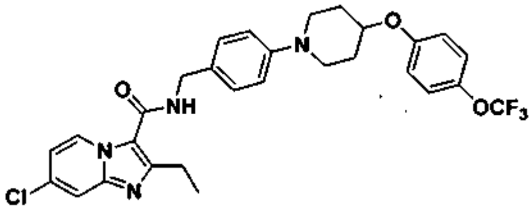
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.71 (d, J = 6.0 Hz, 2H), 6.12 – 6.14 (m, 1H), 6.34 – 6.36 (m, 2H), 6.92 (dd, J = 2.0, 7.6 Hz, 1H), 7.08 – 7.09 (m, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 21H), 7.60 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 9.38 (d, J = 7.6 Hz, 1H).

6-Chloro-2-ethyl-N-(4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)benzyl)imidazo-[1,2-a]pyridine-3-carboxamide (139)



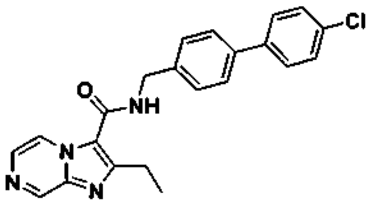
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 1.90 – 1.98 (m, 2H), 2.07 – 2.13 (m, 2H), 2.96 (q, J = 7.6 Hz, 2H), 3.10 – 3.16 (m, 2H), 3.48 – 3.54 (m, 2H), 4.42 – 4.48 (m, 1H), 3.22 (t, J = 4.8 Hz, 4H), 4.61 (d, J = 5.6 Hz, 2H), 6.00 – 6.20 (m, 1H), 6.91 (d, J = 7.2 Hz, 2H), 6.96 (d, J = 8.8Hz, 2H), 7.14 (d, J = 8.4 Hz, 1H), 7.26 – 7.31 (m, 3H), 7.54 (d, J = 9.6 Hz, 1H), 9.53 (d, J = 1.6 Hz, 1H).

7-Chloro-2-ethyl-N-(4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)benzyl)imidazo-[1,2-a]pyridine-3-carboxamide (140)



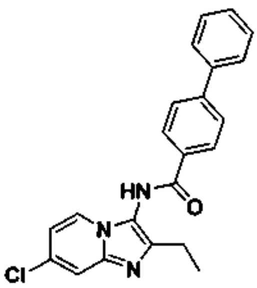
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 1.89 – 1.98 (m, 2H), 2.07 – 2.13 (m, 2H), 2.95 (q, J = 7.6 Hz, 2H), 3.09 – 3.16 (m, 2H), 3.47 – 3.53 (m, 2H), 4.42 – 4.48 (m, 1H), 3.22 (t, J = 4.8 Hz, 4H), 4.60 (d, J = 5.6 Hz, 2H), 5.99 – 6.01 (m, 1H), 6.88 - 6.93 (m, 3H), 6.96 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.8Hz, 2H), 7.26 – 7.29 (m, 2H), 7.59 (d, J = 2.0 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H).

N-((4'-Chlorobiphenyl-4-yl)methyl)-2-ethylimidazo[1,2-a]pyrazine-3-carboxamide (141)



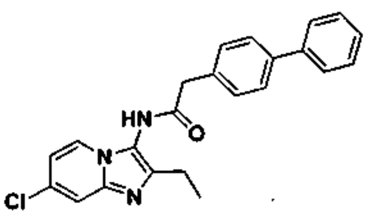
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (t, J = 7.6 Hz, 3H), 3.06 (q, J = 7.6 Hz, 2H), 4.76 (d, J = 5.6 Hz, 2H), 6.23 – 6.25 (m, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 8.03 (d, J = 4.4 Hz, 1H), 9.11 (s, 1H), 9.28 (d, J = 4.8 Hz, 1H).

N-(7-Chloro-2-ethylimidazo[1,2-a]pyridin-3-yl)biphenyl-4-carboxamide (142)



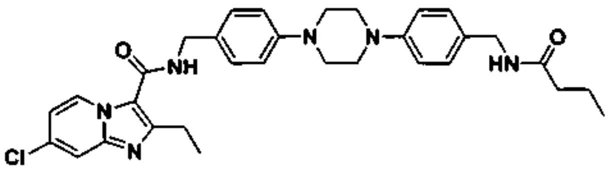
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 7.6 Hz, 3H), 2.75 (q, J = 7.2 Hz, 2H), 6.78 (dd, J = 1.2, 7.2, 1H), 6.89 (dd, J = 1.2, 7.2 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.48 – 7.53 (m, 3H), 7.58 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 8.02 (brs, 1H), 8.07 (d, J = 8.0 Hz, 2H).

2-(Biphenyl-4-yl)-N-(7-chloro-2-ethylimidazo[1,2-a]pyridin-3-yl)acetamide (143)



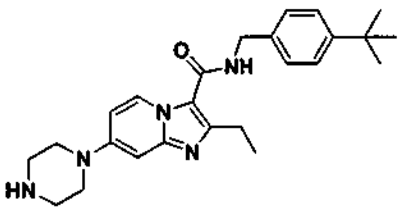
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (t, J = 7.6 Hz, 3H), 2.62 (q, J = 7.6 Hz, 2H), 3.89 (s, 2H), 6.74 (dd, J = 2.0, 7.2 Hz, 1H), 7.00 (brs, 1H), 7.44 – 7.53 (m, 5H), 7.61 (d, J = 7.2 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H).

N-(4-(4-(4-(Butyramidomethyl)phenyl)piperazin-1-yl)benzyl)-7-chloro-2-ethylimidazo-[1,2-a]pyridine-3-carboxamide (144)



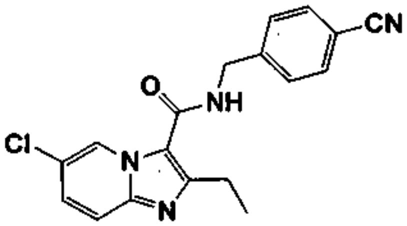
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 6.4 Hz, 3H), 1.37 (t, J = 6.0 Hz, 3H), 1.65 – 1.71 (m, 2H), 2.15 (t, J = 6.4 Hz, 2H), 2.94(q, J = 6.0 Hz, 2H), 3.33 (s, 8H), 4.36 (d, J = 4.4 Hz, 2H), 4.61 (d, J = 4.0 Hz, 2H), 5.59 (brs, 1H), 6.01 (brs, 1H), 6.88 – 6.98 (m, 5H), 7.19 (d, J = 7.2 Hz, 2H), 7.29 (d, J = 7.2 Hz, 2H), 7.58 (s, 1H), 9.35 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 573.

__N-(4-tert-Butylbenzyl)-2-ethyl-7-(piperazin-1-yl)imidazo[1,2-a]pyridine-3-carboxamide (145)__



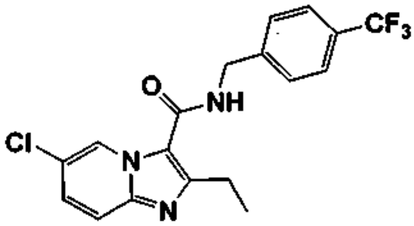
^{1}H NMR (400 MHz, DMSO) δ 1.20 (t, *J* = 7.6 Hz, 3H), 1.24 (s, 9H), 2.78 – 2.80 (m, 4H), 2.86 (q, *J* = 7.6 Hz, 2H), 3.13 – 3.15 (m, 4H), 4.42 (d, *J* = 6.0 Hz, 2H), 6.66 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 87.4 Hz, 2H), 7.99 (brt, *J* = 6.0 Hz, 1H), 8.75 (d, *J* = 8.0 Hz, 1H); LCMS (electrospray) m/z (M+H)$^+$ 420; mp 186.1 - 186.9 °C.

__6-Chloro-N-(4-cyanobenzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (146)__



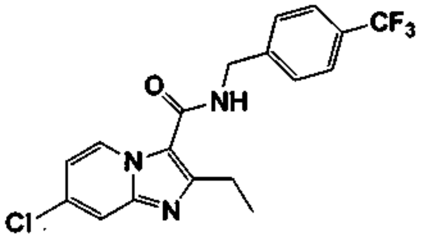
White solid; mp = 223 - 224 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, *J* = 7.6 Hz, 3H), 3.02 (q, *J* = 7.2 Hz, 2H), 4.76 (d, *J* = 6.0 Hz, 2H), 6.21 – 6.23 (m, 1H), 7.33 (dd, *J* = 2.0, 9.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 9.53 (d, *J* = 2.0 Hz, 1H)); LCMS (electrospray) m/z (M+H)$^+$ 339.16

__6-Chloro-2-ethyl-N-(4-(trifluoromethyl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (147)__



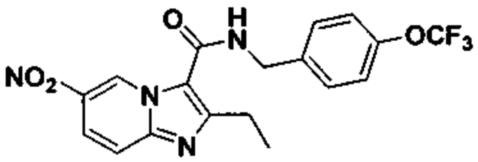
White solid; mp = 179 - 180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, *J* = 7.6 Hz, 3H), 3.01 (q, *J* = 7.6 Hz, 2H), 4.77 (d, *J* = 6.0 Hz, 2H), 6.19 – 6.21 (m, 1H), 7.32 (dd, *J* = 2.0, 9.2 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 9.6 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 9.54 (d, *J* = 2.0 Hz, 1H)); LCMS (electrospray) m/z (M+H)$^+$ 382.15

7-Chloro-2-ethyl-N-(4-(trifluoromethyl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (148)



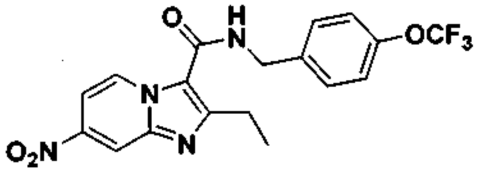
White solid; mp = 196.2 – 196.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.4 Hz, 3H), 3.00 (q, J = 7.6 Hz, 2H), 4.76 (d, J = 6.4 Hz, 2H), 6.92 (dd, J = 2.0, 7.2 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 9.36 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 382.15

2-Ethyl-6-nitro-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (149)



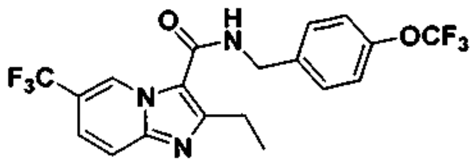
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.6 Hz, 3H), 3.49 (q, J = 7.6 Hz, 2H), 4.66 (d, J = 6.0 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 10.0 Hz, 1H), 7.82 (brs, 1H), 7.99 (dd, J = 10.0, 2.0 Hz, 1H), 9.11 (d, J = 1.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 409.23

2-Ethyl-7-nitro-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (150)



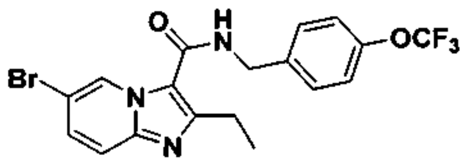
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (t, J = 7.6 Hz, 3H), 3.05 (q, J = 7.6 Hz, 2H), 4.57 (d, J = 5.6 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.76 (dd, J = 7.6, 2.4 Hz, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.79 (brs, 1H), 9.06 (d, J = 8.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 409.35

2-Ethyl-N-(4-(trifluoromethoxy)benzyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamide (151)



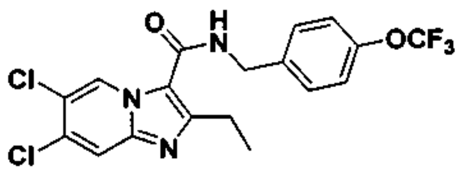
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, *J* = 7.6 Hz, 3H), 3.02 (q, *J* = 7.6 Hz, 2H), 4.71 (d, *J* = 5.6 Hz, 2H), 6.21 (brs, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.48 (dd, *J* = 9.2, 1.2 Hz, 1H), 7.69 (d, *J* = 9.2 Hz, 1H), 9.84 (d, *J* = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 432.42

6-Bromo-2-ethyl-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (152)



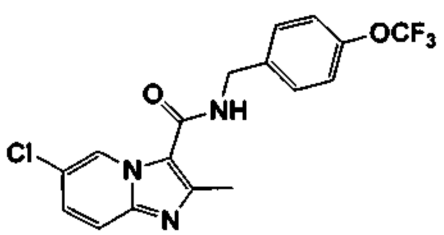
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, *J* = 7.6 Hz, 3H), 2.99 (q, *J* = 7.6 Hz, 2H), 4.71 (d, *J* = 5.6 Hz, 2H), 6.14 (brs, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.39-7.42 (m, 3H), 7.51 (d, *J* = 9.2 Hz, 1H), 9.63 (d, *J* = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 444.12

6,7-Dichloro-2-ethyl-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (153)



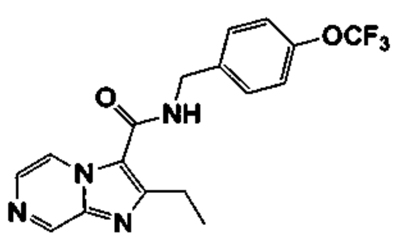
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.6 Hz, 3H), 2.99 (q, *J* = 7.6 Hz, 2H), 4.70 (d, *J* = 6.0 Hz, 2H), 6.14 (brs, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.72 (s, 1H), 9.66 (s, 1H); LCMS (electrospray) m/z $(M+H)^+$ 432.15

6-Chloro-2-methyl-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (154)



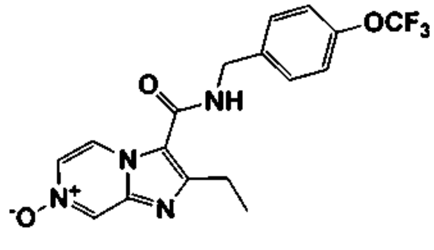
White solid; mp = 192 – 193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 4.71 (d, J = 6.0 Hz, 2H), 6.12 – 6.14 (m, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.32 (dd, J = 2.0, 9.6 Hz, 1H), 7.42 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 9.6 Hz, 1H), 9.65 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 384.20

2-Ethyl-N-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyrazine-3-carboxamide (155)



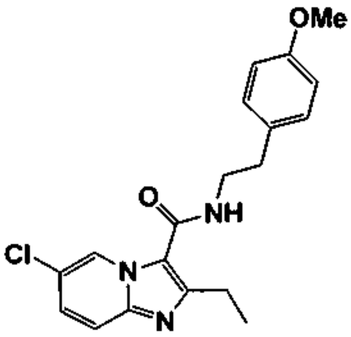
White solid; mp = 176 - 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (t, J = 7.6 Hz, 3H), 3.04 (q, J = 7.6 Hz, 2H), 4.71 (d, J = 5.6 Hz, 2H), 6.26 – 6.27 (m, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 4.8 Hz, 1H), 9.10 (d, J = 1.2 Hz, 1H), 9.25 (dd, J = 1.2, 4.8 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 365.12

2-Ethyl-3-((4-(trifluoromethoxy)benzyl)carbamoyl)imidazo[1,2-a]pyrazine 7-oxide (156)



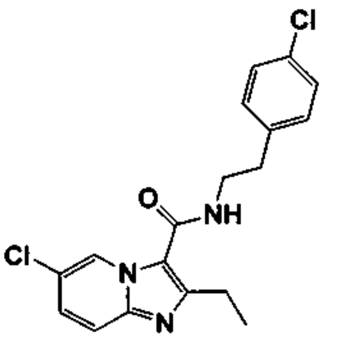
White solid; mp = 215 - 216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.70 (d, J = 6.0 Hz, 2H), 6.19 – 6.20 (m, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.69 (dd, J = 1.6, 5.6 Hz, 1H).8.57 (d, J = 2.0 Hz, 1H), 9.29 (d, J = 6.0 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 381.13

6-Chloro-2-ethyl-N-(4-methoxyphenethyl)imidazo[1,2-a]pyridine-3-carboxamide (157)



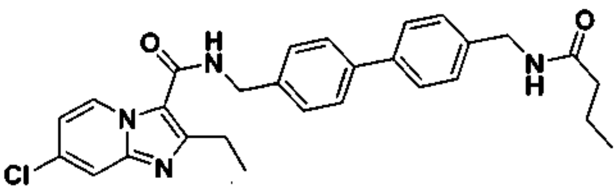
White solid; mp = 129 – 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.4 Hz, 3H), 2.72 (q, *J* = 7.6 Hz, 2H), 2.92 (t, *J* = 6.8 Hz, 2H), 3.77 (q, *J* = 5.6 Hz, 2H), 3.80 (s, 3H), 5.73 – 5.74 (m, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.51 (dd, *J* = 0.8, 9.6 Hz, 1H), 9.49 (d, *J* = 2.0 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 358.21

6-Chloro-N-(4-chlorophenethyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (158)



White solid; mp = 158 - 159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.4 Hz, 3H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.96 (t, *J* = 6.6 Hz, 2H), 3.78 (q, *J* = 6.0 Hz, 2H), 5.73 – 5.74 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 2.0, 9.6 Hz, 1H), 9.48 (d, *J* = 1.6 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 362.16

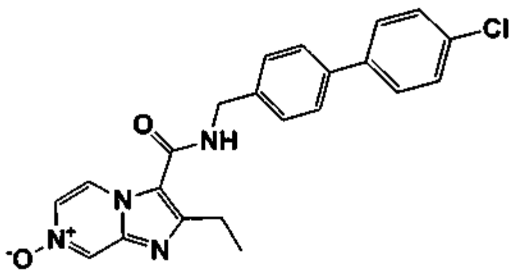
***N*-((4'-(Butyramidomethyl)biphenyl-4-yl)methyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (159)**



White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 0.95 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.6 Hz, 3H), 1.64 – 1.75 (m, 2H), 2.19 (t, *J* = 7.2 Hz, 2H), 2.97 (q, *J* = 7.6 Hz, 2H), 4.48 (d, *J* = 5.6 Hz, 2H), 4.73 (d, *J* = 5.6 Hz, 2H), 5.71 (brs, 1H), 6.12 (brt, *J* = 5.6 Hz, 1H), 6.90 (dd, *J* = 2.0, 7.2

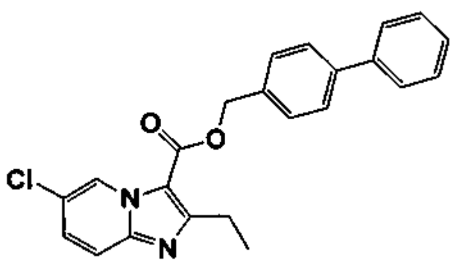
Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.51 – 7.60 (m, 5H), 9.37 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 489.

3-(((4'-Chloro-[1,1'-biphenyl]-4-yl)methyl)carbamoyl)-2-ethylimidazo[1,2-a]pyrazine 7-oxide (160)



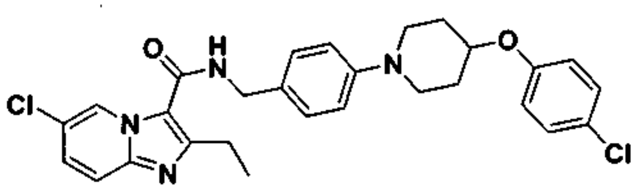
White solid; mp = 238 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.6 Hz, 3H), 3.00 (q, J = 7.6 Hz, 2H), 4.73(d, J = 6.0 Hz, 2H), 6.21 (t, J = 4.8 Hz, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.69 (dd, J = 2.0, 6.4 Hz, 1H). 8.56 – 8.57 (m, 1H), 9.31 (d, J = 6.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 407.12

[1,1'-Biphenyl]-4-ylmethyl 6-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxylate (161)



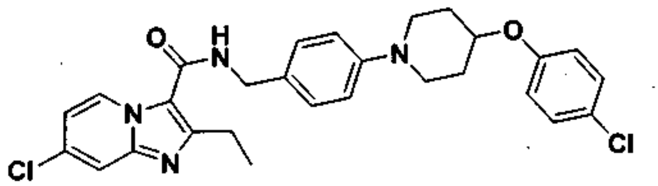
White solid; mp = 122.3 – 123.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.6 Hz, 3H), 3.13 (q, J = 7.6 Hz, 2H), 5.48 (s, 2H), 7.34 – 7.38 (m, 2H), 7.45 (dd, J = 7.2, 8.0 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.57 – 7.65 (m, 5H), 9.45 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 390.20

6-Chloro-N-(4-(4-(4-chlorophenoxy)piperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a] pyridine-3-carboxamide (162)



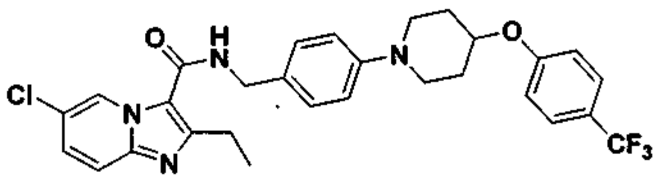
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.6 Hz, 3H), 1.94 (m, 2H), 2.06-2.10 (m, 2H), 2.96 (q, *J* = 7.6 Hz, 2H), 3.09-3.14 (m, 2H), 3.15-3.52 (m, 2H), 4.43 (m, 1H), 4.61 (d, *J* = 5.6 Hz, 2H), 6.01 (brs, 1H), 6.85 (d, *J* = 9.2 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.20-7.31 (m, 5H), 7.53 (d, *J* = 10.4 Hz, 1H), 9.53 (d, *J* = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 523.29

7-Chloro-N-(4-(4-(4-chlorophenoxy)piperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a] pyridine-3-carboxamide (163)



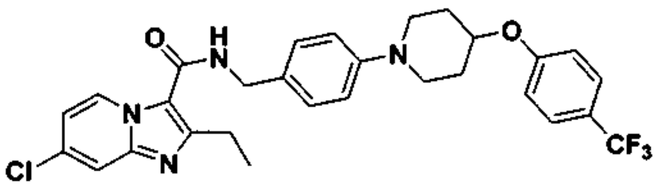
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.91-1.96 (m, 2H), 2.06-2.11 (m, 2H), 2.96 (q, *J* = 7.6 Hz, 2H), 2.97-3.15 (m, 2H), 3.47-3.52 (m, 2H), 4.43 (m, 1H), 4.60 (d, *J* = 5.6 Hz, 2H), 6.00 (brs, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.90 (dd, *J* = 7.6, 2.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 7.21-7.28 (m, 4H), 7.58 (d, *J* = 1.6 Hz, 1H), 9.36 (d, *J* = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 523.29

6-Chloro-2-ethyl-N-(4-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)benzyl) imidazo[1,2-a]pyridine-3-carboxamide (164)



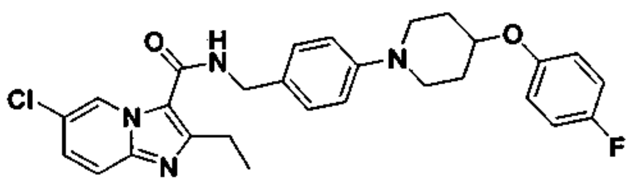
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.6 Hz, 3H), 1.94-1.99 (m, 2H), 2.10-2.15 (m, 2H), 2.96 (q, *J* = 7.6 Hz, 2H), 3.12-3.18 (m, 2H), 3.47-3.53 (m, 2H), 4.53-4.57 (m, 1H), 4.61 (d, *J* = 5.2 Hz, 2H), 6.02 (brs, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.27-7.31 (m, 3H), 7.51-7.55 (m, 3H), 9.53 (d, *J* = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 557.37

7-Chloro-2-ethyl-N-(4-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)benzyl) imidazo[1,2-a]pyridine-3-carboxamide (165)



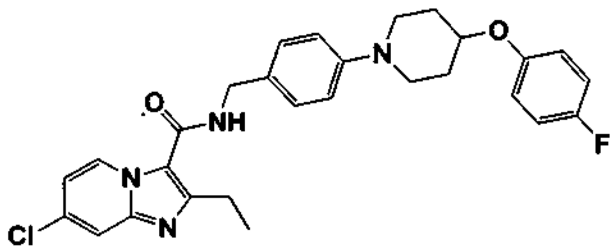
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.6 Hz, 3H), 1.94-1.98 (m, 2H), 2.09-2.11 (m, 2H), 2.95 (q, *J* = 7.6 Hz, 2H), 3.12-3.18 (m, 2H), 3.47-3.53 (m, 2H), 4.55 (m, 1H), 4.60 (d, *J* = 5.6 Hz, 2H), 6.00 (brs, 1H), 6.90 (dd, *J* = 7.6, 2.0 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 2.0 Hz, 1H), 9.36 (d, *J* = 8.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 557.37

6-Chloro-2-ethyl-N-(4-(4-(4-fluorophenoxy)piperidin-1-yl)benzyl)imidazo[1,2-a] pyridine-3-carboxamide (166)



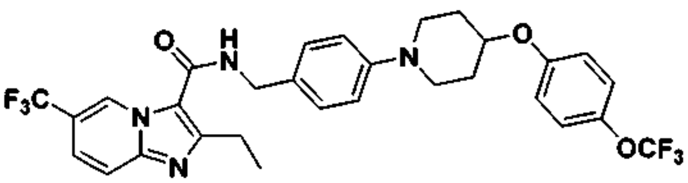
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.6 Hz, 3H), 1.91-1.94 (m, 2H), 2.06-2.11 (m, 2H), 2.96 (q, *J* = 7.6 Hz, 2H), 3.08-3.14 (m, 2H), 3.47-3.54 (m, 2H), 4.37-4.39 (m, 1H), 4.61 (d, *J* = 5.6 Hz, 2H), 6.01 (brs, 1H), 6.86-6.89 (m, 2H), 6.95-7.00 (m, 4H), 7.26-7.30 (m, 3H), 7.53 (d, *J* = 8.8 Hz, 1H), 9.53 (d, *J* = 1.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 507.31

7-Chloro-2-ethyl-N-(4-(4-(4-fluorophenoxy)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (167)



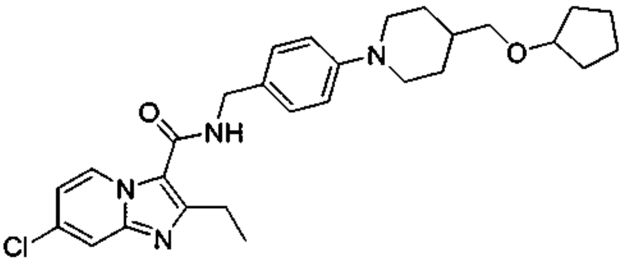
White solid; mp = 138 - 139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.6 Hz, 3H), 1.88 – 1.96 (m, 2H), 2.05 – 2.12 (m, 2H), 2.95 (q, *J* = 7.6 Hz, 2H), 3.08 – 3.14 (m, 2H), 3.48 – 3.54 (m, 2H), 4.35 – 4.41 (m, 2H), 4.60 (d, *J* = 5.6 Hz, 2H), 5.99 - 6.01 (m, 1H), 6.86 – 6.91 (m, 3H), 6.91 – 7.00 (m, 4H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 2.0 Hz, 1H), 9.36 (d, *J* = 7.6 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 507.31

2-Ethyl-N-(4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)benzyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamide (168)



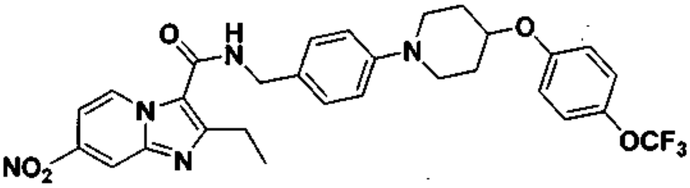
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 1.90-1.98 (m, 2H), 2.08-2.13 (m, 2H), 2.99 (q, J = 7.6 Hz, 2H), 3.10-3.15 (m, 2H), 3.47-3.54 (m, 2H), 4.43-4.46 (m, 1H), 4.62 (d, J = 5.6 Hz, 2H), 6.05 (brs, 1H), 6.91 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.46 (dd, J = 9.2, 2.0 Hz, 1H), 7.69 (d, J = 9.2 Hz, 1H), 9.85 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 607.56

7-Chloro-*N*-(4-(4-(cyclopentyloxymethyl)piperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide(169)



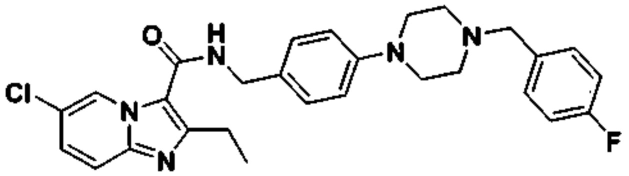
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); □1.23 – 1.38 (m, 2H), 1.31 (t, J = 7.6 Hz, 3H), 1.47 – 1.52 (m, 2H), 1.56 – 1.70 (m, 7H), 1.80 – 1.83 (m, 2H), 2.64 – 2.70 (m, 2H), 2.87 (q, J = 7.6 Hz, 2H), 3.21 (d, J = 6.8 Hz, 2H), 3.63 – 3.66 (m, 2H), 3.81 – 3.86 (m, 1H), 4.53 (d, J = 5.2 Hz, 2H), 6.07 (brt, J = 5.2 Hz, 1H), 6.82 (dd, J = 1.6, 7.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 1.6 Hz, 1H), 9.26 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) □13.3, 23.4, 23.6, 29.3, 32.3, 36.4, 43.3, 49.6, 73.7, 81.5, 114.5, 115.1, 115.6, 116.7, 128.1, 128.5, 128.7, 128.8, 133.4, 146.0, 151.5, 161.1.

2-Ethyl-7-nitro-N-(4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)benzyl) imidazo[1,2-a]pyridine-3-carboxamide (170)



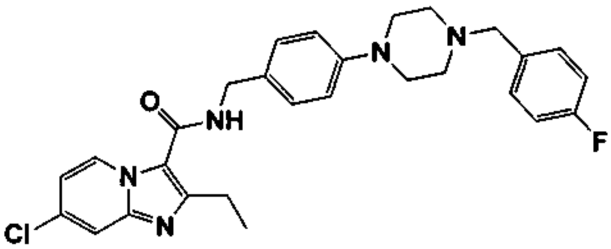
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.6 Hz, 3H), 1.95 (m, 2H), 2.10 (m, 2H), 3.01 (q, J = 7.6 Hz, 2H), 3.11-3.16 (m, 2H), 3.49-3.53 (m, 2H), 4.45 (m, 1H), 4.63 (d, J = 5.2 Hz, 2H), 6.11 (brs, 1H), 6.91 (d, J = 9.2 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 7.6 Hz, 1H), 8.53 (s, 1H), 9.54 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 584.58

6-Chloro-2-ethyl-N-(4-(4-(4-fluorobenzyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (171)



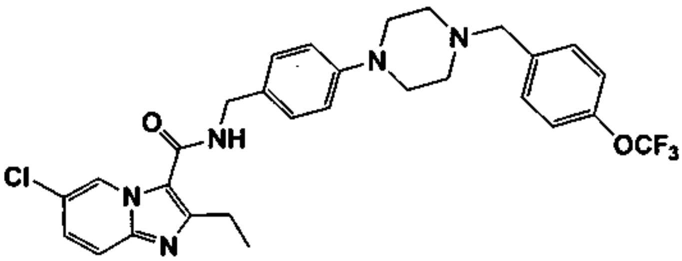
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 2.59 (m, 4H), 2.95 (q, J = 7.6 Hz, 2H), 3.20 (m, 4H), 3.52 (s, 2H), 4.60 (d, J = 5.6 Hz, 2H), 6.00 (brs, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.01 (t, J = 8.4 Hz, 2H), 7.26-7.32 (m, 5H), 7.53 (d, J = 9.6 Hz, 1H), 9.52 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 506.29

7-Chloro-2-ethyl-N-(4-(4-(4-fluorobenzyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (172)



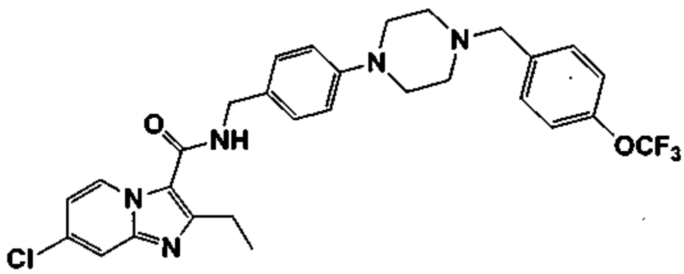
White solid; mp = 141 - 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.8 Hz, 3H), 2.59 (t, J = 4.8 Hz, 4H), 2.94 (q, J = 7.2 Hz, 2H), 3.20 (t, J = 5.0 Hz, 4H), 3.53 (s, 2H), 4.59 (d, J = 5.2 Hz, 2H), 5.98 – 6.00 (m, 1H), 6.88 – 6.92 (m, 3H), 7.01 (dd, J = 8.8, 8.8 Hz, 2H), 7.25 – 7.27 (m, 4H), 7.31 (dd, J = 5.6, 8.0 Hz , 2H), 7.58 (d, J = 2.0 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 506.36

6-Chloro-2-ethyl-N-(4-(4-(4-(trifluoromethoxy)benzyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (173)



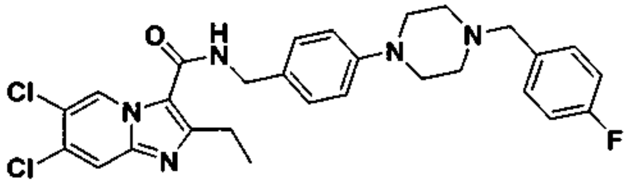
White solid; mp = 138.1 – 138.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.6 Hz, 3H), 2.60 (t, J = 5.0 Hz, 4H), 2.95 (q, J = 7.6 Hz, 2H), 3.21 (t, J = 5.0 Hz, 4H), 3.56 (s, 2H), 4.60 (d, J = 5.6 Hz, 2H), 6.00 – 6.02 (m, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.26 – 7.30 (m, 3H), 7.38 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 9.2 Hz, 1H), 9.53 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 572.40

7-Chloro-2-ethyl-N-(4-(4-(4-(trifluoromethoxy)benzyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (174)



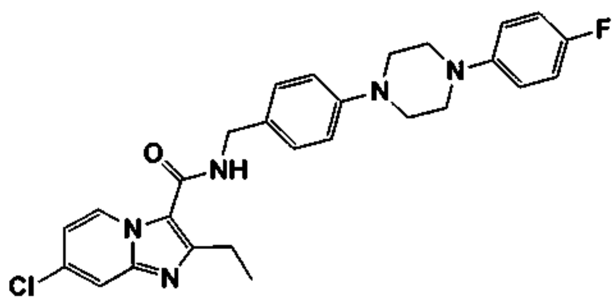
White solid; mp = 137.1 – 137.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.6 Hz, 3H), 2.60 (t, J = 4.8 Hz, 4H), 2.94 (q, J = 7.6 Hz, 2H), 3.21 (t, J = 4.8 Hz, 4H), 3.56 (s, 2H), 4.60 (d, J = 5.6 Hz, 2H), 5.99 – 6.00 (m, 1H), 6.88 – 6.93 (m, 3H), 7.18 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.58(d, J = 1.6 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 572.40

6,7-Dichloro-2-ethyl-N-(4-(4-(4-fluorobenzyl)piperazin-1-yl)benzyl)imidazo[1,2-a] pyridine-3-carboxamide (175)



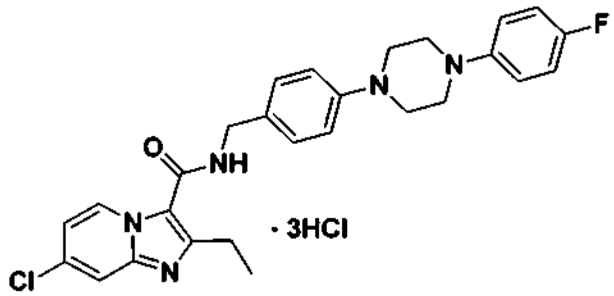
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (t, J = 7.6 Hz, 3H), 2.50 (m, 4H), 2.95 (q, J = 7.6 Hz, 2H), 3.08 (m, 4H), 3.48 (s, 2H), 4.41 (d, J = 6.0 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.14 (dd, J = 9.2 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.33-7.36 (m, 2H), 8.06 (s, 1H), 8.44 (t, 1H), 9.20 (s, 1H); LCMS (electrospray) m/z $(M+H)^+$ 540.36

7-Chloro-2-ethyl-N-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (176)



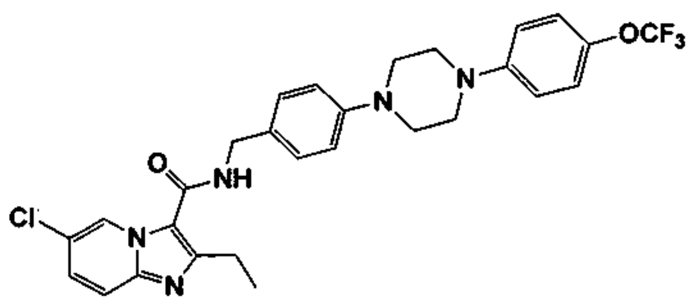
White solid; mp = 212 - 213 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 3.26 (t, J = 4.8 Hz, 4H), 3.35 (t, J = 4.8 Hz, 4H), 4.62 (d, J = 5.6 Hz, 2H), 6.01 – 6.03 (m, 1H), 6.89 – 7.02 (m, 7H), 7.30 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 2.0 Hz, 1H), 9.37 (d, J = 7.2 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 492.28

7-Chloro-2-ethyl-N-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide trihydrochloride (177)



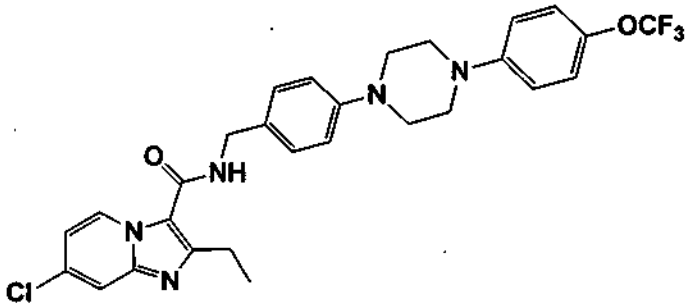
White solid; mp = 204.4 – 206.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (t, J = 7.6 Hz, 3H), 3.14 (q, J = 7.6 Hz, 2H), 3.54 – 3.70 (m, 8H), 4.56 (d, J = 6.0 Hz, 2H), 7.26 (dd, J = 8.4, 8.8 Hz, 2H), 7.36 – 7.50 (m, 6H), 7.63 (dd, J = 2.4, 7.6 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 9.13 (d, J = 7.2 Hz, 1H), 9.26 (t, J = 5.6 Hz, 1H).

6-Chloro-2-ethyl-N-(4-(4-(4-(trifluoromethoxy)phenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (178)



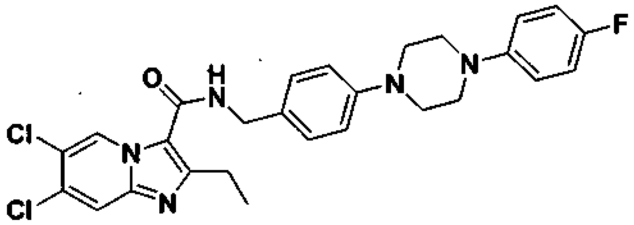
White solid; mp = 206.5 – 207.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.96 (q, J = 7.6 Hz, 2H), 3.30 – 3.40 (m, 8H), 4.63 (d, J = 5.2 Hz, 2H), 6.03 – 6.04 (m, 1H), 6.95 (d, J = 9.2 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.27 – 7.32 (m, 3H), 7.54 (d, J = 9.6 Hz, 1H), 9.53 – 9.34 (m, 1H); LCMS (electrospray) m/z $(M+H)^+$ 558.32

7-Chloro-2-ethyl-N-(4-(4-(4-(trifluoromethoxy)phenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (179)



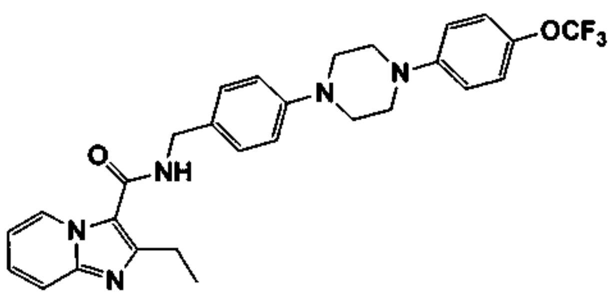
White solid; mp = 216.3 – 217.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 3.30 – 3.40 (m, 8H), 4.62 (d, J = 5.6 Hz, 2H), 6.01 – 6.02 (m, 1H), 6.90 (dd, J = 2.0, 7.2 Hz, 1H), 6.94 (d, J = 9.2 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 1.6 Hz, 1H), 9.37 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 558.32

6,7-Dichloro-2-ethyl-N-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a] pyridine-3-carboxamide (180)



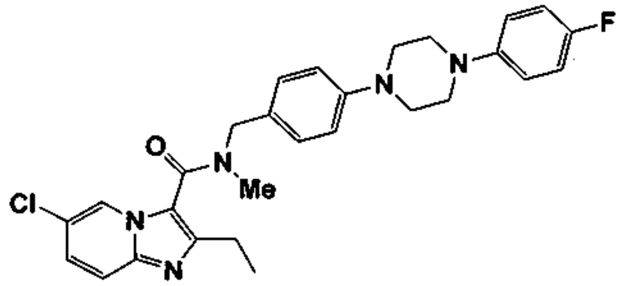
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 3.24-3.27 (m, 4H), 3.34-3.36 (m, 4H), 4.62 (d, J = 5.6 Hz, 2H), 6.03 (brs, 1H), 6.91-7.02 (m, 6H), 7.30 (d, J = 8.8 Hz, 2H), 7.71 (s, 1H), 9.67 (s, 1H); LCMS (electrospray) m/z $(M+H)^+$ 526.35

2-Ethyl-N-(4-(4-(4-(trifluoromethoxy)phenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (181)



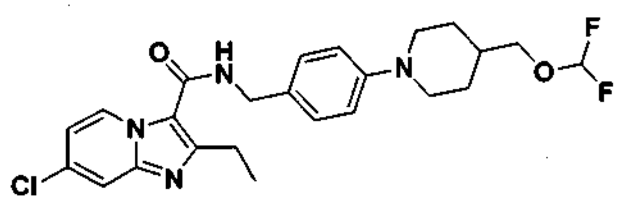
White solid; mp = 178 – 179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.97 (q, J = 7.2 Hz, 2H), 3.31 – 3.38 (m, 8H), 4.63 (d, J = 5.6 Hz, 2H), 6.05 (t, J = 5.0 Hz, 1H), 6.89 – 6.99 (m, 5H), 7.14 (d, J = 8.8 Hz, 2H), 7.29 – 7.32 (m, 3H), 7.60 (d, J = 9.2 Hz, 1H), 9.40 (d, J = 6.8 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 524.45

6-Chloro-2-ethyl-N-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)-N-methylimidazo[1,2-a]pyridine-3-carboxamide (182)



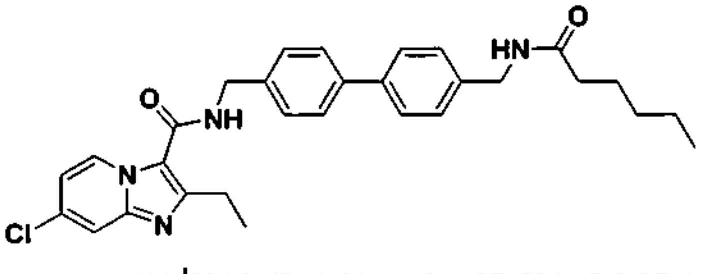
White solid; mp = 148 - 149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.4 Hz, 3H), 2.78 (q, J = 7.6 Hz, 2H), 2.99 (s, 3H), 3.24 – 3.27 (m, 4H), 3.33 – 3.36 (m, 4H), 4.66 (s, 2H), 6.92 – 7.02 (m, 6H), 7.12 – 7.20 (m, 2H), 7.21 (dd, J = 2.0, 9.6 Hz, 1H), 7.52 (d, J = 9.6 Hz, 1H), 8.46 (d, J = 1.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 506.36

7-Chloro-*N*-(4-(4-((difluoromethoxy)methyl)piperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (183)



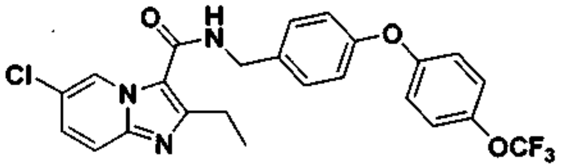
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7. 6 Hz, 3H), 1.41 – 1.48 (m, 2H), 1.70 – 1.86 (m, 3H), 2.72 (t, J = 12.4 Hz, 2H), 2.93 (q, J = 7.6 Hz, 2H), 3.69 – 3.73 (m, 4H), 4.58 (d, J = 5.6 Hz, 2H), 6.00 (brs, 1H), 6.20 (t, J = 75.2 Hz, due to F2), 6.88 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 1.6 Hz, 1H), 9.34 (d, J = 7.6 Hz, 1H).; LCMS (electrospray) m/z $(M+H)^+$ 477.

7-Chloro-2-ethyl-*N*-((4'-(hexanamidomethyl)biphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (184)



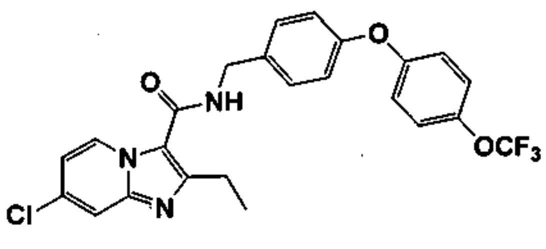
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 0.87 (t, J = 6.8 Hz, 3H), 1.30 – 1.35 (m, 4H), 1.40 (t, J = 7.6 Hz, 3H), 1.63 – 1.71 (m, 2H), 2.21 (t, J = 7.6 Hz, 2H), 3.03 (q, J = 7.6 Hz, 2H), 4.47 (d, J = 5.6 Hz, 2H), 4.72 (d, J = 6.0 Hz, 2H), 5.74 (brs, 1H), 6.99 (dd, J = 2.0, 7.2 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.51 – 7.59 (m, 5H), 7.74 (brs, 1H), 9.32 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 517.

6-Chloro-2-ethyl-N-(4-(4-(trifluoromethoxy)phenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (185)



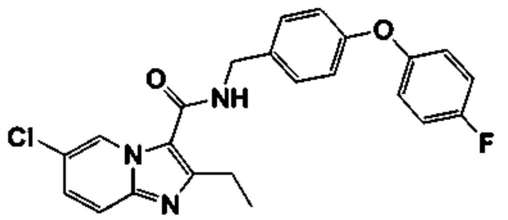
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.68 (d, J = 6.0 Hz, 2H), 6.11 (brs, 1H), 7.00 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.30 (dd, J = 9.6, 2.0 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 9.2 Hz, 1H), 9.53 (d, J = 1.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 490.17

7-Chloro-2-ethyl-N-(4-(4-(trifluoromethoxy)phenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (186)



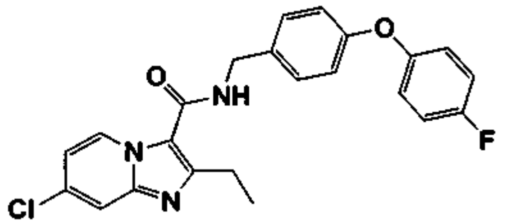
White solid; mp = 141 - 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 4.68 (d, J = 5.6 Hz, 2H), 6.09 – 6.11 (m, 1H), 6.91 (dd, J = 2.0, 7.6 Hz, 1H), 6.98 – 7.02 (m, 4H), 7.18 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 2.0 Hz, 1H), 9.37 (d, J = 7.2 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 490.24

6-Chloro-2-ethyl-N-(4-(4-fluorophenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (187)



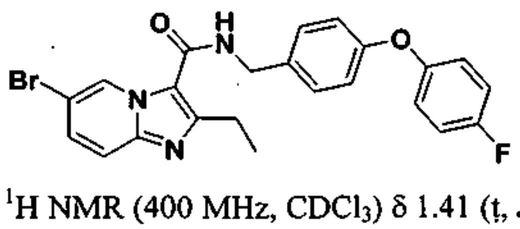
White solid; mp = 168 - 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.4 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.67 (d, J = 6.0 Hz, 2H), 6.09 – 6.11 (m, 1H), 6.96 – 7.06 (m, 6H), 7.30 (dd, J = 2.0, 9.6 Hz, 1H), 7.34 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 9.6 Hz, 1H), 9.53 (d, J = 1.2 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 424.26

7-Chloro-2-ethyl-N-(4-(4-fluorophenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (188)



White solid; mp = 146 - 147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.97 (q, J = 7.6 Hz, 2H), 4.66 (d, J = 5.6 Hz, 2H), 6.07 – 6.09 (m, 1H), 6.91 (dd, J = 2.2, 7.4 Hz, 1H), 6.95 – 7.06 (m, 6H), 7.33 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 2.2 Hz, 1H), 9.37 (d, J = 7.2 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 424.26

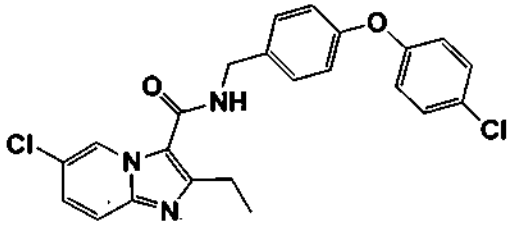
6-Bromo-2-ethyl-N-(4-(4-fluorophenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (189)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 4.66 (d, J = 5.6 Hz, 2H), 6.09 (brs, 1H), 6.95-7.06 (m, 6H), 7.34 (d, J = 8.8 Hz, 2H), 7.40 (dd, J = 9.6, 1.6

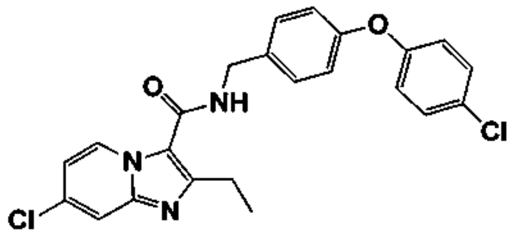
Hz, 1H), 7.49 (d, J = 9.6 Hz, 1H), 9.63 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 470.10

6-Chloro-N-(4-(4-chlorophenoxy)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (190)



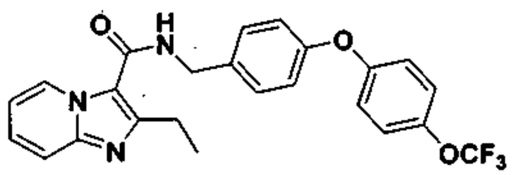
White solid; mp = 159 – 160.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.2 Hz, 2H), 4.68 (d, J = 5.6 Hz, 2H), 6.10 – 6.11 (m, 1H), 6.94 (d, J = 9.2 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.27 – 7.32 (m, 3H), 7.36 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 9.6 Hz, 1H), 9.54 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 440.18

7-Chloro-N-(4-(4-chlorophenoxy)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (191)



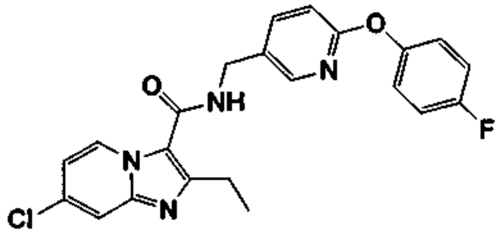
White solid; mp = 167.1 – 167.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 4.67 (d, J = 5.6 Hz, 2H), 6.08 – 6.10 (m, 1H), 6.91 (dd, J = 2.4, 7.6 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 2.0 Hz, 1H), 9.37 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 440.18

2-Ethyl-N-(4-(4-(trifluoromethoxy)phenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (192)



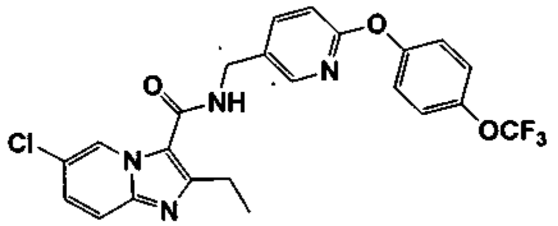
^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.6 Hz, 3H), 3.01 (q, *J* = 7.6 Hz, 2H), 4.69 (d, *J* = 6.0 Hz, 2H), 6.12 (brs, 1H), 6.92 (t, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 9.2 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.31-7.36 (m, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 9.40 (d, *J* = 6.8 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 456.23

7-Chloro-2-ethyl-N-((6-(4-fluorophenoxy)pyridin-3-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (193)



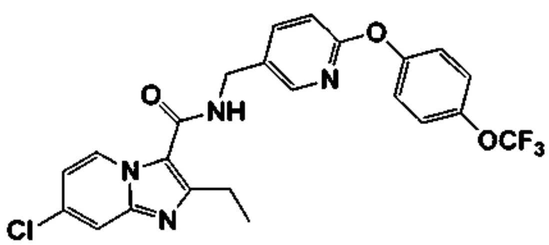
White solid; mp = 167.0 – 167.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.6 Hz, 3H), 2.97 (q, *J* = 7.6 Hz, 2H), 4.64 (d, *J* = 6.0 Hz, 2H), 6.09 (t, *J* = 5.6 Hz, 1H), 6.90 – 6.93 (m, 2H), 7.06 – 7.11 (m, 4H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.80 (dd, *J* = 2.8, 8.8 Hz, 1H), 8.20 (d, *J* = 2.0 Hz, 1H), 9.34 (d, *J* = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 425.28

6-Chloro-2-ethyl-N-((6-(4-(trifluoromethoxy)phenoxy)pyridin-3-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (194)



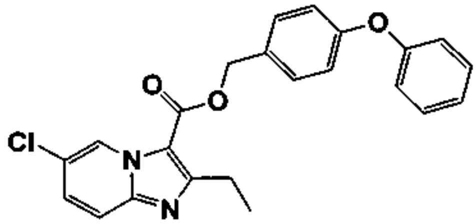
White solid; mp = 154 – 155 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.8 Hz, 3H), 2.98 (q, *J* = 7.6 Hz, 2H), 4.66 (d, *J* = 6.0 Hz, 2H), 6.14 (t, *J* = 5.6 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 9.2 Hz, 2H), 7.24 (d, *J* = 9.2 Hz, 2H), 7.32 (dd, *J* = 2.0, 9.6 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.80 (dd, *J* = 2.4, 8.4 Hz, 1H), 8.20 (d, *J* = 2.4 Hz, 1H), 9.51 (d, *J* = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 491.26

7-Chloro-2-ethyl-N-((6-(4-(trifluoromethoxy)phenoxy)pyridin-3-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (195)



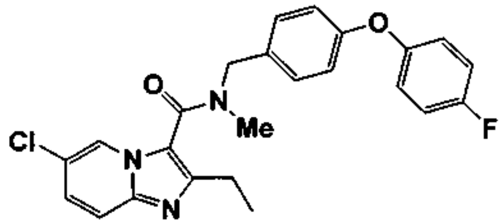
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.4 Hz, 3H), 2.97 (q, J = 7.6 Hz, 2H), 4.66 (d, J = 6.0 Hz, 2H), 6.14 (t, J = 5.4 Hz, 1H), 6.92 (dd, J = 2.0, 7.6 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 9.2 Hz, 2H), 7.24 (d, J = 9.2 Hz, 2H), 7.60 (d, J = 1.6 Hz, 1H), 7.79 (dd, J = 2.4, 8.4 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 9.35 (d, J = 7.6 Hz, 1H).

4-Phenoxybenzyl 6-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxylate (196)



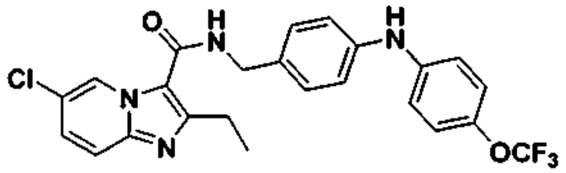
White solid; mp = 123.3 – 123.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J = 7.4 Hz, 3H), 3.10 (q, J = 7.6 Hz, 2H), 4.67 (s, 2H), 7.02 (d, J = 8.4 Hz, 4H), 7.12 (dd, J = 7.2, 7.6 Hz, 1H), 7.34 (dd, J = 7.2, 7.6 Hz, 3H), 7.43 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 9.6 Hz, 1H), 9.42 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 407.12

6-Chloro-2-ethyl-N-(4-(4-fluorophenoxy)benzyl)-N-methylimidazo[1,2-a]pyridine-3-carboxamide (197)



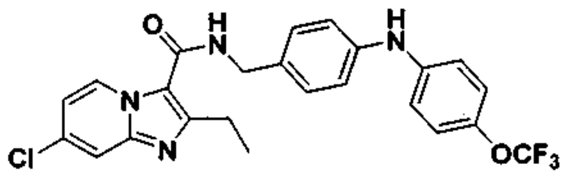
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.4 Hz, 3H), 2.78 (q, J = 7.6 Hz, 2H), 3.01 (s, 3H), 4.70 (s, 2H), 6.94 – 7.06 (m, 6H), 7.21 – 7.26 (m, 3H), 8.47 (d, J = 9.2 Hz, 1H), 8.47 (d, J = 1.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 438.20

6-Chloro-2-ethyl-N-(4-(4-(trifluoromethoxy)phenylamino)benzyl)imidazo[1,2-a] pyridine-3-carboxamide (198)



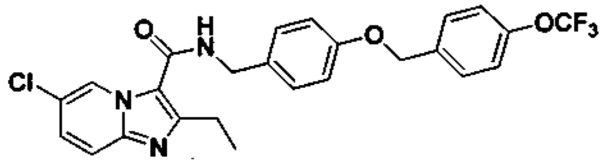
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 4.64 (d, J = 5.6 Hz, 2H), 5.74 (s, 1H), 6.07 (brs, 1H), 7.04 (d, J = 7.2 Hz, 2H), 7.06 (d, J = 7.2 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 7.28-7.32 (m, 3H), 7.54 (d, J = 9.2 Hz, 1H), 9.54 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 489.22

7-Chloro-2-ethyl-N-(4-(4-(trifluoromethoxy)phenylamino)benzyl)imidazo[1,2-a] pyridine-3-carboxamide (199)



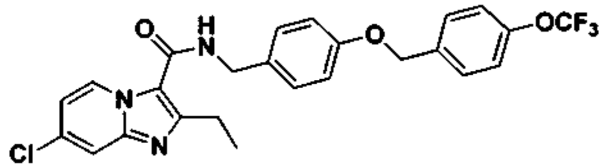
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 4.63 (d, J = 5.6 Hz, 2H), 5.74 (s, 1H), 6.05 (brs, 1H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.04 (d, J = 9.2 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 9.2 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 1.6 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 489.22

6-Chloro-2-ethyl-N-(4-(4-(trifluoromethyl)benzyloxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (200)



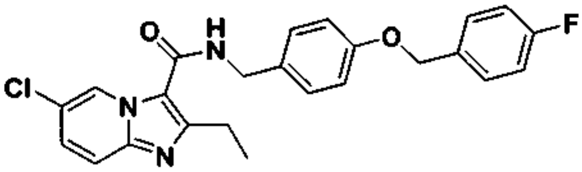
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.96 (q, J = 7.6 Hz, 2H), 4.64 (d, J = 5.6 Hz, 2H), 5.06 (s, 2H), 6.05 (brs, 1H), 6.97 (d, J = 8.4 Hz, 2H), 7.20-7.33 (m, 5H), 7.46 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 9.2 Hz, 2H), 9.53 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 504.25

7-Chloro-2-ethyl-N-(4-(4-(trifluoromethyl)benzyloxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (201)



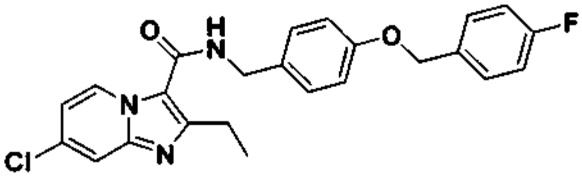
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 4.63 (d, J = 5.6 Hz, 2H), 5.06 (s, 2H), 6.03 (brs, 1H), 6.90 (dd, J = 7.6, 2.0 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 2.0 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 504.25

6-Chloro-2-ethyl-N-(4-(4-fluorobenzyloxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (202)



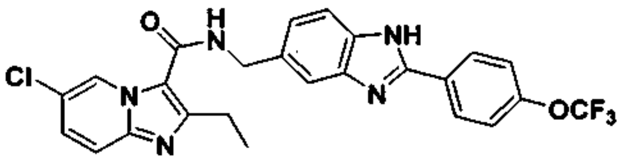
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.96 (q, J = 7.6 Hz, 2H), 4.63 (d, J = 5.6 Hz, 2H), 5.03 (s, 2H), 6.04 (brs, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.28-7.32 (m, 3H), 7.40 (dd, J = 8.8 Hz, 2H), 7.53 (d, J = 9.2 Hz, 1H), 9.53 (d, J = 1.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 438.20

7-Chloro-2-ethyl-N-(4-(4-fluorobenzyloxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (203)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 4.62 (d, J = 5.6 Hz, 2H), 5.03 (s, 2H), 6.02 (brs, 1H), 6.90 (dd, J = 7.6, 2.4 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.07 (dd, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.40 (dd, J = 8.8 Hz, 2H), 7.58 (d, J = 1.6 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 438.20

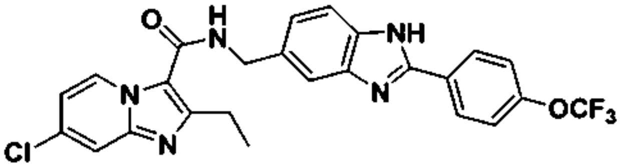
6-Chloro-2-ethyl-N-((2-(4-(trifluoromethoxy)phenyl)-1H-benzo[d]imidazol-5-yl)methyl) imidazo[1,2-a]pyridine-3-carboxamide (204)



^{1}H NMR (400 MHz, DMSO-d_6) 1.26 (m, 3H), 2.97-3.03 (m, 2H), 4.65 (t,□ J = 6.4 Hz, 2H), 7.24 (dd, J = 18.4, 8.0 Hz, 1H), 7.45 (d, J = 9.6, 2.4 Hz, 1H), 7.51-7.56 (m, 3H), 7.65-7.68

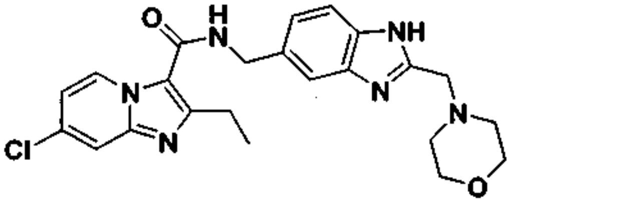
(m, 2H), 8.24-8.28 (m, 1H), 8.52-8.56 (m, 1H), 9.09-7.10 (m, 1H), 12.96 (ss, 1H); LCMS (electrospray) m/z $(M+H)^+$ 514.38

7-Chloro-2-ethyl-N-((2-(4-(trifluoromethoxy)phenyl)-1H-benzo[d]imidazol-5-yl)methyl) imidazo[1,2-a]pyridine-3-carboxamide (205)



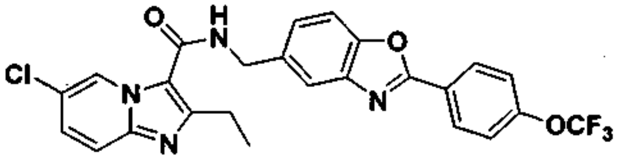
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 2.97 (q, J = 7.6 Hz, 2H), 4.82 (d, J = 5.6 Hz, 2H), 6.19 (brs, 1H), 6.90 (dd, J = 7.6, 2.0 Hz, 1H), 7.30 (m, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.50-7.52 (m, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.81 (m, 1H), 8.07 (d, J = 8.8 Hz, 2H), 9.37 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 514.31

7-Chloro-2-ethyl-N-((2-(morpholinomethyl)-1H-benzo[d]imidazol-5-yl)methyl) imidazo[1,2-a]pyridine-3-carboxamide (206)



^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.28 (m, 3H), 2.44 (m, 4H), 2.98 (q, J = 7.6 Hz, 2H), 3.59 (m, 4H), 3.69 (s, 2H), 4.61 (m, 2H), 6.19 (brs, 1H), 7.09 (dd, J = 9.6, 2.0 Hz, 1H), 7.18 (dd, J = 9.6, 7.2 Hz, 1H), 7.41 (m, 1H), 7.51 (m, 1H), 7.79 (d, J = 2.0 Hz, 1H), 8.52 (m, 1H), 8.96 (d, J = 7.6 Hz, 1H), 9.37 (d, J = 7.6 Hz, 1H), 12.27 (m, 1H); LCMS (electrospray) m/z $(M+H)^+$ 453.39

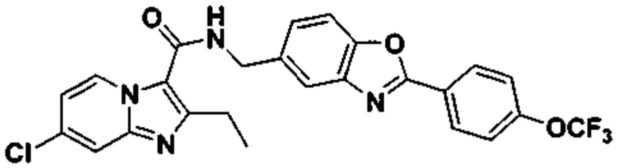
6-Chloro-2-ethyl-N-((2-(4-(trifluoromethoxy)phenyl)benzo[d]oxazol-5-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (207)



White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.40 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.82 (d, J = 6.0 Hz, 2H), 6.20 (brs, 1H), 7.31 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.42 (dd, J = 1.6 Hz, 8.4 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.77

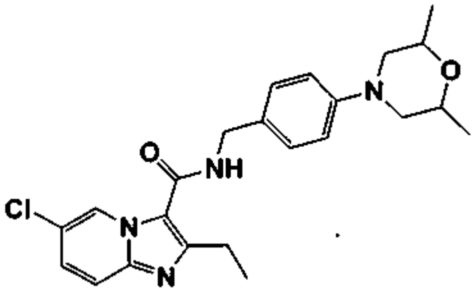
(s, 1H), 8.29 (d, J = 8.8 Hz, 2H), 9.55 (d, J = 1.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 515, 517 (Cl^- isotope pattern).

7-Chloro-2-ethyl-N-((2-(4-(trifluoromethoxy)phenyl)benzo[d]oxazol-5-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (208)



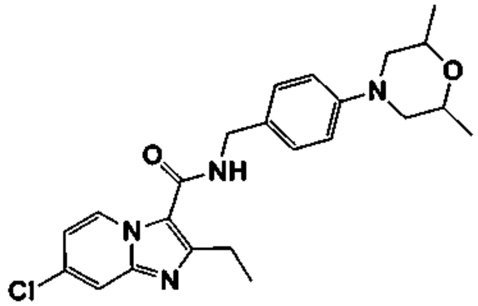
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.40 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 4.82 (d, J = 6.0 Hz, 2H), 6.19 (brs, 1H), 6.92 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.41 (dd, J = 2.0 Hz, 8.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.77 (s, 1H), 8.28 (d, J = 8.8 Hz, 2H), 9.38 (d, J = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 515, 517 (Cl^- isotope pattern).

6-Chloro-N-(4-(2,6-dimethylmorpholino)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (209)



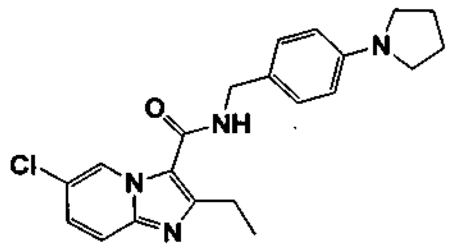
White solid; mp = 176 – 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H),), 1.27 (s, 3H), 1.39 (t, J = 7.6 Hz, 3H), 2.42 (t, J = 11.2 Hz, 2H), 2.95 (q, J = 7.2 Hz, 2H), 3.46 (d, J = 10.4 Hz, 2H), 3.78 – 3.82 (m, 2H), 4.61 (d, J = 5.6 Hz, 2H), 6.00 – 6.02 (m, 1H), 6.91 (d, J = 8.8 Hz, 1H), 7.26 – 7.31 (m, 3H), 7.54 (d, J = 9.2 Hz, 1H), 9.53 (d, J = 2.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 427.32

7-Chloro-N-(4-(2,6-dimethylmorpholino)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (210)



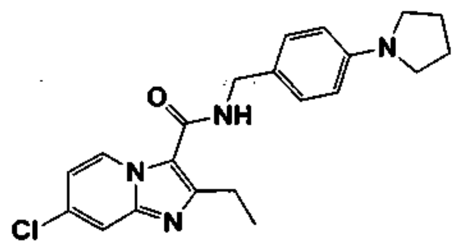
White solid; mp = 165 – 166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.27 (s, 3H), 1.38 (t, J = 7.6 Hz, 3H), 2.42 (t, J = 11.2 Hz, 2H), 2.94 (q, J = 7.6 Hz, 2H), 3.45 (d, J = 10.4 Hz, 2H), 3.76 – 3.84 (m, 2H), 4.60 (d, J = 5.6 Hz, 2H), 5.99 – 6.01 (m, 1H), 6.89 – 6.92 (m, 3H), 7.28 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 2.0 Hz, 1H), 9.35 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 427.32

6-Chloro-2-ethyl-N-(4-(pyrrolidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (211)



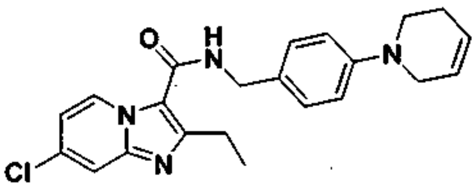
White solid; mp = 222 – 223 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.4 Hz, 3H), 1.99 – 2.03 (m, 4H), 2.94 (q, J = 7.6 Hz, 2H), 3.29 (t, J = 6.6 Hz, 4H), 4.57 (d, J = 5.6 Hz, 2H), 5.95 – 5.97 (m, 1H), 6.56 (d, J = 8.4 Hz, 2H), 7.22 – 7.30 (m, 6H), 7.53 (d, J = 9.6 Hz, 1H), 9.53 (d, J = 1.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 383.24

7-Chloro-2-ethyl-N-(4-(pyrrolidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (212)



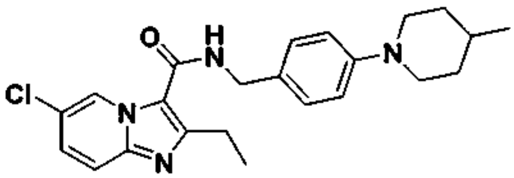
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 – 1.42 (m, 3H), 1.93 – 1.96 (m, 2H), 1.99 – 2.02 (m, 2H), 2.90 – 2.99 (m, 2H), 3.28 (t, J = 6.4 Hz, 2H), 3.38 (t, J = 6.4 Hz, 2H), 4.57 (d, J = 4.8 Hz, 2H), 5.95 – 6.02 (m, 1H), 6.56 (d, J = 8.4 Hz, 2H), 6.85 – 6.92 (m, 1H), 7.14 – 7.31 (m, 3H), 7.57 – 7.59 (m, 1H), 9.36 (d, J = 7.6 Hz, 1H)

7-Chloro-N-(4-(5,6-dihydropyridin-1(2H)-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (213)



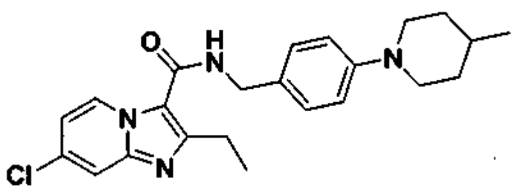
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 2.29-2.32 (m, 2H), 2.94 (q, J = 7.6 Hz, 2H), 3.38 (t, J = 5.6 Hz, 2H), 3.68-3.72 (m, 2H), 4.59 (d, J = 5.6 Hz, 2H), 5.79-5.82 (m, 1H), 5.88-5.91 (m, 1H), 5.99 (brs, 1H), 6.88-6.93 (m, 3H), 7.27 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 1.6 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 395.35

6-Chloro-2-ethyl-N-(4-(4-methylpiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (214)



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.4 Hz, 3H), 1.35 (m, 2H), 1.38 (t, J = 7.6 Hz, 3H), 1.53 (m, 1H), 1.72-1.76 (m, 2H), 2.66-2.73 (m, 2H), 2.95 (q, J = 7.6 Hz, 2H), 3.64-3.67 (m, 2H), 4.59 (d, J = 5.6 Hz, 2H), 5.99 (brs, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 7.29 (dd, J = 9.6, 2.0 Hz, 1H), 7.53 (d, J = 9.6 Hz, 1H), 9.53 (d, J = 1.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 411.40

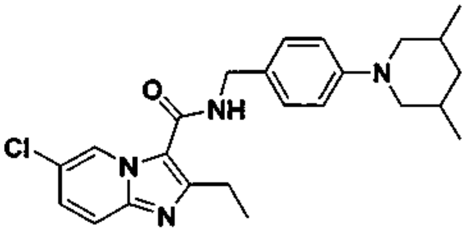
7-Chloro-2-ethyl-N-(4-(4-methylpiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (215)



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.8 Hz, 3H), 1.35 (m, 2H), 1.37 (t, J = 7.6 Hz, 3H), 1.51-1.53 (m, 1H), 1.72-1.75 (m, 2H), 2.66-2.73 (m, 2H), 2.94 (q, J = 7.6 Hz, 2H), 3.64-3.67 (m, 2H), 4.59 (d, J = 5.6 Hz, 2H), 5.98 (brs, 1H), 6.90 (dd, J = 7.6, 2.4 Hz, 1H), 6.93 (d, J =

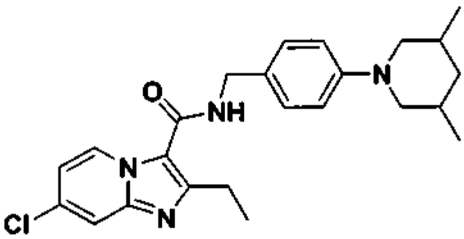
8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 2.4 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 411.40

6-Chloro-*N*-(4-(3,5-dimethylpiperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (216)



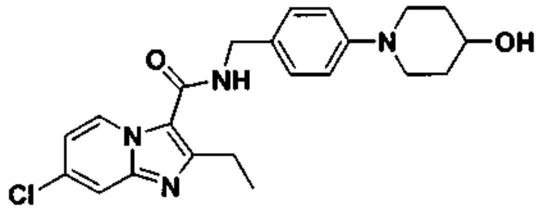
Pale yellow solid; mp = 157.2 – 158.0 °C; ^1H NMR (400 MHz, $CDCl_3$); δ 0.91 (d, J = 6.4 Hz, 6H), 1.35 (t, J = 7.6 Hz, 3H), 1.73 – 1.81 (m, 4H), 2.16 (dd, J = 11.6, 11.6 Hz, 2H), 2.90 (q, 7.6 Hz, 2H), 3.58 – 3.61 (m, 2H), 4.56 (d, J = 5.6 Hz, 2H), 6.01 (brs, 1H), 6.90 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 2.0, 9.6 Hz, 1H), 7.49 (d, J = 9.6 Hz, 1H), 9.49 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 13.3, 19.6, 23.6, 30.9, 42.2, 43.4, 57.2, 115.4, 116.6, 117.0, 121.5, 126.3, 127.8, 128.2, 128.9, 144.5, 151.3, 151.4, 161.1; LCMS (electrospray) m/z $(M+H)^+$ 425, 427 (Cl^- isotope pattern).

7-Chloro-*N*-(4-(3,5-dimethylpiperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (217)



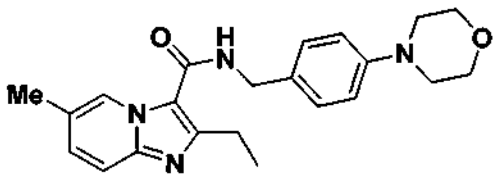
Pale yellow solid; mp = 181.5 – 182.8 °C; ^1H NMR (400 MHz, $CDCl_3$); δ 0.92 (d, J = 6.8 Hz, 6H), 1.35 (t, J = 7.6 Hz, 3H), 1.74 – 1.82 (m, 4H), 2.17 (dd, J = 11.6, 11.6 Hz, 2H), 2.90 (q, 7.6 Hz, 2H), 3.59 – 3.62 (m, 2H), 4.57 (d, J = 5.2 Hz, 2H), 6.01 (brs, 1H), 6.87 (dd, J = 2.0, 7.6 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 2.0 Hz, 1H), 9.33 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 13.4, 19.6, 23.6, 30.9, 42.2, 43.4, 57.2, 114.7, 115.1, 115.7, 116.6, 127.8, 128.6, 128.9, 133.6, 146.1, 151.3, 151.6, 161.1; LCMS (electrospray) m/z $(M+H)^+$ 425, 427 (Cl^- isotope pattern).

7-Chloro-2-ethyl-*N*-(4-(4-hydroxypiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (218)



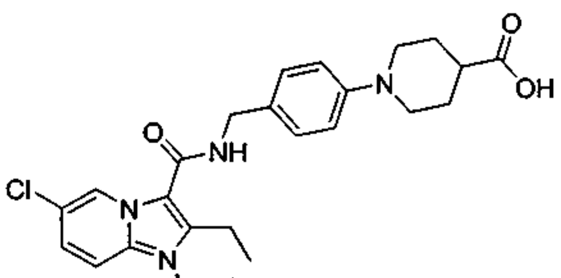
Pale yellow solid; mp = 179.1 – 180.0 °C; ^{1}H NMR (400 MHz, DMSO-*d6*); δ 1.22 (t, *J* = 7.2Hz, 3H), 1.39 – 1.48 (m, 2H), 1.76 – 1.81 (m, 2H), 2.76 – 2.82 (m, 2H), 2.92 (q, *J* = 7.2 Hz, 2H), 3.46 – 3.51 (m, 2H), 3.57 – 3.62 (m, 1H), 4.39 (d, *J* = 5.6 Hz, 2H), 4.64 (d, *J* = 4.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.07 (dd, *J* = 2.0, 7.2 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 2.0 Hz, 1H), 8.37 (t, *J* = 5.6 Hz, 1H), 8.93 (d, *J* = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 413, 415 (Cl^- isotope pattern).

2-ethyl-6-methyl-N-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (219)



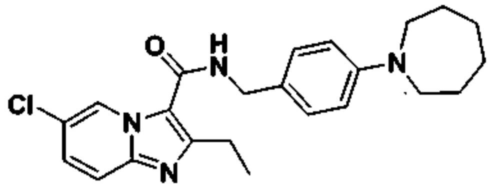
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.2 Hz, 3H), 2.35 (s, 3H), 2.94 (q, *J* = 7.6 Hz, 2H), 3.15 (t, *J* = 4.8 Hz, 4H). 3.86 (t, *J* = 4.Hz, 4H), 4.61 (d, *J* = 5.2 Hz, 2H), 6.00 (brs, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.16 (dd, *J* = 2.0 Hz, 9.2 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 9.2 Hz, 1H), 9.20 (s, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 379.

1-(4-((6-Chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamido)methyl)phenyl)piperidine-4-carboxylic acid (220)



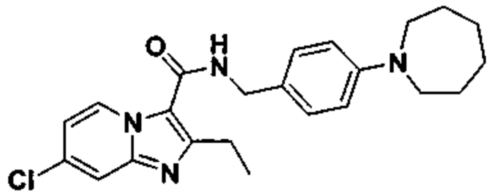
White solid; ^{1}H NMR (400 MHz, DMSO-d^6); δ 1.23 (t, *J* = 7.6 Hz, 3H), 1.57 – 1.67 (m, 2H), 1.85 – 1.89 (m, 2H), 2.34 – 2.41 (m, 1H), 2.68 – 2.74 (m, 2H), 2.94 (q, *J* = 7.6 Hz, 2H), 3.58 – 3.61 (m, 2H), 4.41 (d, *J* = 5.6 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.43 (dd, J = 2.0, 9.6 Hz, 1H), 7.64 (d, J = 9.6 Hz, 1H), 8.38 (brt, J = 5.6 Hz, 1H), 9.05 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z 441 $(M+H)^+$.

N-(4-(Azepan-1-yl)benzyl)-6-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (221)



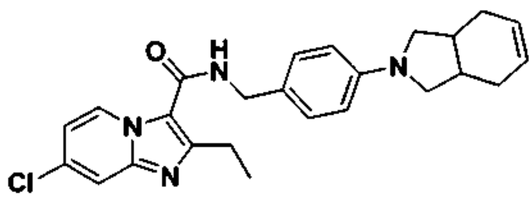
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 1.38 (m, 4H), 1.53-1.56 (m, 4H), 2.95 (q, J = 7.6 Hz, 2H), 3.45 (t, J = 5.6 Hz, 4H), 4.56 (d, J = 5.6 Hz, 2H), 5.97 (brs, 1H), 6.68 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.28 (dd, J = 9.6, 2.0 Hz, 2H), 7.53 (d, J = 9.6 Hz, 1H), 9.53 (d, J = 2.4 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 411.40

N-(4-(Azepan-1-yl)benzyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (222)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 1.52-1.55 (m, 4H), 1.78 (m, 4H), 2.94 (q, J = 7.6 Hz, 2H), 3.45 (t, J = 6.0 Hz, 4H), 4.56 (d, J = 5.2 Hz, 2H), 5.95 (brs, 1H), 6.67 (d, J = 8.8 Hz, 2H), 6.89 (dd, J = 7.6, 2.4 Hz, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 2.4 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 411.40

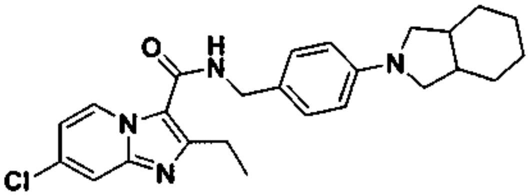
7-Chloro-N-(4-(3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (223)



White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36 (t, J = 7.6 Hz, 3H), 1.96 (dd, J = 4.0 Hz, 16.4 Hz, 2H), 2.25 – 2.31 (m, 2H), 2.45(dd, J = 5.2 Hz, 8.8 Hz, 2H), 2.92 (q, J = 7.6 Hz, 2H), 3.11 (dd, J = 5.2 Hz, 8.8 Hz, 2H), 3.39 (dd, J = 6.4 Hz, 8.8 Hz, 2H), 4.55 (d, J = 5.2 Hz, 2H), 5.67 (s, 2H), 5.94 (brs, 1H), 6.51 (d, J = 8.8 Hz, 2H), 6.89 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.22

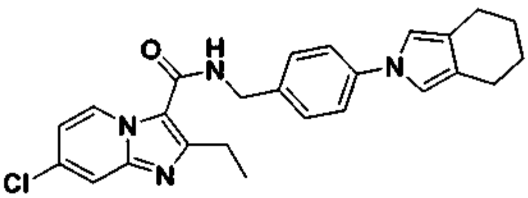
(d, J = 8.8 Hz, 2H), 7.57 (d, J = 2.0 Hz, 1H), 9.35 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 435, 437 (Cl^- isotope pattern).

N-(4-(1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)benzyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (224)



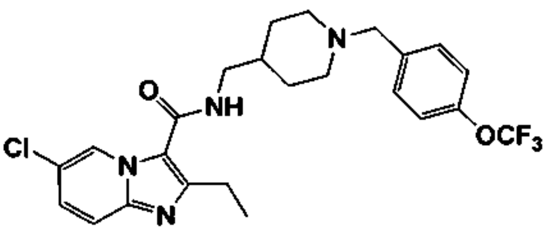
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36 (t, J = 7.6 Hz, 3H), 1.40 – 2.03 (m, 8H), 2.29 – 2.34 (m, 2H), 2.92 (q, J = 7.2 Hz, 2H), 3.16 (dd, J = 5.2 Hz, 9.2 Hz, 2H), 3.29 (dd, J = 6.8 Hz, 8.8 Hz, 2H), 4.55 (d, J = 5.2 Hz, 2H), 5.97 (brs, 1H), 6.49 (d, J = 8.4 Hz, 2H), 6.88 (dd, J = 2.4 Hz, 7.6 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 2.4 Hz, 1H), 9.33 (d, J = 7.6 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 437, 439 (Cl^- isotope pattern)

7-Chloro-2-ethyl-N-(4-(4,5,6,7-tetrahydro-2H-isoindol-2-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (225)



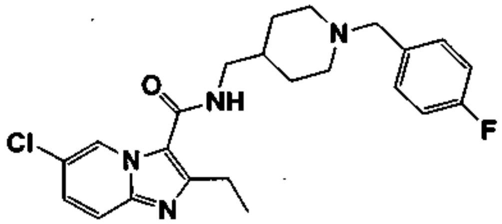
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.39 (t, J = 7.6 Hz, 3H), 1.74 – 1.77 (m, 4H), 2.63 (m, 4H), 2.97 (q, J = 7.6 Hz, 2H), 4.68 (d, J = 6.0 Hz, 2H), 6.14 (brs, 1H), 6.78 (s, 2H), 6.91 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 2.0 Hz, 1H), 9.36 (d, J = 7.2 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 433, 435 (Cl^- isotope pattern).

6-Chloro-2-ethyl-N-((1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (226)



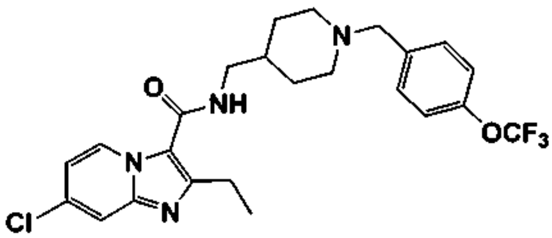
White solid; mp = 171 - 172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 – 1.41 (m, 2H), 1.44 (t, J = 7.6 Hz, 3H), 1.63 – 1.72 (m, 1H), 1.74 – 1.77 (m, 2H), 1.99 – 2.05 (m, 2H), 2.90 – 2.93 (m, 2H), 3.00 (q, J = 7.6 Hz, 2H), 3.41 (t, J = 6.2 Hz, 2H), 3.51 (s, 2H), 5.89 (t, J = 5.4Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.28 (dd, J = 2.4, 9.6 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 9.6 Hz, 1H), 9.49 (d, J = 1.6 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 495.34

6-Chloro-2-ethyl-N-((1-(4-fluorobenzyl)piperidin-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (227)



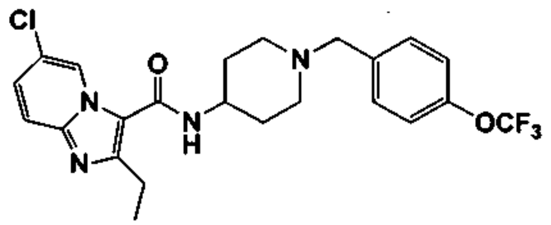
White solid; mp = 176 - 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 – 1.39 (m, 2H), 1.44 (t, J = 7.6 Hz, 3H), 1.62 – 1.70 (m, 1H), 1.72 – 1.76 (m, 2H), 1.95 – 2.00 (m, 2H), 2.88 – 2.91 (m, 2H), 2.99 (q, J = 7.6 Hz, 2H), 3.05 (t, J = 6.4 Hz, 2H), 3.46 (s, 2H), 5.87 – 5.89 (m, 1H), 6.99 (dd, J = 8.4, 8.8 Hz, 2H), 7.25 – 7.30 (m, 3H), 7.53 (d, J = 9.6 Hz, 1H), 9.48 (d, J = 1.6 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 429.29

7-Chloro-2-ethyl-N-((1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (228)



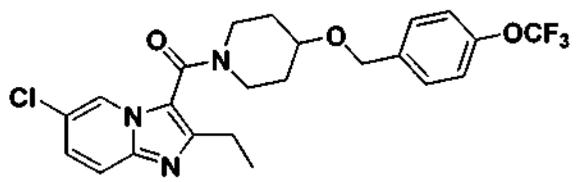
White solid; mp = 145 - 146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 – 1.39 (m, 2H), 1.44 (t, J = 7.6 Hz, 3H), 1.62 – 1.69 (m, 1H), 1.72 – 1.76 (m, 2H), 1.96 – 2.02 (m, 2H), 2.88 – 2.91 (m, 2H), 2.99 (q, J = 7.6 Hz, 2H), 3.41 (t, J = 6.4 Hz, 2H), 3.48 (s, 2H), 5.87 (t, J = 5.4 Hz, 1H), 6.88 (dd, J = 2.0, 7.6 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 2.4 Hz, 1H), 9.31 (d, J = 7.2 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 495.20

6-Chloro-2-ethyl-N-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (229)



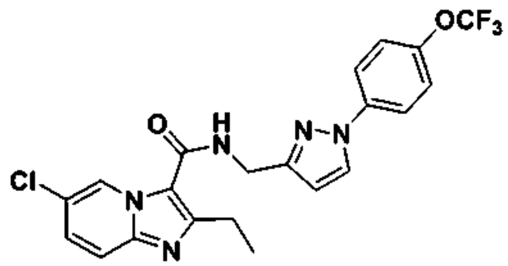
White solid; mp = 157 - 158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.6 Hz, 3H), 1.56 – 1.66 (m, 2H), 2.05 – 2.10 (m, 1H), 2.22 – 2.27 (m, 2H), 2.81 – 2.84 (m, 2H), 2.98 (q, J = 7.6 Hz, 2H), 3.53 (s, 2H), 4.08 – 4.11 (m, 1H), 5.69 – 5.71 (m, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.29 (dd, J = 2.0, 9.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 9.2 Hz, 1H), 9.46 (d, J = 1.6 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 481.26

(6-Chloro-2-ethylimidazo[1,2-a]pyridin-3-yl)(4-(4-(trifluoromethoxy)benzyloxy) piperidin-1-yl)methanone (230)



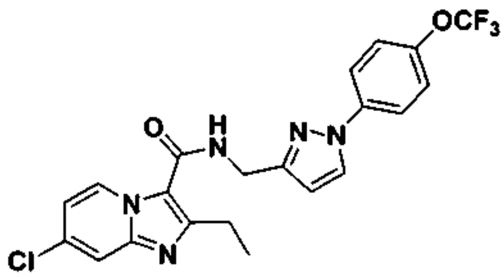
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.2 Hz, 3H), 1.71-1.78 (m, 2H), 1.94 (m, 2H), 2.78 (q, J = 7.6 Hz, 2H), 3.51 (m, 2H), 3.74 (m, 1H), 3.89 (m, 2H), 4.58 (s, 2H), 7.19-7.23 (m, 3H), 7.38 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 9.6 Hz, 1H), 8.48 (s, 1H); LCMS (electrospray) m/z $(M+H)^+$ 481.26

6-Chloro-2-ethyl-N-((1-(4-(trifluoromethoxy)phenyl)-1H-pyrazol-3-yl)methyl) imidazo[1,2-a]pyridine-3-carboxamide (231)



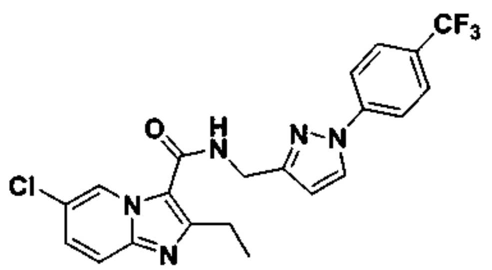
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (t, J = 7.6 Hz, 3H), 3.12 (q, J = 7.6 Hz, 2H), 4.80 (d, J = 4.8 Hz, 2H), 6.49 (d, J = 2.4 Hz, 2H), 6.69 (brs, 1H), 7.29-7.33 (m, 3H), 7.55 (d, J = 9.2 Hz, 1H), 7.70 (d, J = 9.2 Hz, 2H), 7.90 (d, J = 2.4 Hz, 1H), 9.56 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 464.19

7-Chloro-2-ethyl-N-((1-(4-(trifluoromethoxy)phenyl)-1H-pyrazol-3-yl)methyl) imidazo[1,2-a]pyridine-3-carboxamide (232)



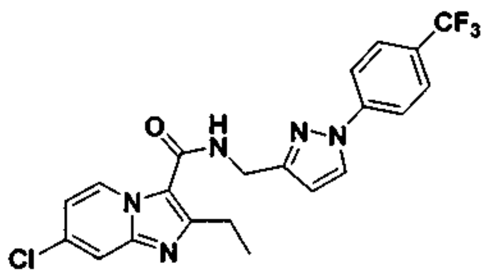
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (t, J = 7.6 Hz, 3H), 3.11 (q, J = 7.6 Hz, 2H), 4.79 (d, J = 5.2 Hz, 2H), 6.48 (d, J = 2.4 Hz, 2H), 6.68 (brs, 1H), 6.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 2.0 Hz, 1H), 7.70 (d, J = 6.8 Hz, 2H), 7.90 (d, J = 2.0 Hz, 1H), 9.39 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 464.19

6-Chloro-2-ethyl-N-((1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)methyl)imidazo [1,2-a]pyridine-3-carboxamide (233)



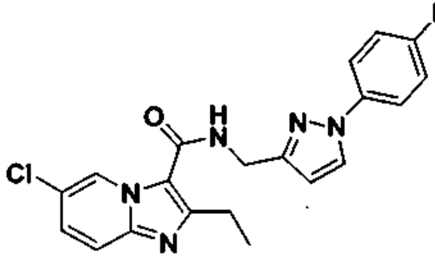
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (t, J = 7.6 Hz, 3H), 3.02 (q, J = 7.6 Hz, 2H), 4.62 (d, J = 5.6 Hz, 2H), 6.59 (d, J = 2.8 Hz, 1H), 7.46 (dd, J = 9.2, 1.6 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 8.55 (t, J = 5.6 Hz, 1H), 8.62 (d, J = 2.4 Hz, 1H), 9.10 (d, J = 2.0 Hz, 2H); LCMS (electrospray) m/z $(M+H)^+$ 448.37

7-Chloro-2-ethyl-N-((1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)methyl)imidazo [1,2-a]pyridine-3-carboxamide (234)



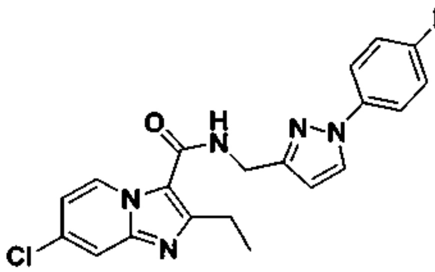
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (t, J = 7.6 Hz, 3H), 3.02 (q, J = 7.6 Hz, 2H), 4.61 (d, J = 5.6 Hz, 2H), 6.58 (d, J = 2.8 Hz, 1H), 7.11 (dd, J = 7.6, 2.0 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.8 Hz, 2H), 8.52 (t, J = 5.6 Hz, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.97 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 448.13

6-Chloro-2-ethyl-N-((1-(4-fluorophenyl)-1H-pyrazol-3-yl)methyl)imidazo[1,2-a] pyridine-3-carboxamide (235)



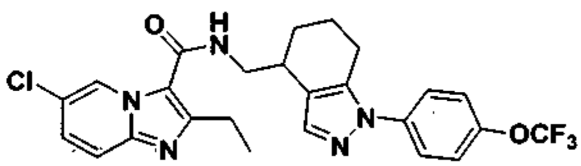
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (t, J = 7.6 Hz, 3H), 3.11 (q, J = 7.6 Hz, 2H), 4.79 (d, J = 4.8 Hz, 2H), 6.46 (d, J = 2.0 Hz, 1H), 6.70 (brs, 1H), 7.16 (dd, J = 8.8 Hz, 2H), 7.30 (dd, J = 9.2, 2.0 Hz, 1H), 7.55 (d, J = 9.6 Hz, 1H), 7.61-7.64 (m, 2H), 7.85 (d, J = 2.4 Hz, 1H), 9.56 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 398.32

7-Chloro-2-ethyl-N-((1-(4-fluorophenyl)-1H-pyrazol-3-yl)methyl)imidazo[1,2-a] pyridine-3-carboxamide (236)



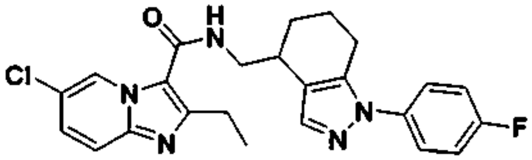
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, J = 7.6 Hz, 3H), 3.11 (q, J = 7.6 Hz, 2H), 4.78 (d, J = 4.8 Hz, 2H), 6.46 (d, J = 2.0 Hz, 1H), 6.69 (brs, 1H), 6.91 (dd, J = 7.6, 2.4 Hz, 1H), 7.16 (dd, J = 8.8 Hz, 2H), 7.59-7.64 (m, 3H), 7.85 (d, J = 2.4 Hz, 1H), 9.39 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 398.14

6-Chloro-2-ethyl-N-((1-(4-(trifluoromethoxy)phenyl)-4,5,6,7-tetrahydro-1H-indazol-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (237)



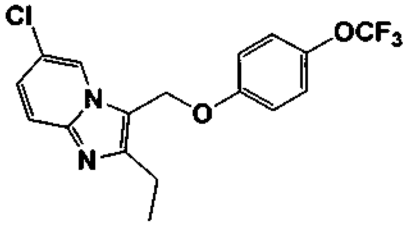
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.6 Hz, 3H), 1.89-1.98 (m, 3H), 2.27 (m, 1H), 2.77-2.84 (m, 2H), 2.96 (q, J = 7.6 Hz, 2H), 5.40 (m, 1H), 5.96 (d, J = 8.0 Hz, 1H), 7.29-7.34 (m, 3H), 7.54-7.58 (m, 3H), 7.70 (s, 1H), 9.54 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 504.25

6-Chloro-2-ethyl-N-((1-(4-fluorophenyl)-4,5,6,7-tetrahydro-1H-indazol-4-yl)methyl) imidazo[1,2-a]pyridine-3-carboxamide (238)



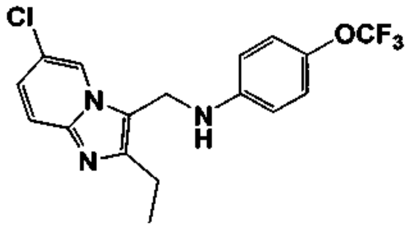
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 1.88-1.97 (m, 3H), 2.26 (m, 1H), 2.74-2.78 (m, 2H), 2.96 (q, J = 7.6 Hz, 2H), 5.40 (m, 1H), 5.96 (d, J = 7.6 Hz, 1H), 7.17 (dd, J = 8.0, 8.8 Hz, 2H), 7.31 (dd, J = 9.2, 2.0 Hz, 1H), 7.48-7.50 (m, 2H), 7.55 (d, J = 9.2 Hz, 1H), 7.68 (s, 1H), 9.54 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 438.40

6-Chloro-2-ethyl-3-((4-(trifluoromethoxy)phenoxy)methyl)imidazo[1,2-a]pyridine (239)



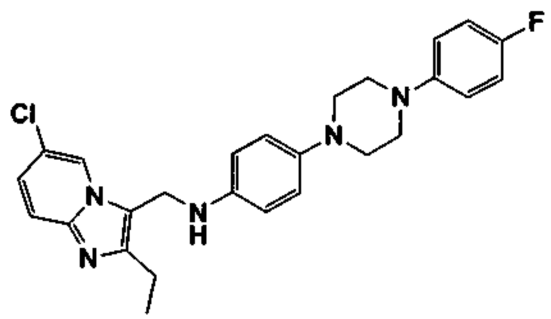
White solid; mp = 127 - 128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.6 Hz, 3H), 2.82 (q, J = 7.6 Hz, 2H), 5.27 (s, 2H), 7.00 (d, J = 9.2 Hz, 2H), 7.19 (d, J = 9.2 Hz, 2H), 7.53 (dd, J = 0.8, 9.2 Hz, 1H), 8.12 (dd, J = 0.8, 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 371.07

N-((6-Chloro-2-ethylimidazo[1,2-a]pyridin-3-yl)methyl)-4-(trifluoromethoxy)aniline (240)



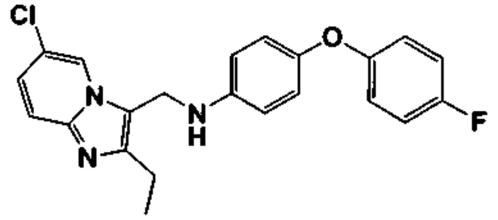
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (J = 7.6 Hz, 3H), 2.82 (q, J = 7.2 Hz, 2H), 3.67 (t, J = 4.6 Hz, 1H), 4.50 (d, J = 5.2 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.51 (dd, J = 2.0, 9.6 Hz, 1H), 7.51 (d, J = 9.6 Hz, 1H), 8.10 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 370.11

N-((6-Chloro-2-ethylimidazo[1,2-a]pyridin-3-yl)methyl)-4-(4-(4-fluorophenyl)piperazin-1-yl)aniline (241)



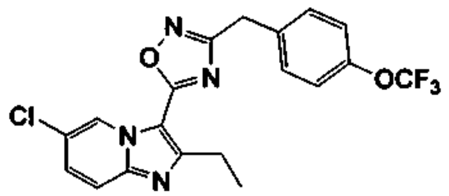
White solid; mp = 191 - 192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (*J* = 7.6 Hz, 3H), 2.82 (q, *J* = 7.2 Hz, 2H), 3.22 – 3.24 (m, 4H), 3.26 – 3.28 (m, 4H), 3.40 (br s, 1H), 4.50 (s, 2H), 6.75 (d, J = 8.8 Hz, 2H), 6.92 – 7.01 (m, 6H), 7.14 (dd, J = 1.6, 9.2 Hz, 1H), 7.51 (d, *J* = 9.6 Hz, 1H), 8.18 (d, *J* = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 464.32

N-((6-Chloro-2-ethylimidazo[1,2-a]pyridin-3-yl)methyl)-4-(4-fluorophenoxy)aniline (242)



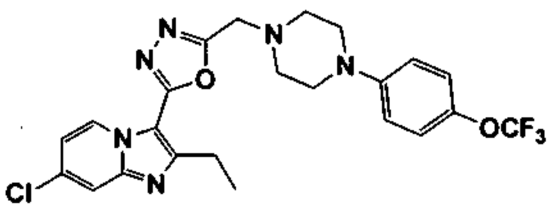
White solid; mp = 148.6 – 148.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.4 Hz, 3H), 2.82 (q, *J* = 7.6 Hz, 2H), 4.50 (s, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.90 – 7.01 (m, 6H), 7.15 (dd, *J* = 2.0, 9.6 Hz, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 8.16 (d, *J* = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 396.17

5-(6-Chloro-2-ethylimidazo[1,2-a]pyridin-3-yl)-3-(4-(trifluoromethoxy)benzyl)-1,2,4-oxadiazole (243)



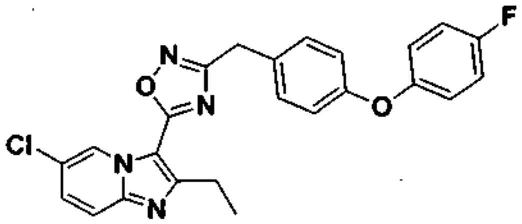
Pale yellow solid; mp = 146.4 – 146.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.6 Hz, 3H), 3.22 (q, *J* = 7.2 Hz, 2H), 4.20 (s, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.40 (dd, *J* = 2.0, 9.6 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 9.6 Hz, 1H), 8.47 (d, *J* = 1.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 423.10

2-(7-Chloro-2-ethylimidazo[1,2-a]pyridin-3-yl)-5-((4-(4-(trifluoromethoxy)phenyl)piperazin-1-yl)methyl)-1,3,4-oxadiazole (244)



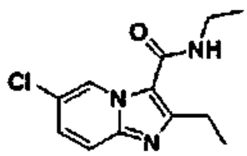
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) 1.41 (t,□ J = 7.4 Hz, 3H), 2.83 (t, J = 4.8 Hz, 4H), 3.16 (q, J = 7.6 Hz, 2H), 3.23 (t, J = 4.8 Hz, 4H), 4.02 (s, 2H), 6.88 (d, J = 9.2 Hz, 2H), 7.05 (dd, J = 2.0, 9.6 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 1.6 Hz, 1H), 9.42 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 507.24

5-(6-Chloro-2-ethylimidazo[1,2-a]pyridin-3-yl)-3-(4-(4-fluorophenoxy)benzyl)-1,2,4-oxadiazole (245)



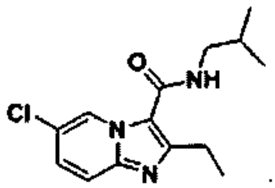
Yellow solid; mp = 129.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ□1.41 (t, J = 7.8 Hz, 3H), 3.22 (q, J = 7.2 Hz, 2H), 4.16 (s, 2H), 6.93 – 7.04 (m, 6H), 7.36 – 7.39 (m, 3H), 7.63 (d, J = 9.6 Hz, 1H), 9.48 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 449

6-Chloro-N,2-diethylimidazo[1,2-a]pyridine-3-carboxamide (246)



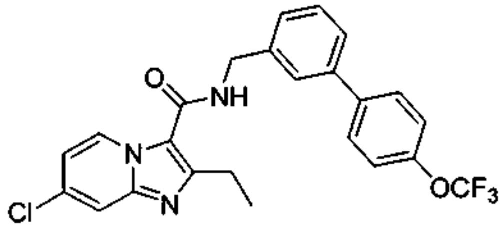
White solid; mp = 176.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.29 (t, J = 7.2 Hz, 3H), 1.43 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.2 Hz, 2H), 3.51 – 3.57 (m, 2H), 5.79 (brs, 1H), 7.27 (dd, J = 2.4 Hz, 9.6 Hz, 1H), 7.51 (d, J = 9.6 Hz, 1H), 9.45 (d, J = 2.4 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 252.

6-Chloro-2-ethyl-N-isobutylimidazo[1,2-a]pyridine-3-carboxamide (247)



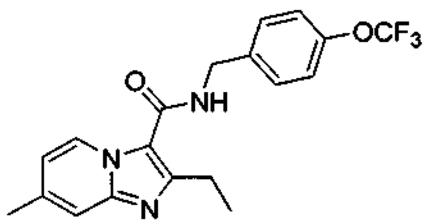
White solid; mp = 162.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.01 (d, J = 6.8 Hz, 6H), 1.45 (t, J = 7.6 Hz, 3H), 1.90 – 1.97 (m, 1H), 3.01 (q, J = 7.6 Hz, 2H), 3.34 (t, J = 6.8 Hz, 2H), 5.86 (brs, 1H), 7.28 (dd, J = 2.0 Hz, 9.6 Hz, 1H), 7.53 (d, J = 9.6 Hz, 1H), 9.47 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 280.

7-Chloro-2-ethyl-*N*-((4'-(trifluoromethoxy)biphenyl-3-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (248)



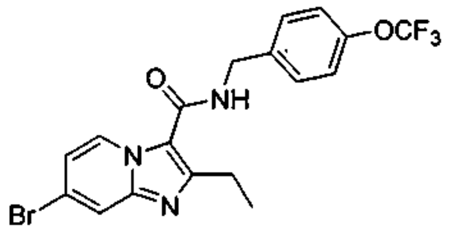
White solid; mp = 192.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, J = 7.2 Hz, 3H), 2.95 (q, J = 7.2 Hz, 2H), 4.75 (d, J = 6.0 Hz, 2H), 6.19 (brt, J = 6.0 Hz, 1H), 6.88 (dd, J = 2.0, 7.6 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.43 (dd, J = 7.2, 7.6 Hz, 1H), 7.48 – 7.59 (m, 5H), 9.33 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z 474, 476 $(M+H)^+$ (Cl^- isotope pattern).

2-Ethyl-7-methyl-*N*-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (249)



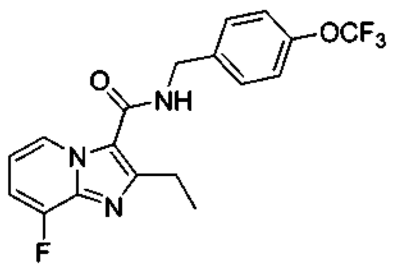
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.33 (t, J = 7.6 Hz, 3H), 2.91 (q, J = 7.6 Hz, 2H), 4.64 (d, J = 5.2 Hz, 2H), 6.25 (brt, J = 5.2 Hz, 1H), 6.69 (dd, J = 1.6, 7.2 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.30 (s, 1H), 7.35 (d, J = 8.4 Hz, 2H), 9.19 (d, J = 7.2 Hz, 1H).

7-Bromo-2-ethyl-*N*-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (250)



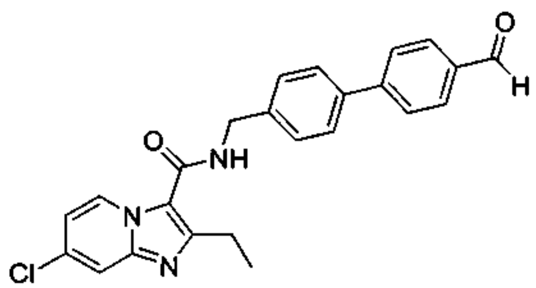
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, J = 7.6 Hz, 3H), 2.94 (q, J = 7.6 Hz, 2H), 4.67 (d, J = 5.6 Hz, 2H), 6.18 (brt, J = 5.6 Hz, 1H), 6.99 (dd, J = 1.6, 7.2 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 1.6 Hz, 1H), 9.25 (d, J = 7.2 Hz, 1H).

2-Ethyl-8-fluoro-*N*-(4-(trifluoromethoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide(251)



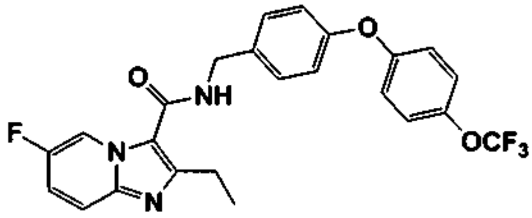
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.38 (t, J = 7.6 Hz, 3H), 2.97 (q, J = 7.6 Hz, 2H), 4.68 (d, J = 6.0 Hz, 2H), 6.25 (brs, 1H), 6.79 – 6.84 (m, 1H), 7.00 (dd, J = 8.0, 9.6 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 9.16 (d, J = 6.8 Hz, 1H).

7-Chloro-2-ethyl-*N*-((4'-formylbiphenyl-4-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide(252)



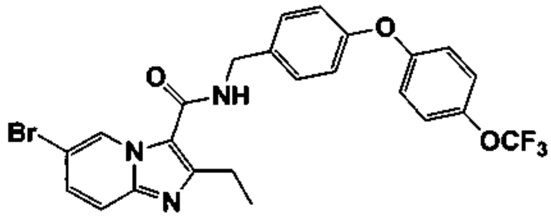
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.40 (t, J = 7.6 Hz, 3H), 2.97 (q, J = 7.6 Hz, 2H), 4.75 (d, J = 6.0 Hz, 2H), 6.18 (brt, J = 6.0 Hz, 1H), 6.89 (dd, J = 2.4, 7.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 2.4 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 9.36 (d, J = 7.6 Hz, 1H), 10.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.8, 43.4, 114.9, 115.9, 127.8, 128.0, 128.4, 128.7, 130.5, 133.8, 135.5, 138.7, 139.3, 146.3, 146.7, 151.9, 161.4, 192.0 (hidden 1 aromatic carbon).

2-Ethyl-6-fluoro-N-(4-(4-(trifluoromethoxy)phenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (253)



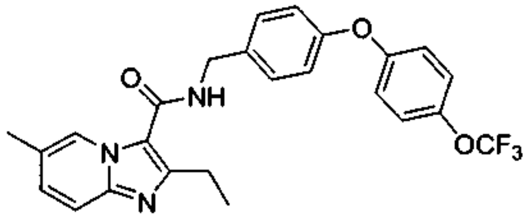
White solid; mp = 133.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.6 Hz, 3H), 3.00 (q, *J* = 7.6 Hz, 2H), 4.68 (d, *J* = 5.6 Hz, 2H), 6.12 – 6.14 (m, 1H), 6.98 – 7.03 (m, 4H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.23 – 7.28 (m, 1H), 7.58 (dd, *J* = 5.2, 9.6 Hz, 1H), 9.44 – 9.46 (m, 1H); LCMS (electrospray) m/z $(M+H)^+$ 474.

6-Bromo-2-ethyl-N-(4-(4-(trifluoromethoxy)phenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (254)



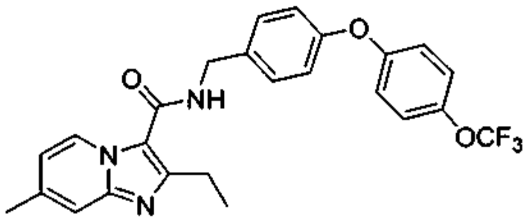
White solid; mp = 152.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.4 Hz, 3H), 2.99 (q, *J* = 7.6 Hz, 2H), 4.68 (d, *J* = 5.6 Hz, 2H), 6.12 - 6.14 (m, 1H), 6.98 – 6.03 (m, 4H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.40 (dd, *J* = 2.0, 9.6 Hz, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), 9.63 (d, *J* = 1.2 Hz, 1H)); LCMS (electrospray) m/z $(M+H)^+$ 534, 536 (Br^- isotope pattern).

2-Ethyl-6-methyl-*N*-(4-(4-(trifluoromethoxy)phenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (255)



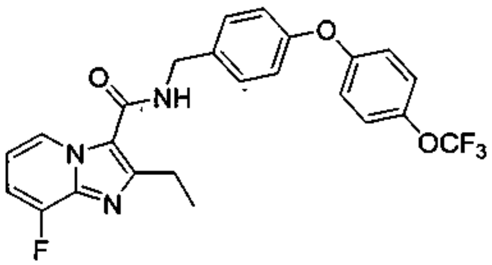
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.31 (t, *J* = 7.6 Hz, 3H), 2.30 (s, 3H), 2.90 (q, *J* = 7.6 Hz, 2H), 4.62 (d, *J* = 5.6 Hz, 2H), 6.32 (brt, *J* = 5.6 Hz, 1H), 6.93 – 6.96 (m, 4H), 7.11 – 7.14 (m, 3H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 9.11 (s, 1H); LCMS (electrospray) m/z 470 $(M+H)^+$.

2-Ethyl-7-methyl-*N*-(4-(4-(trifluoromethoxy)phenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (256)



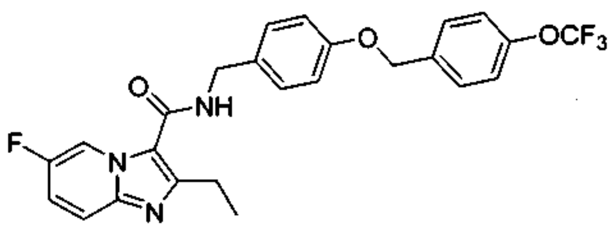
Pale yellow solid; mp = 133.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36 (t, *J* = 7.6 Hz, 3H), 2.39 (s, 3H), 2.93 (q, *J* = 7.6 Hz, 2H), 4.65 (d, *J* = 5.6 Hz, 2H), 6.13 (brt, *J* = 5.6 Hz, 1H), 6.71 (dd, *J* = 1.6, 7.2 Hz, 1H), 6.96 – 7.00 (m, 4H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.37 (m, 3H), 9.23 (d, *J* = 7.2 Hz, 1H); LCMS (electrospray) m/z 470 $(M+H)^+$.

2-Ethyl-8-fluoro-*N*-(4-(4-(trifluoromethoxy)phenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (257)



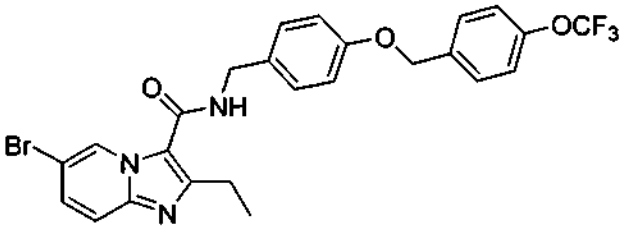
Pale yellow solid; mp = 105.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, *J* = 7.6 Hz, 3H), 2.96 (q, *J* = 7.6 Hz, 2H), 4.65 (d, *J* = 5.6 Hz, 2H), 6.29 (brt, *J* = 5.6 Hz, 1H), 6.77 – 6.82 (m, 1H), 6.96 – 7.02 (m, 5H), 7.13 – 7.17 (m, 2H), 7.32 – 7.35 (m, 2H), 9.12 (dd, *J* = 0.8, 7.2 Hz, 1H); LCMS (electrospray) m/z 474 $(M+H)^+$.

2-Ethyl-6-fluoro-*N*-(4-(4-(trifluoromethoxy)benzyloxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (258)



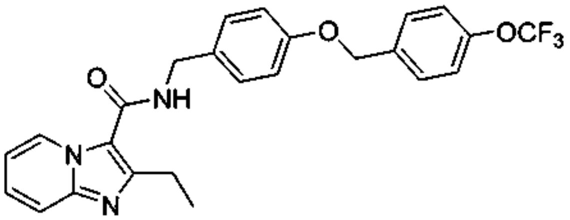
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, *J* = 7.2 Hz, 3H), 2.93 (q, *J* = 7.2 Hz, 2H), 4.62 (d, *J* = 5.6 Hz, 2H), 5.06 (s, 2H), 6.06 (brt, *J* = 5.6 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.22 – 7.26 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.47 – 7.58 (m, 1H), 9.43 – 9.45 (m, 1H); LCMS (electrospray) m/z 488 $(M+H)^+$.

6-Bromo-2-ethyl-*N*-(4-(4-(trifluoromethoxy)benzyloxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (259)



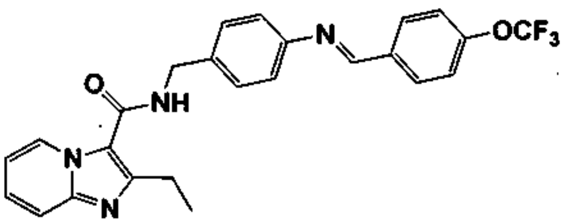
Pale yellow solid; mp = 189.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36(t, *J* = 7.6 Hz, 3H), 2.92 (q, *J* = 7.6 Hz, 2H), 4.62 (d, *J* = 5.6 Hz, 2H), 5.05 (s, 2H), 6.06 (brt, *J* = 5.6 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.36 (dd, *J* = 2.0, 9.2 Hz, 1H), 7.43 – 7.49 (m, 3H), 9.60 (d, *J* = 2.0 Hz, 1H); LCMS (electrospray) m/z 548, 550 $(M+H)^+$ (Br^- isotope pattern).

2-Ethyl-*N*-(4-(4-(trifluoromethoxy)benzyloxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (260)



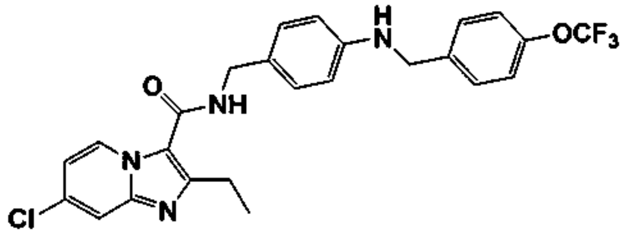
White solid; mp = 138.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, *J* = 7.6 Hz, 3H), 2.91 (q, *J* = 7.6 Hz, 2H), 4.60 (d, *J* = 5.6 Hz, 2H), 5.03 (s, 2H), 6.14 (brt, *J* = 5.6 Hz, 1H), 6.85 (ddd, *J* = 1.2, 7.2, 7.2 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.30 (m, 3H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 9.2 Hz, 1H), 9.33 (d, *J* = 7.2 Hz, 1H); LCMS (electrospray) m/z 470 $(M+H)^+$.

(E)-7-Chloro-2-ethyl-N-(4-((4-(trifluoromethoxy)benzylidene)amino)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (261)



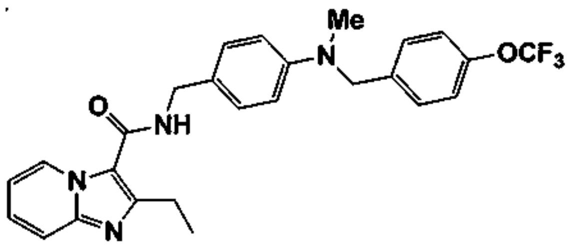
Off-white solid; mp = 194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.4 Hz, 3H), 3.00 (q, *J* = 7.6 Hz, 2H), 4.72 (d, *J* = 5.2 Hz, 2H), 6.14 (t, *J* = 5.2 Hz, 1H), 6.90 – 6.94 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.35 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.94 (d, J = 8.8 Hz, 2H), 8.45 (s, 1H), 9.41 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 467.

7-Chloro-2-ethyl-N-(4-((4-(trifluoromethoxy)benzyl)amino)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (262)



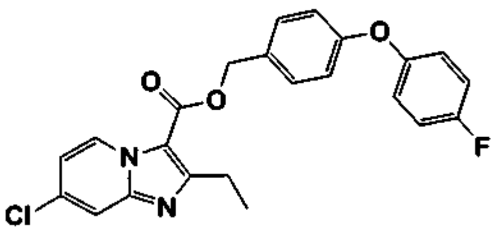
White solid; mp = 169.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.6 Hz, 3H), 2.05 – 2.12 (m, 2H), 2.93 (q, *J* = 7.2 Hz, 2H), 4.18 (br s, 1H), 4.55 (d, *J* = 5.2 Hz, 2H), 5.99 - 6.01 (m, 1H), 6.60 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 4H), 7.38(d, J = 8.0 Hz, 2H), 7.56 (s, 1H), 9.33 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 503.

2-Ethyl-N-(4-(methyl(4-(trifluoromethoxy)benzyl)amino)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (263)



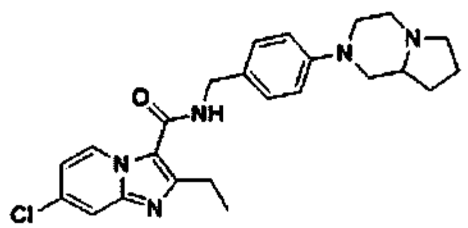
Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.6 Hz, 3H), 2.96 (q, *J* = 7.6 Hz, 2H), 3.03 (s, 3H), 4.53 (s, 2H), 4.59 (d, *J* = 5.6 Hz, 2H), 5.98 – 5.99 (m, 1H), 6.72 (d, *J* = 8.8Hz, 2H), 6.89 – 6.92 (m, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.29 – 7.33 (m, 1H), 7.60 (d, J = 8.8 Hz, 1H), 9.39 (d, J = 6.8 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 505.

7-Chloro-2-ethyl-N-(4-(4-fluorophenoxy)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (264)



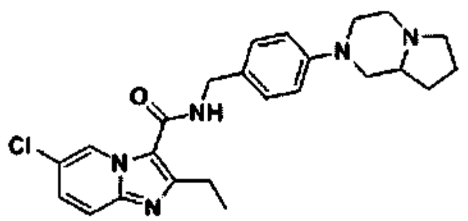
White solid; mp = 89.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.298 (t, J = 7.6 Hz, 3H), 3.07 (q, J = 7.6 Hz, 2H), 5.37 (s, 2H), 6.93 – 7.05 (m, 7H),7.41 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 2.0 Hz, 1H), 9.24 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 425.

__7-Chloro-2-ethyl-N-(4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (265)__



White solid; mp = 159.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.20 (t, J = 7.2 Hz, 3H), 1.85 – 1.92 (m, 2H), 2.01 – 2.03 (m, 2H), 2.17 – 2.21 (m, 2H), 2.39 – 2.58 (m, 5H), 3.14 – 3.16 (m, 2H), 3.61 (d, J = 11.6 Hz, 1H), 3.75 (d, J = 10.0 Hz, 1H), 4.59 (d, J = 5.2 Hz, 2H), 6.01 (brs, 1H), 6.88 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 1.6 Hz, 1H), 9.34 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 438.

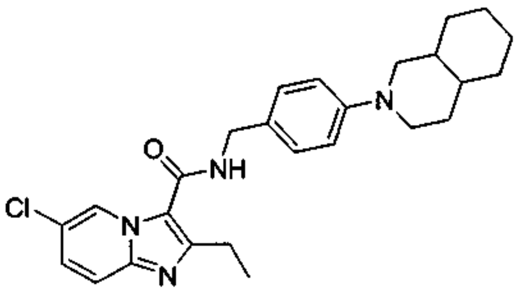
__6-Chloro-2-ethyl-N-(4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (266)__



White solid; mp = 163.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.38 (t, J = 7.6 Hz, 3H), 1.47 – 1.53 (m, 2H), 1.65 – 1.85 (m, 2H), 2.17 (t, J = 8.8 Hz, 2H), 2.34 – 2.40 (m, 1H), 2.54 (t, J = 10.8 Hz, 1H), 2.89 – 2.97 (m, 3H), 3.13 (m, 2H), 3.61 (d, J = 12.4 Hz, 1H), 3.76 (d, J = 10.4

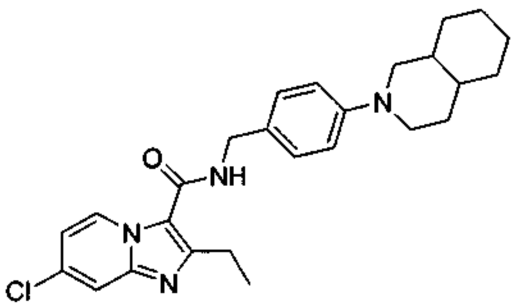
Hz, 1H), 4.60 (d, J = 5.6 Hz, 2H), 6.01 (brs, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.25 – 7.29 (m, 3H), 7.52 (d, J = 9.6 Hz, 1H), 9.51 (s, 1H); LCMS (electrospray) m/z $(M+H)^+$ 438.

6-Chloro-2-ethyl-*N*-(4-(octahydroisoquinolin-2(1H)-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (267)



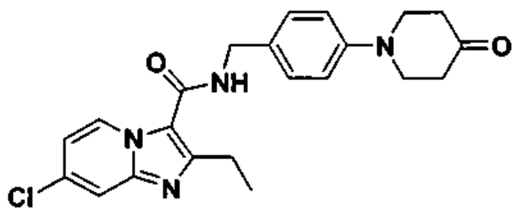
White solid; mp = 141.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 0.94 – 1.03 (m, 3H), 1.24 – 1.42 (m, 4H), 1.34 (t, J = 7.2 Hz, 3H), 1.57 – 1.66 (m, 3H), 1.73 – 1.74 (m, 2H), 2.30 – 2.35 (m, 1H), 2.65 – 2.72 (m, 1H), 2.89 (q, J = 7.2 Hz, 2H), 3.48 – 3.53 (m, 1H), 3.67 – 3.71 (m, 1H), 4.56 (d, J = 5.6 Hz, 2H), 6.03 (brt, J = 5.6 Hz, 1H), 6.89 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H) 7.24 (dd, J = 2.0, 9.2 Hz, 1H), 7.48 (d, J = 9.2 Hz, 1H), 9.48 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.5, 26.1, 26.5, 30.5, 32.8, 33.0, 41.6, 41.8, 43.3, 50.3, 56.2, 115.4, 116.5, 116.9, 121.5, 126.3, 127.8, 128.2, 128.8, 144.5, 151.3, 151.5, 161.1; LCMS (electrospray) m/z 451, 453 $(M+H)^+$ (Cl^- isotope pattern).

7-Chloro-2-ethyl-*N*-(4-(octahydroisoquinolin-2(1H)-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (268)



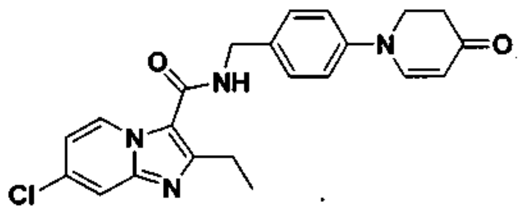
White solid; mp = 174.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ, 0.93 – 1.01 (m, 3H), 1.24 – 1.40 (m, 4H), 1.30 (t, J = 7.6 Hz, 3H), 1.56 – 1.64 (m, 3H), 1.71 – 1.72 (m, 2H), 2.27 – 2.33 (m, 1H), 2.63 – 2.69 (m, 1H), 2.86 (q, J = 7.6 Hz, 2H), 3.48 – 3.50 (m, 1H), 3.65 – 3.68 (m, 1H), 4.53 (d, J = 5.2 Hz, 2H), 6.10 (brt, J = 5.2 Hz, 1H), 6.81 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.51 (s, 1H), 9.25 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.4, 26.1, 26.4, 30.5, 32.8, 33.0, 41.6, 41.7, 43.3, 50.2, 56.1, 114.5, 115.1, 115.6, 116.4, 127.8, 128.4, 128.7, 133.4, 145.9, 151.4, 151.5, 161.1; LCMS (electrospray) m/z 451, 453 $(M+H)^+$ (Cl^- isotope pattern).

7-Chloro-2-ethyl-*N*-(4-(4-oxopiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (269)



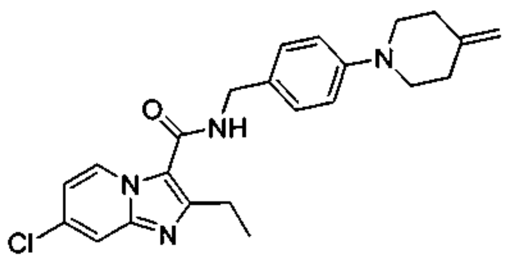
Pale yellow solid; ^1H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, J = 7.2 Hz, 3H), 2.54 (t, J = 6.6 Hz, 4H), 2.93 (q, J = 7.2 Hz, 2H), 3.60 (t, J = 6.0 Hz, 4H), 4.61 (d, J = 5.6 Hz, 2H), 6.04 (brt, J = 5.6 Hz, 1H), 6.89 (dd, J = 2.4, 7.6 Hz, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 2.4 Hz, 1H), 9.35 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 411, 413 (Cl^- isotope pattern).

7-Chloro-2-ethyl-*N*-(4-(4-oxo-3,4-dihydropyridin-1(2H)-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (270)



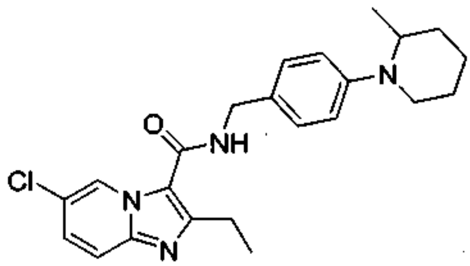
Pale yellow solid; mp = 201.3 – 202.8 °C; ^1H NMR (400 MHz, $CDCl_3$); δ 1.38 (t, J = 7.6 Hz, 3H), 2.64 (t, J = 7.6 Hz, 2H), 2.95 (q, J = 7.6 Hz, 2H), 3.98 (t, J = 7.2 Hz, 2H), 4.66 (d, J = 5.6 Hz, 2H), 5.23 (d, J = 8.0 Hz, 1H), 6.13 (t, J = 5.6 Hz, 1H), 6.89 (dd, J = 2.4, 7.6 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 9.34 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 409, 411 (Cl^- isotope pattern).

7-Chloro-2-ethyl-*N*-(4-(4-methylenepiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (271)



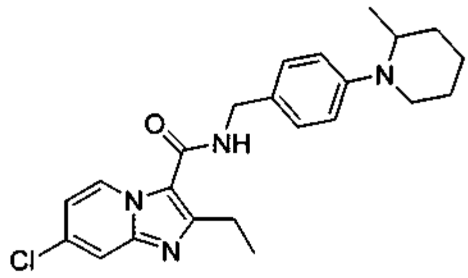
White solid; mp = 168.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.33 (t, *J* = 7.2 Hz, 3H), 2.32 – 2.34 (m, 4H), 2.89 (q, *J* = 7.2 Hz, 2H), 3.23 – 3.25 (m, 4H), 4.56 (d, *J* = 5.2 Hz, 2H), 4.73 (s, 2H), 6.07 (brs, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.54 (s, 1H), 9.29 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.5, 34.2, 43.3, 51.2, 108.5, 114.6, 115.1, 115.7, 116.7, 128.3, 128.5, 128.9, 133.5, 145.8, 146.0, 150.8, 151.5, 161.1; LCMS (electrospray) m/z 409, 411 $(M+H)^+$ (Cl^- isotope pattern).

6-chloro-2-ethyl-*N*-(4-(2-methylpiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (272)



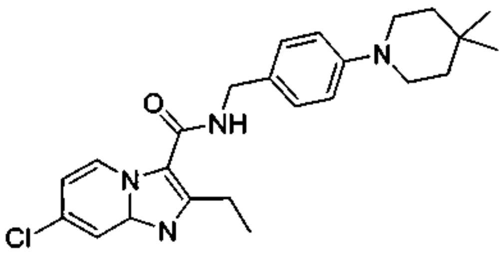
Sticky pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 0.99 (d, *J* = 6.4 Hz, 3H), 1.32 (t, *J* = 7.6 Hz, 3H), 1.55 – 1.70 (m, 4H), 1.81 – 1.88 (m, 2H), 2.91 (q, *J* = 7.6 Hz, 2H), 2.92 – 2.98 (m, 1H), 3.21 – 3.26 (m, 1H), 3.93 – 3.96 (m, 1H), 4.58 (d, *J* = 5.2 Hz, 2H), 6.01 (brt, *J* = 5.2 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.26 (dd, *J* = 2.0, 9.2 Hz, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), 9.50 (d, *J* =2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 13.7, 19.6, 23.6, 26.2, 31.6, 43.4, 44.6, 51.2, 115.4, 117.0, 117.5, 121.6, 126.3, 127.9, 128.2, 128.8, 144.5, 151.1, 151.4, 161.1; LCMS (electrospray) m/z 411, 413 $(M+H)^+$ (Cl^- isotope pattern).

7-chloro-2-ethyl-*N*-(4-(2-methylpiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (273)



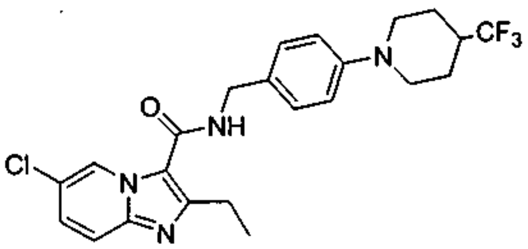
White solid; mp = 117.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.00 (d, J= 6.4 Hz, 3H), 1.35 (t, J = 7.6 Hz, 3H), 1.56 – 1.69 (m, 4H), 1.75 – 1.90 (m, 2H), 2.92 (q, J = 7.6 Hz, 2H), 2.96 – 2.99 (m, 1H), 3.23 – 3.28 (m, 1H), 3.95 – 3.98 (m, 1H), 4.59 (d, J = 5.6 Hz, 2H), 6.08 (brt, J = 5.6 Hz, 1H), 6.87 (dd, J = 2.0, 7.6 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 2.0 Hz, 1H), 9.32 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 13.7, 19.5, 23.5, 26.1, 31.6, 43.3, 44.5, 51.2, 114.6, 115.1, 115.7, 117.4, 127.8, 128.5, 128.8, 133.5, 146.0, 151.0, 151.5, 161.1; LCMS (electrospray) m/z 411, 413 $(M+H)^+$ (Cl^- isotope pattern).

7-Chloro-*N*-(4-(4,4-dimethylpiperidin-1-yl)benzyl)-2-ethyl-1,8a-dihydroimidazo[1,2-a]pyridine-3-carboxamide (274)



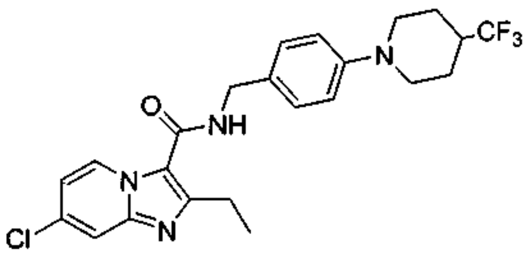
White solid; mp = 121.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 0.97 (s, 6H), 1.34 (t, J = 7.2 Hz, 3H), 1.49 – 1.52 (m, 4H), 2.89 (q, J = 7.2 Hz, 2H), 3.15 – 3.17 (m, 4H), 4.57 (d, J = 5.2 Hz, 2H), 6.00 (brt, J = 5.2 Hz, 1H), 6.86 (dd, J = 2.0, 7.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 2.0 Hz, 1H), 9.32 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.5, 28.0, 29.8, 38.5, 43.4, 45.9, 114.7, 115.7, 116.4, 127.9, 128.6, 128.9, 129.0, 133.6, 146.1, 151.5, 151.6, 161.2; LCMS (electrospray) m/z 425, 427 $(M+H)^+$ (Cl^- isotope pattern).

6-Chloro-2-ethyl-*N*-(4-(4-(trifluoromethyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (275)



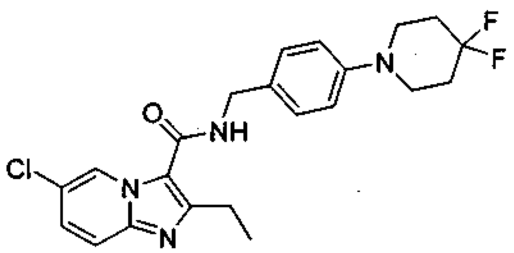
White solid; mp = 197.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, J = 7.6 Hz, 3H), 1.68 – 1.82 (m, 2H), 1.94 – 1.97 (m, 2H), 2.12 – 2.18 (m, 1H), 2.66 – 2.73 (m, 2H), 2.91 (q, J = 7.6 Hz, 2H), 3.73 – 3.77 (m, 2H), 4.58 (d, J = 5.6 Hz, 2H), 6.04 (brt, J = 5.2 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.25 – 7.29 (m, 3H), 7.50 (d, J = 9.2 Hz, 1H), 9.50 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z 465, 467 $(M+H)^+$ (Cl^- isotope pattern).

7-Chloro-2-ethyl-*N*-(4-(4-(trifluoromethyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (276)



White solid; mp = 209.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.34 (t, J = 7.6 Hz, 3H), 1.68 – 1.78 (m, 2H), 1.94 – 1.98 (m, 2H), 2.11 – 2.20 (m, 1H), 2.66 – 2.73 (m, 2H), 2.90 (q, J = 7.6 Hz, 2H), 3.73 – 3.77 (m, 2H), 4.58 (d, J = 5.2 Hz, 2H), 6.03 (brt, J = 5.2 Hz, 1H), 6.86 (dd, J = 2.4, 7.6 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 2.4 Hz, 1H), 9.32 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z 465, 467 $(M+H)^+$ (Cl^- isotope pattern).

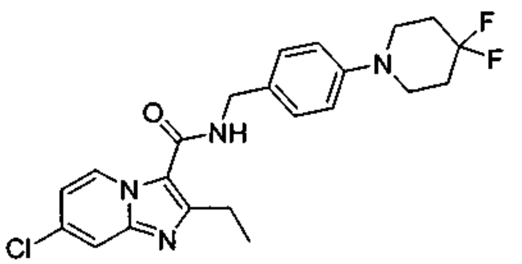
6-chloro-N-(4-(4,4-difluoropiperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (277)



White solid; mp = 194.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36 (t, J = 7.6 Hz, 3H), 1.98 – 2.13 (m, 4H), 2.92 (q, J = 7.6 Hz, 2H), 3.33 – 3.36 (m, 4H), 4.59 (d, J = 5.6 Hz, 2H), 6.04

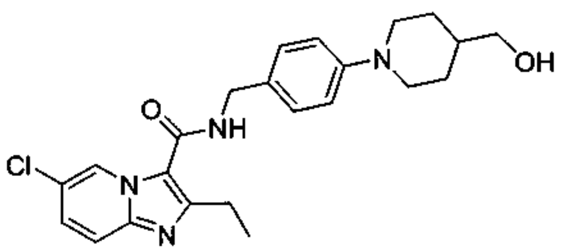
(brt, J = 5.6 Hz, 1H), 6.91 – 6.95 (m, 2H), 7.25 – 7.30 (m, 3H), 7.52 (d, J = 9.6 Hz, 1H), 9.51 (d, J = 2.0 Hz, 1H); LCMS (electrospray) m/z 433, 435 $(M+H)^+$ (Cl^- isotope pattern).

7-Chloro-*N*-(4-(4,4-difluoropiperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (278)



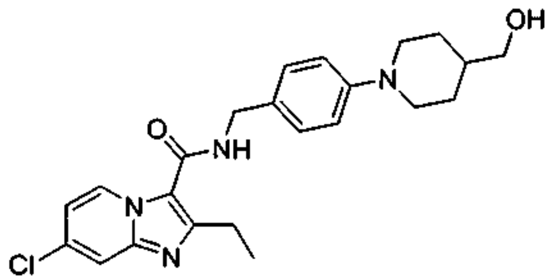
White solid; mp = 166.3 °C; ^1H NMR (400 MHz, $CDCl_3$); δ1.34 (t, J = 7.2 Hz, 3H), 2.03 – 2.12 (m, 4H), 2.90 (q, J = 7.2 Hz, 2H), 3.32 – 3.35 (m, 4H), 4.58 (d, J = 5.2 Hz, 2H), 6.06 (brt, J = 5.2 Hz, 1H), 6.86 (dd, J = 2.0, 7.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 2.0 Hz, 1H), 9.31 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z 433, 435 $(M+H)^+$ (Cl^- isotope pattern).

6-Chloro-2-ethyl-*N*-(4-(4-(hydroxymethyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (279)



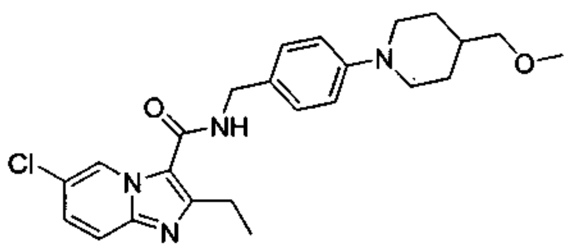
Pale yellow solid; mp = 161.1 °C; ^1H NMR (400 MHz, $CDCl_3$); δ 1.23 – 1.41 (m, 2H), 1.33 (t, J = 7.6 Hz, 3H), 1.59 – 1.65 (m, 1H), 1.80 – 1.84 (m, 2H), 2.64 – 2.71 (m, 2H), 2.89 (q, J = 7.6 Hz, 2H), 3.50 (d, J = 6.4 Hz, 2H), 3.66 – 3.69 (m, 2H), 4.55 (d, J = 5.2 Hz, 2H), 6.09 (brt, J = 5.2 Hz, 1H), 6.89 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.23 (dd, J = 2.0, 9.2 Hz, 1H), 7.47 (d, J = 9.2 Hz, 1H), 9.45 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.4, 28.7, 38.6, 43.3, 49.6, 67.6, 115.3, 116.8, 116.9, 121.5, 126.2, 128.2, 128.3, 128.8, 144.4, 151.3, 151.4, 161.1; LCMS (electrospray) m/z 427, 429 $(M+H)^+$ (Cl^- isotope pattern).

7-Chloro-2-ethyl-*N*-(4-(4-(hydroxymethyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (280)



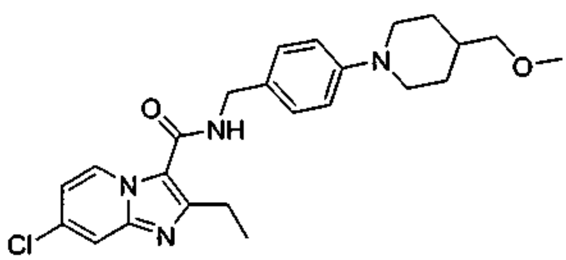
White solid; mp = 179.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.33 (t, *J* = 7.6 Hz, 3H), 1.35 – 1.42 (m, 2H), 1.60 – 1.67 (m, 1H), 1.82 – 1.85 (m, 2H), 1.98 (brs, 1H), 2.66 – 2.73 (m, 2H), 2.91 (q, *J* = 7.6 Hz, 2H), 3.52 (d, *J* = 6.4 Hz, 2H), 3.68 – 3.71 (m, 2H), 4.56 (d, *J* = 5.6 Hz, 2H), 6.04 (brt, *J* = 5.6 Hz, 1H), 6.86 (dd, *J* = 2.0, 7.6 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 2.0 Hz, 1H), 9.30 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.5, 28.7, 38.6, 43.3, 49.7, 67.7, 114.7, 115.1, 115.7, 116.8, 128.3, 128.6, 128.8, 133.6, 146.1, 151.5, 151.6, 161.1; LCMS (electrospray) m/z 427, 429 $(M+H)^+$ (Cl^- isotope pattern).

6-Chloro-2-ethyl-*N*-(4-(4-(methoxymethyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (281)



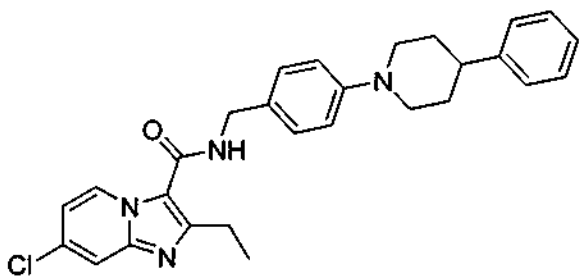
White solid; mp = 162.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.34-1.57 (m, 2H), 1.36 (t, *J* = 7.6 Hz, 3H), 1.70 – 1.85 (m, 3H), 2.68 – 2.74 (m, 2H), 2.88 (q, *J* = 7.6 Hz, 2H), 3.25 (d, *J* = 6.4 Hz, 2H), 3.53 (s, 3H), 3.68 – 3.71 (m, 2H), 4.58 (d, *J* = 5.6 Hz, 2H), 5.98 (brt, *J* = 5.6 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.24 – 7.30 (m, 3H), 7.51 (d, *J* = 10.0 Hz, 1H), 9.52 (d, *J* = 1.6 Hz, 1H); LCMS (electrospray) m/z 441, 443 $(M+H)^+$ (Cl^- isotope pattern).

7-Chloro-2-ethyl-*N*-(4-(4-(methoxymethyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (282)



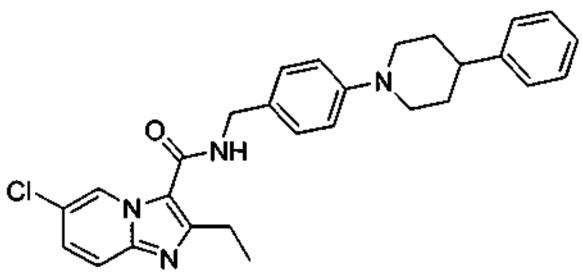
White solid; mp = 172.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.33 - 1.43 (m, 2H), 1.35 (t, *J* = 7.6 Hz, 3H), .72 - 1.85 (m, 3H), 2.67 - 2.74 (m, 2H), 2.90 (q, *J* = 7.6 Hz, 2H), 3.25 (d, *J* = 6.4 Hz, 2H), 3.35 (s, 3H), 3.68 - 3.71 (m, 2H), 4.58 (d, *J* = 5.2 Hz, 2H), 5.97 (brt, *J* = 5.2 Hz, 1H), 6.88 (dd, *J* = 2.4, 7.6 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 2.4 Hz, 1H), 9.34 (d, *J* = 7.6 Hz, 1H); LCMS (electrospray) m/z 441, 443 $(M+H)^+$ (Cl^- isotope pattern).

7-Chloro-2-ethyl-*N*-(4-(4-phenylpiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (283)



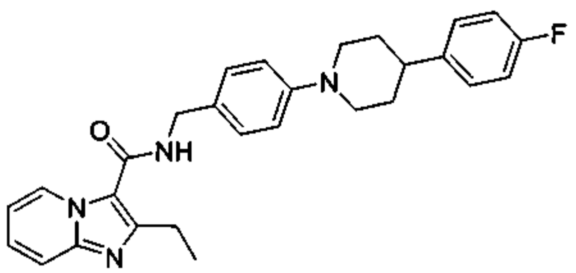
White solid; mp = 164.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36 (t, *J* = 7.6 Hz, 3H), 1.87 – 1.98 (m, 4H), 2.67 – 2.68 (m, 1H), 2.80 – 2.85 (m, 2H), 2.91 (q, *J* = 7.6 Hz, 2H), 3.80 – 3.83 (m, 2H), 4.59 (d, *J* = 5.6 Hz, 2H), 6.01 (brt, *J* = 5.6 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.19 – 7.33 (m, 7H), 7.57 (s, 1H), 9.34 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.6, 33.3, 42.6, 43.4, 50.5, 114.7, 115.1, 115.8, 116.9, 126.5, 127.0, 128.5, 128.6, 128.7, 128.9, 133.6, 146.1, 146.2, 151.5, 151.6, 161.2; LCMS (electrospray) m/z 473, 475 $(M+H)^+$ (Cl^- isotope pattern).

6-Chloro-2-ethyl-*N*-(4-(4-phenylpiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (284)



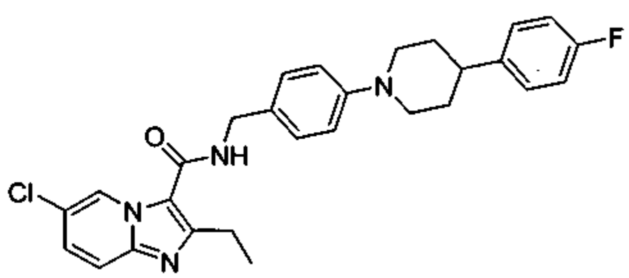
Pale yellow solid; mp = 138.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36 (t, J = 7.6 Hz, 3H), 1.84 – 1.97 (m,4H), 2.62 – 2.69 (m, 1H), 2.79 – 2.86 (m, 2H), 2.92 (q, J = 7.6 Hz, 2H), 3.80 – 3.83 (m, 2H), 4.60 (d, J = 5.2 Hz, 2H), 6.07 (brt, J = 5.2 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 7.19 – 7.33 (m, 8H), 7.50 (d, J = 9.6 Hz, 1H), 9.50 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.5, 33.3, 42.5, 43.3, 50.5, 115.4, 116.9, 117.0, 121.6, 126.3, 126.4, 126.9, 128.2, 128.4, 128.6, 128.9, 144.4, 146.0, 151.3, 151.4, 161.1; LCMS (electrospray) m/z 473, 475 $(M+H)^+$ (Cl^- isotope pattern).

2-Ethyl-*N*-(4-(4-(4-fluorophenyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide(285)



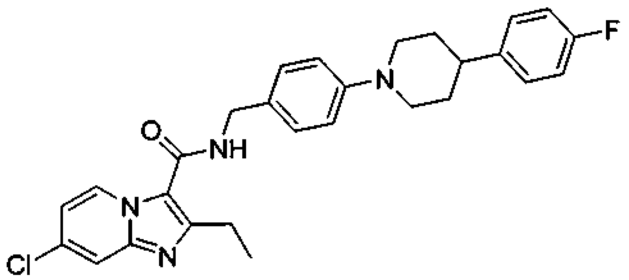
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, J = 7.6 Hz, 3H), 1.81 – 1.95 (m, 4H), 2.60 – 2.67 (m, 1H), 2.77 – 2.85 (m, 2H), 2.94 (q, J = 7.6 Hz, 2H), 3.79 – 3.82 (m, 2H), 4.61 (d, J = 5.6 Hz, 2H), 6.02 (brs, 1H), 6.89 (ddd, J = 1.2, 6.8, 6.8 Hz, 1H), 6.96 – 7.02 (m, 4H), 7.17 – 7.23 (m, 2H), 7.25 – 7.33 (m, 3H), 7.8 (d, J = 8.8 Hz, 1H), 9.39 (d, J = 6.8 Hz, 1H).

6-Chloro-2-ethyl-*N*-(4-(4-(4-fluorophenyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (286)



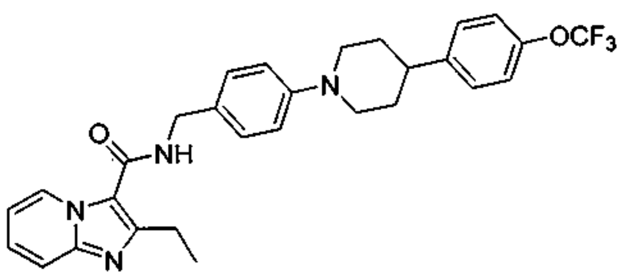
White solid; mp = 164.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, J = 7.6 Hz, 3H), 1.76 – 1.95 (m, 4H), 2.60 – 2.66 (m, 1H), 2.78 – 2.85 (m, 2H), 2.92 (q, J = 7.6 Hz, 2H), 3.79 – 3.82 (m, 2H), 4.60 (d, J = 5.2 Hz, 2H), 6.03 (brt, J = 5.2 Hz, 1H), 6.96 – 7.01 (m, 4H), 7.17 – 7.21 (m, 2H), 7.26 – 7.29 (m, 3H), 7.51 (d, J = 9.6 Hz, 1H), 9.52 (d, J = 1.6 Hz, 1H); LCMS (electrospray) m/z 491 $(M+H)^+$.

7-Chloro-2-ethyl-*N*-(4-(4-(4-fluorophenyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (287)



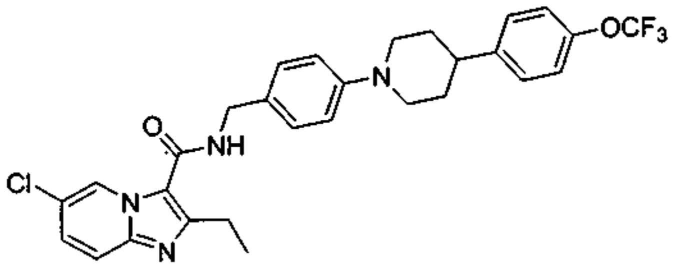
White solid; mp = 182.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, J = 7.6 Hz, 3H), 1.79 – 1.95 (m, 4H), 2.59 – 2.67 (m, 1H), 2.78 – 2.85 (m, 2H), 2.91 (q, J = 7.6 Hz, 2H), 3.79 – 3.82 (m, 2H), 4.59 (d, J = 5.6 Hz, 2H), 6.03 (brt, J = 5.6 Hz, 1H), 6.87 (dd, J = 2.4, 7.6 Hz, 1H), 6.96 – 7.01 (m, 4H), 7.17 – 7.21 (m, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 2.4 Hz, 1H), 9.33 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z 491 $(M+H)^+$.

2-Ethyl-*N*-(4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide(288)



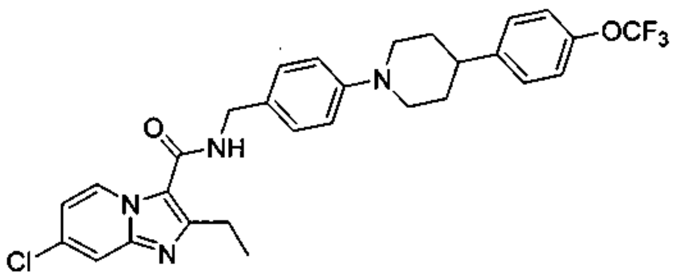
Pale yellow solid; mp = 146.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, J = 7.6 Hz, 3H), 1.81 – 1.96 (m, 4H), 2.63 – 2.69 (m, 1H), 2.79 – 2.86 (m, 2H), 2.94 (q, J = 7.6 Hz, 2H), 3.80 – 3.83 (m, 2H), 4.61 (d, J = 5.6 Hz, 2H), 6.01 (brt, J = 5.6 Hz, 1H), 6.88 (ddd, J = 0.8, 6.8, 6.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.24 – 7.33 (m, 5H), 7.58 (d, J = 8.8 Hz, 1H), 9.39 (d, J = 6.8 Hz, 1H).

6-Chloro-2-ethyl-*N*-(4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (289)



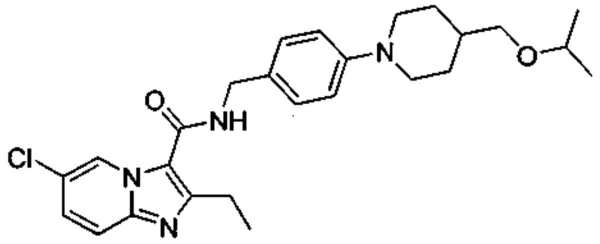
White solid; mp = 164.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, J = 7.6 Hz, 3H), 1.81 – 1.96 (m, 4H), 2.63 – 2.70 (m, 1H), 2.79 – 2.86 (m, 2H), 2.92 (q, J = 7.6 Hz, 2H), 3.80 – 3.83 (m, 2H), 4.60 (d, J = 5.2 Hz, 2H), 6.04 (brt, J = 5.2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.24 – 7.29 (m, 5H), 7.51 (d, J = 9.6 Hz, 1H), 9.51 (d, J = 1.6 Hz, 1H).

7-Chloro-2-ethyl-*N*-(4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide(290)



White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36 (t, J = 7.6 Hz, 3H), 1.82 – 1.96 (m, 4H), 2.64 – 2.70 (m, 1H), 2.79 – 2.86 (m, 2H), 2.91 (q, J = 7.6 Hz, 2H), 3.80 – 3.83 (m, 2H), 4.59 (d, J = 5.36 Hz, 2H), 6.04 (brs, 1H), 6.87 (dd, J = 1.6, 7.2 Hz, 1H), 6.97 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.24 – 7.28 (m, 4H), 7.57 (d, J = 1.6 Hz, 1H), 9.34 (d, J = 7.2 Hz, 1H).

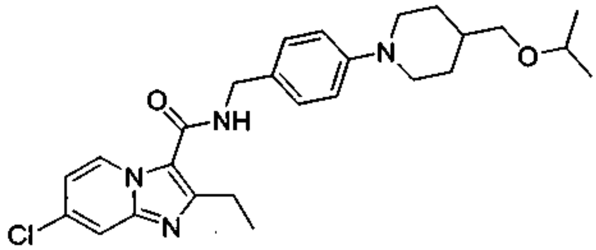
6-Chloro-2-ethyl-*N*-(4-(4-(isopropoxymethyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide(291)



White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.29 (d, J = 6.0 Hz, 6H), 1.46 – 1.56 (m, 2H), 1.50 (t, J = 7.6 Hz, 3H), 1.81 – 1.89 (m, 1H), 1.99 – 2.02 (m, 2H), 2.82 – 2.89 (m, 2H), 3.06

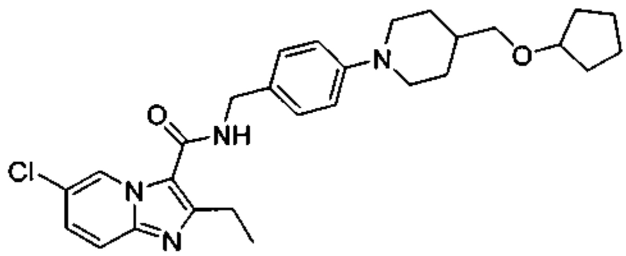
(q, J = 7.6 Hz, 2H), 3.43 (d, J = 6.4 Hz, 2H), 3.66 – 3.72 (m, 1H), 3.82 – 3.85 (m, 2H), 4.73 (d, J = 5.6 Hz, 2H), 6.17 (brt, J = 5.6 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.40 (dd, J = 2.0, 9.2 Hz, 1H), 7.65 (d, J = 9.2 Hz, 1H), 9.65 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 22.2, 23.6, 29.4, 36.6, 43.4, 49.7, 71.8, 73.3, 115.4, 116.8, 117.0, 121.5, 126.3, 128.2, 128.8, 144.5, 151.4, 151.6, 161.1 (hidden 1 aromatic carbon).

7-Chloro-2-ethyl-*N*-(4-(4-(isopropoxymethyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide(292)



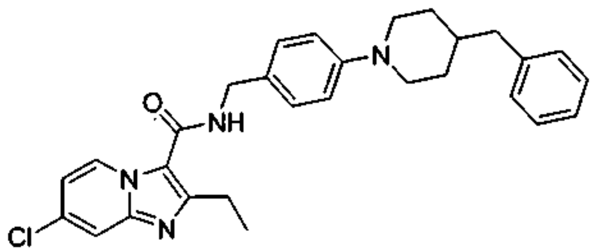
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.14 (d, J = 6.0 Hz, 6H), 1.31 – 1.41 (m, 2H), 1.34 (t, J = 7.6 Hz, 3H), 1.66 – 1.73 (m, 1H), 1.84 – 1.87 (m, 2H), 2.67 – 2.74 (m, 2H), 2.90 (q, J = 7.6 Hz, 2H), 3.27 (d, J = 6.8 Hz, 2H), 3.50 – 3.56 (m, 1H), 3.67 – 3.70 (m, 2H), 4.57 (d, J = 5.6 Hz, 2H), 5.99 (brt, J = 5.6 Hz, 1H), 6.86 (dd, J = 2.0, 7.2 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 1.6 Hz, 1H), 9.33 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 22.2, 23.6, 29.4, 36.6, 43.4, 49.7, 71.8, 73.3, 114.7, 115.2, 115.8, 116.8, 128.2, 128.6, 128.8, 133.6, 146.1, 151.6, 151.7, 161.2.

6-Chloro-*N*-(4-(4-(cyclopentyloxymethyl)piperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide(293)



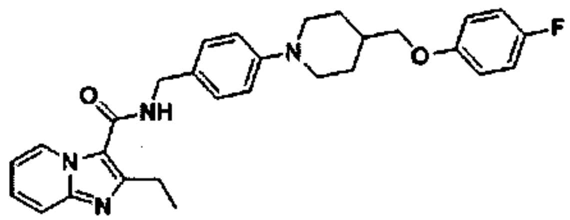
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.28 – 1.38 (m, 2H), 1.32 (t, J = 7.6 Hz, 3H), 1.46 – 1.51 (m, 2H), 1.58 – 1.66 (m, 7H), 1.79 – 1.83 (m, 2H), 2.63 – 2.70 (m, 2H), 2.87 (q, J = 7.6 Hz, 2H), 3.21 (d, J = 6.4 Hz, 2H), 3.63 – 3.66 (m, 2H), 3.82 – 3.83 (m, 1H), 4.54 (d, J = 5.2 Hz, 2H), 6.08 (brt, J = 5.2 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.19 – 7.25 (m, 3H), 7.45 (d, J = 9.2 Hz, 1H), 9.44 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 23.4, 23.6, 29.3, 32.3, 36.4, 43.3, 49.6, 73.7, 81.5, 115.3, 116.6, 116.8, 121.4, 126.2, 128.0, 128.1, 128.7, 144.4, 151.3, 151.5, 161.0.

N-(4-(4-Benzylpiperidin-1-yl)benzyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (294)



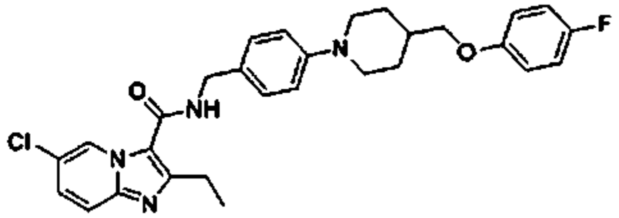
White solid; mp = 63.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.33 (t, J = 7.6 Hz, 3H), 1.37 – 1.44 (m, 2H), 1.63 – 1.70 (m, 1H), 1.72 – 1.76 (m, 2H), 2.56 (d, J = 6.8 Hz, 2H), 2.61 – 2.67 (m, 2H), 2.89 (q, J = 7.6 Hz, 2H), 3.63 – 3.66 (m, 2H), 4.56 (d, J = 5.2 Hz, 2H), 6.08 (brs, 1H), 6.84 – 6.87 (m, 1H), 6.89 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.2 Hz, 2H), 7.19 – 7.30 (m, 5H), 7.54 (d, J = 1.6 Hz, 1H), 9.29 – 9.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.5, 32.0, 37.9, 43.2, 43.3, 49.9, 114.6, 115.1, 115.7, 116.7, 126.0, 128.2, 128.3, 128.5, 128.8, 129.2, 133.5, 140.5, 146.0, 151.5, 151.6, 161.1; LCMS (electrospray) m/z 487, 489 $(M+H)^+$ (Cl^- isotope pattern).

2-Ethyl-N-(4-(4-((4-fluorophenoxy)methyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (295)



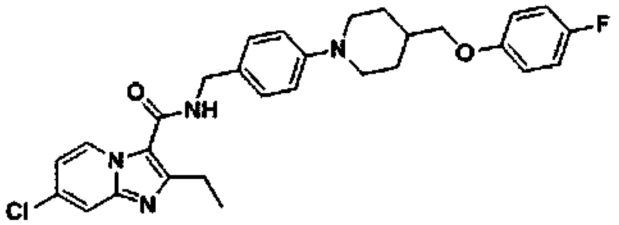
White solid; mp = 144.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.39 (t, J = 7.2 Hz, 3H), 1.46 – 1.60 (m, 3H), 1.94 – 1.96 (m, 2H), 2.73 – 2.78 (m, 2H), 2.96 (q, J = 7.2 Hz, 2H), 3.73 (d, J = 12.0, 2H), 3.80 (d, J = 6.0 Hz, 2H), 4.61 (d, J = 5.2 Hz, 2H), 5.99 (brs, 1H), 6.82 – 6.84 (m, 1H), 6.89 – 6.92 (m, 2H), 6.94 – 6.98 (m, 4H), 7.25 – 7.29 (m, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 8.40 (d, J = 7.2 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 487.

6-Chloro-2-ethyl-N-(4-(4-((4-fluorophenoxy)methyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (296)



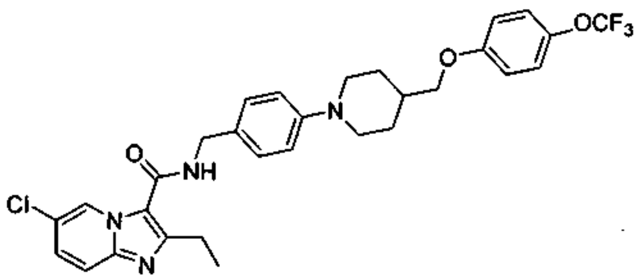
White solid; mp = 171.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.38 (t, J = 7. 6 Hz, 3H), 1.50 – 1.56 (m, 2H), 1.94 – 1.96 (m, 3H), 2.72 – 2.79 (m, 2H), 2.95 (q, J = 7.6 Hz, 2H), 3.74 (d, J = 12.4 Hz, 2H), 3.80 (d, J = 5.6 Hz, 2H), 4.60 (d, J = 5.6 Hz, 2H), 6.01 (brs, 1H), 6.81 – 6.84 (m, 2H), 6.94 – 6.98 (m, 4H), 7.27 – 7.29 (m, 3H), 7.53 (d, J = 9.6 Hz, 1H), 9.52 (d, J = 2.0 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 521.

7-Chloro-2-ethyl-N-(4-(4-((4-fluorophenoxy)methyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (297)



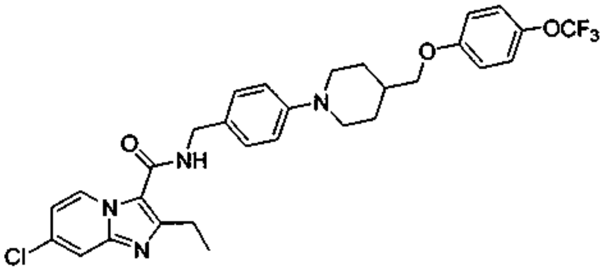
White solid; mp = 186.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, J = 7. 6 Hz, 3H), 1.50 – 1.61 (m, 2H), 1.94 – 1.96 (m, 3H), 2.76 (t, J = 10.8 Hz, 2H), 2.93 (q, J = 7.6 Hz, 2H), 3.74 (d, J = 12.0 Hz, 2H), 3.80 (d, J = 5.6 Hz, 2H), 4.59 (d, J = 5.6 Hz, 2H), 6.00 (brs, 1H), 6.80 – 6.84 (m, 2H), 6.88 – 6.90 (m, 1H), 6.94 – 6.98 (m, 4H), 7.25 – 7.27 (m, 2H), 7.58 (d, J = 1.6 Hz, 1H), 9.34 (d, J = 8.0 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 521.

6-chloro-2-ethyl-*N*-(4-(4-((4-(trifluoromethoxy)phenoxy)methyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (298)



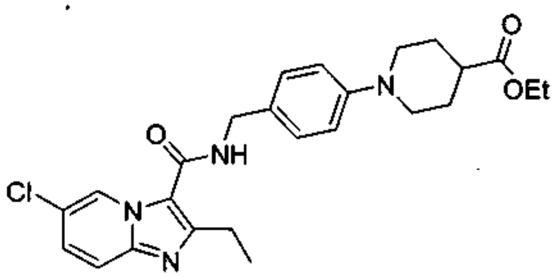
Pale yellow solid; mp = 183.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, J = 7.6 Hz, 3H), 1.46 – 1.57 (m, 2H), 1.93 – 1.96 (m, 3H), 2.72 – 2.78 (m, 2H), 2.91 (q, J = 7.6 Hz, 2H), 3.71 – 3.74 (m, 2H), 3.81 (d, J = 6.0 Hz, 2H), 4.58 (d, J = 5.6 Hz, 2H), 6.05 (brt, J = 5.6 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 7.24 – 7.28 (m, 3H), 7.50 (d, J = 9.6 Hz, 1H), 9.50 (d, J = 1.2 Hz, 1H); LCMS (electrospray) m/z 587, 589 $(M+H)^+$ (Cl^- isotope pattern).

7-Chloro-2-ethyl-*N*-(4-(4-((4-(trifluoromethoxy)phenoxy)methyl)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (299)



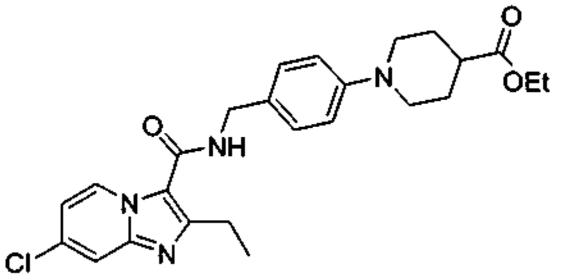
White solid; mp = 189.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.34 (t, J = 7.6 Hz, 3H), 1.46 – 1.56 (m, 2H), 1.93 – 2.02 (m, 3H), 2.71 – 2.78 (m, 2H), 2.90 (q, J = 7.6 Hz, 2H), 3.71 – 3.74 (m, 2H), 3.81 (d, J = 6.0 Hz, 2H), 4.57 (d, J = 5.2 Hz, 2H), 6.05 (brt, J = 5.2 Hz, 1H), 6.84 – 6.87 (m, 3H), 6.93 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 2.0 Hz, 1H), 9.31 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z 587, 589 $(M+H)^+$ (Cl^- isotope pattern).

Ethyl 1-(4-((6-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamido)methyl)phenyl) piperidine-4-carboxylate (300)



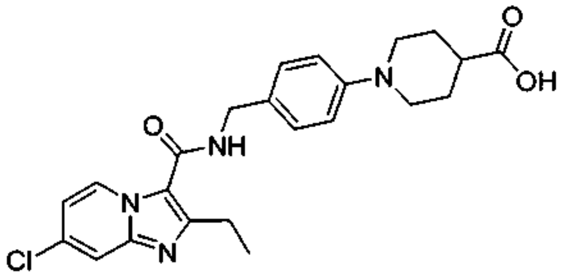
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.23 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.80 – 1.90 (m, 2H), 1.98 – 2.02 (m, 2H), 2.38 – 2.46 (m, 1H), 2.75 – 2.82 (m, 2H), 2.91 (q, J = 7.6 Hz, 2H), 3.61 – 3.65 (m, 2H), 4.11 (q, J = 7.2 Hz, 2H), 4.57 (d, J = 5.6 Hz, 2H), 6.03 (brt, J = 5.6 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 7.23 – 7.28 (m, 3H), 7.49 (d, J = 9.6 Hz, 1H), 9.49 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.4, 23.6, 28.1, 41.6, 43.3, 49.2, 60.6, 115.4, 116.9, 117.0, 121.5, 126.3, 128.2, 128.6, 128.9, 144.5, 151.2, 151.4, 161.1, 174.9.

Ethyl 1-(4-((7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamido)methyl)phenyl) piperidine-4-carboxylate (301)



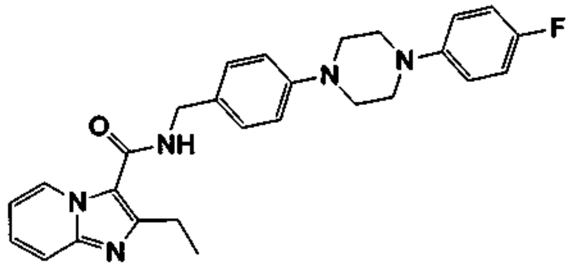
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.21 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.77 – 1.87 (m, 2H), 1.96 – 2.00 (m, 2H), 2.36 – 2.42 (m, 1H), 2.72 – 2.79 (m, 2H), 2.87 (q, J = 7.2 Hz, 2H), 3.58 – 3.63 (m, 2H), 4.09 (q, J = 7.2 Hz, 2H), 4.53 (d, J = 5.6 Hz, 2H), 6.12 (brt, J = 5.6 Hz, 1H), 6.81 (dd, J = 2.0, 7.2 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 2.0, 1H), 9.25 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.3, 23.4, 28.0, 41.0, 43.2, 49.1, 60.5, 114.5, 115.1, 115.6, 116.7, 128.4, 128.6, 128.8, 133.4, 146.0, 151.1, 151.5, 161.1, 174.8.

1-(4-((7-Chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamido)methyl)phenyl) piperidine-4-carboxylic acid (302)



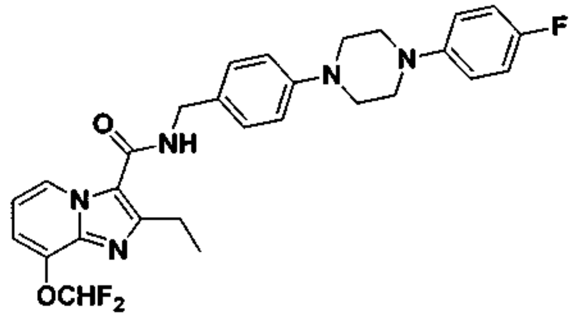
White solid; ^{1}H NMR (400 MHz, DMSO-d^6); δ 1.22 (t, J = 7.6 Hz, 3H), 1.57 – 1.66 (m, 2H), 1.84 – 1.88 (m, 2H), 2.29 – 2.34 (m, 1H), 2.67 – 2.73 (m, 2H), 2.92 (q, J = 7.6 Hz, 2H), 3.57 – 3.60 (m, 2H), 4.40 (d, J = 5.6 Hz, 2H), 5.75 (s, 1H), 6.89 (d, J = 8.4 Hz, 2H), 7.06 (dd, J = 1.6, 7.6 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 1.6 Hz, 1H), 8.37 (brt, J = 5.6 Hz, 1H), 8.93 (d, J = 7.6 Hz, 1H).

2-Ethyl-N-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (303)



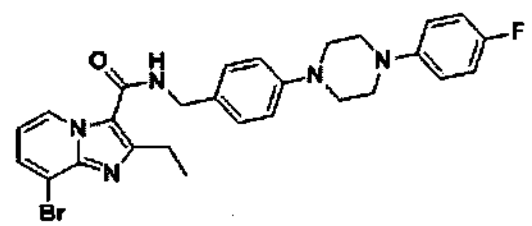
White solid; mp = 189.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.8 Hz, 3H), 2.96 (q, J = 7.6 Hz, 2H), 3.24 – 3.29 (m, 2H), 3.32 – 3.36 (m, 2H), 4.63 (d, J = 5.6 Hz, 2H), 6.02 – 6.04 (m, 1H), 6.90 – 7.01 (m, 7H), 7.30 – 7.34 (m, 2H), 7.60 (d, J = 9.2 Hz, 1H), 9.41 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 458.

8-(Difluoromethoxy)-2-ethyl-N-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (304)



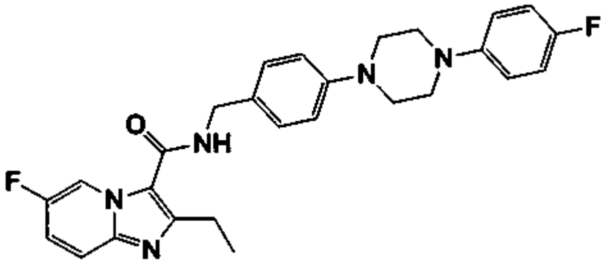
Pale yellow; mp = 186.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 3.24 – 3.27 (m, 4H), 3.34 – 3.36 (m, 4H), 4.63 (d, J = 5.6 Hz, 2H), 6.05 – 6.07 (m, 1H), 6.85 (dd, J = 7.2 Hz, 1H), 6.91 - 7.01 (m, 6H), 7.10 (d, J = 7.6 Hz, 2H), 7.26 (t, J = 74.2 Hz, 1H due to F_2), 9.24 (d, J = 6.8 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 524

8-Bromo-2-ethyl-*N*-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (305)



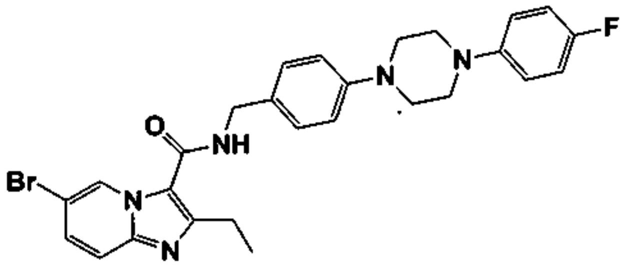
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7. 6 Hz, 3H), 3.00 (q, J = 7.6 Hz, 2H), 3.23 – 3.35 (m, 8H), 4.61 (d, J = 5.6 Hz, 2H), 6.08 (brs, 1H), 6.77 (dd, J = 6.8 Hz, 6.8 Hz, 1H), 6.90 – 7.00 (m, 6H), 7.29 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 7.2 Hz, 1H), 9.38 (d, J = 7.2 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 23.7, 43.4, 49.5, 50.6, 110.7, 113.3, 115.7, 115.9, 116.7, 118.4, 127.6, 129.0, 129.2, 129.4, 144.1, 148.0, 151.0, 151.5, 158.8, 161.3.; LCMS (electrospray) m/z $(M+H)^+$ 538.

2-Ethyl-6-fluoro-N-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (306)



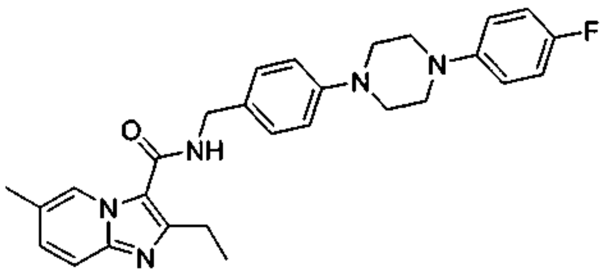
White solid; mp = 200.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.8 Hz, 3H), 2.96 (q, J = 7.6 Hz, 2H), 3.24 – 3.29 (m, 2H), 3.32 – 3.36 (m, 2H), 4.62 (d, J = 5.6 Hz, 2H), 6.03 – 6.05 (m, 1H), 6.92 – 7.01 (m, 6H), 7.22 – 7.27 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.56 (dd, J = 5.0, 9.8 Hz, 1H), 9.44 – 9.46 (m, 1H); LCMS (electrospray) m/z $(M+H)^+$ 476.

6-Bromo-2-ethyl-N-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (307)



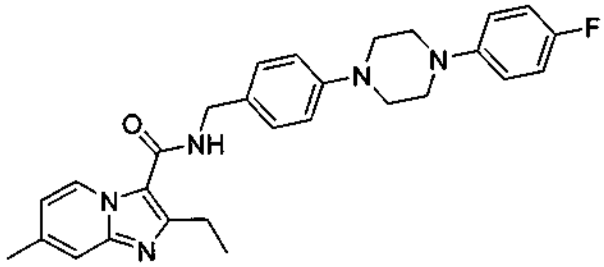
White solid; mp = 218.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 3.24 – 3.29 (m, 2H), 3.31 – 3.36 (m, 2H), 4.62 (d, J = 5.6 Hz, 2H), 6.04 (t, J = 5.0 Hz, 1H), 6.92 – 7.01 (m, 6H), 7.31 (d, J = 8.8 Hz, 2H), 7.39 (dd, J = 2.0, 9.2 Hz, 1H), 7.49 (d, J = 9.6 Hz, 1H), 9.63 (d, J = 1.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 536, 538 (Br^- isotope pattern).

2-Ethyl-*N*-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide (308)



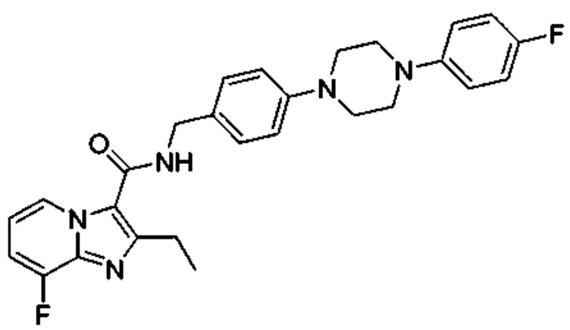
White solid; mp = 187.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, J = 7.6 Hz, 3H), 2.89 (s, 3H), 2.91 (q, J = 7.6 Hz, 2H), 3.22 – 3.24 (m, 4H), 3.31 – 3.33 (m, 4H), 4.60 (d, J = 5.2 Hz, 2H), 6.04 (brt, J = 5.2 Hz, 1H), 6.89 – 6.99 (m, 6H), 7.13 (dd, J = 1.6, 9.2 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 9.2 Hz, 1H), 9.18 (s, 1H); LCMS (electrospray) m/z 472 $(M+H)^+$.

2-Ethyl-*N*-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide (309)



White solid; mp = 203.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, J = 7.6 Hz, 3H), 2.40 (s, 3H), 2.91 (q, J = 7.6 Hz, 2H), 3.23 – 3.26 (m, 4H), 3.32 – 3.34 (m, 4H), 4.60 (d, J = 5.6 Hz, 2H), 6.02 (brt, J = 5:6 Hz, 1H), 6.72 – 6.74 (m, 1H), 6.91 – 7.00 (m, 6H), 7.29 – 7.33 (m, 3H), 9.25 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z 472 $(M+H)^+$.

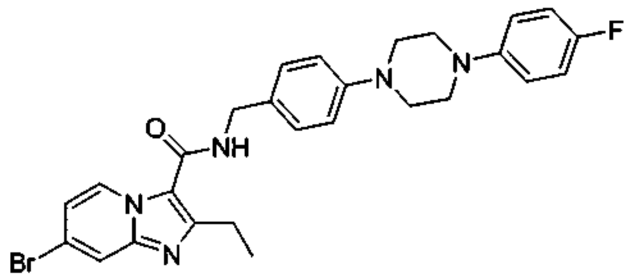
2-Ethyl-8-fluoro-*N*-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (310)



Pale yellow solid; mp = 204.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD); δ 1.34 (t, J = 7.6 Hz, 3H), 2.94 (q, J = 7.6 Hz, 2H), 3.24 – 3.26 (m, 4H), 3.33 – 3.35 (m, 4H), 4.60 (d, J = 5.6

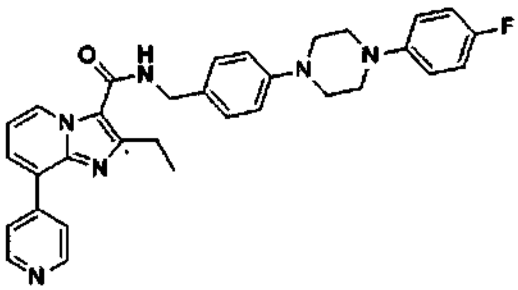
Hz, 2H), 6.44 (brt, J = 5.6 Hz, 1H), 6.81 – 6.86 (m, 1H), 6.92 – 7.06 (m, 7H), 7.29 (d, J = 8.8 Hz, 2H), 9.08 (d, J = 6.8 Hz, 1H); LCMS (electrospray) m/z 476 $(M+H)^+$.

7-Bromo-2-ethyl-*N*-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (311)



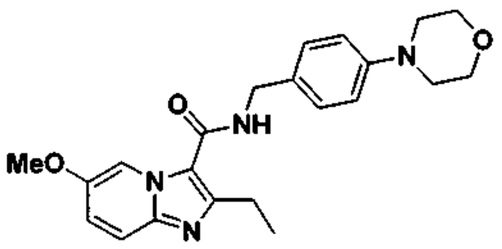
White solid; mp = 214.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36 (t, J = 7.6 Hz, 3H), 2.92 (q, J = 7.6 Hz, 2H), 3.24 – 3.28 (m, 4H), 3.33 – 3.35 (m, 4H), 4.60 (d, J = 5.2 Hz, 2H), 6.02 (brt, J = 5.2 Hz, 1H), 6.91 – 7.02 (m, 7H), 7.28 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 1.6 Hz, 1H), 9.28 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z 536, 538 $(M+H)^+$ (Br^- isotope pattern).

2-Ethyl-*N*-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzyl)-8-(pyridin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (312)



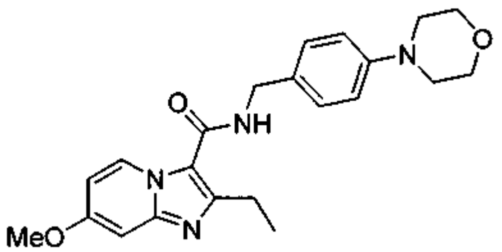
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7. 6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 3.25 (t, J = 5.2 Hz, 4H), 3.34 (t, J = 5.2 Hz, 4H), 4.64 (d, J = 5.6 Hz, 2H), 6.10 (brs, 1H), 6.91 – 7.04 (m, 7H), 7.32 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.2 Hz, 1H), 7.99 (d, J = 5.2 Hz, 2H), 8.72 (d, J = 4.4 Hz, 2H), 9.47 (d, J = 6.8 Hz, 1H).; LCMS (electrospray) m/z $(M+H)^+$ 535.

2-Ethyl-6-fluoro-N-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (313)



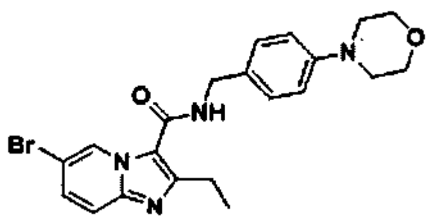
White solid; mp = 193.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.4 Hz, 3H), 2.94 (q, J = 7.6 Hz, 2H), 3.15 – 3.17 (m, 4H), 3.85 – 3.87 (m, 7H), 4.62 (d, J = 52 Hz, 2H), 6.00 – 6.02 (m, 1H), 6.92 (d, J = 9.6 Hz, 2H), 7.11 (dd, J = 2.4, 9.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 9.6 Hz, 1H), 9.10 (d, J = 2.4 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 395

2-Ethyl-7-methoxy-*N*-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide(314)



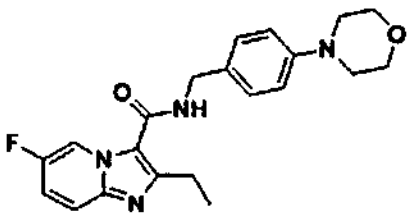
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.33 (t, J = 7.6 Hz, 3H), 2.86 (q, J = 7.6 Hz, 2H), 3.12 – 3.14 (m, 4H), 3.80 – 3.88 (m, 4H), 3.83 (s, 3H), 4.56 (d, J = 5.6 Hz, 2H), 5.98 (brt, J = 5.6 Hz, 1H), 6.56 (dd, J = 2.4, 7.6 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 9.19 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.5, 43.1, 49.4, 55.6, 67.0, 94.5, 107.4, 113.9, 116.0, 128.8, 128.9, 129.6, 148.1, 150.9, 151.0, 159.4, 161.5.

6-Bromo-2-ethyl-N-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (315)



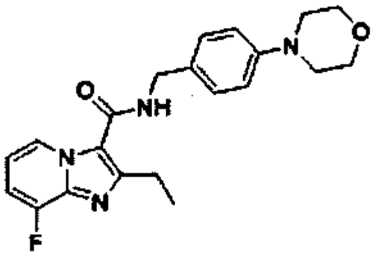
White solid; mp = 228.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.38 (t, J = 7.6 Hz, 3H), 2.95 (q, J = 7.6 Hz, 2H), 3.16 (t, J = 4.8 Hz, 4H), 3.86 (t, J = 4.8 Hz, 4H), 4.61 (d, J = 5.6 Hz, 2H), 6.02 (brs, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.38 (dd, J = 1.6 Hz, 9.6 Hz, 1H), 7.48 (d, J = 9.6 Hz, 1H), 9.61 (d, J = 0.8 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 443.

2-Ethyl-6-fluoro-N-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (316)



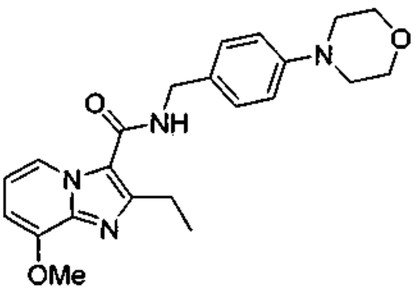
White solid; mp = 181.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.42 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 3.19 (t, J = 4.8 Hz, 4H), 3.89 (t, J = 4.8 Hz, 4H), 4.64 (d, J = 5.2 Hz, 2H), 6.02 (brs, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.26 – 7.33 (m, 3H), 7.60 (dd, J = 5.2 Hz, 5.4 Hz, 1H), 9.48 (dd, J = 2.4 Hz, 5.2 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 383.

2-Ethyl-8-fluoro-N-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (317)



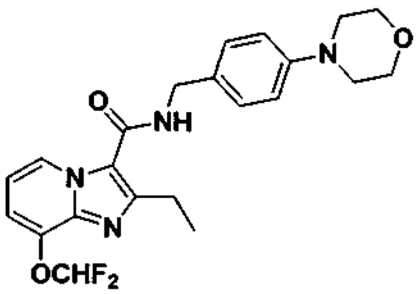
White solid; mp = 197.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.39 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 3.15 – 3.17 (m, 4H), 3.85 – 3.87 (m, 4H), 4.61 (d, J = 5.6 Hz, 2H), 6.05 (brs, 1H), 6.80 – 6.85 (m, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.00 – 7.05 (m, 1H), 7.29 (d, J = 8.8 Hz, 2H), 9.19 (dd, J = 0.8 Hz, 7.2 Hz, 1H) ; LCMS (electrospray) m/z $(M+H)^+$ 383.

2-Ethyl-8-methoxy-*N*-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (318)



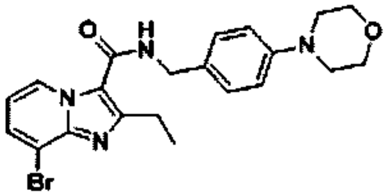
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.33 (t, J = 7.6 Hz, 3H), 2.92 (q, J = 7.6 Hz, 2H), 3.12 – 3.14 (m, 4H), 3.82 – 3.84 (m, 4H), 3.98 (s, 3H), 4.58 (d, J = 5.6 Hz, 1H), 6.08 (brs, 1H), 6.57 (d, J = 7.2 Hz, 1H), 6.75 (dd, J = 7.2, 7.2 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 8.93 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 23.6, 43.2, 49.3, 56.0, 67.0, 103.1, 113.0, 116.0, 120.9, 124.8, 128.9, 129.4, 140.4, 148.2, 149.9, 150.9, 161.5.

8-(Difluoromethoxy)-2-ethyl-N-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (319)



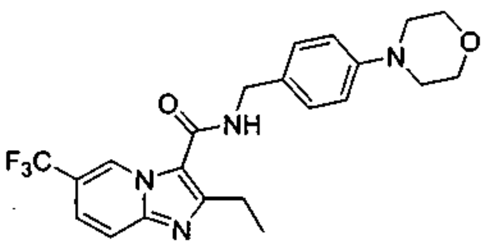
Off-white solid; mp = 163.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 2.97 (q, J = 7.6 Hz, 2H), 3.16 (t, J = 5.0 Hz, 4H), 3.86 (t, J = 4.8 Hz, 4H), 4.62 (d, J = 5.6 Hz, 2H), 6.03 – 6.05 (m, 1H), 6.85 (dd, J = 7.6 Hz, 2H), 6.92 (d, J = 6.8 Hz, 2H), 7.11 (d, J = 7.6 Hz, 1H), 7.26 (t, J = 74.2 Hz, 1H due to F_2), 7.29 (d, J = 8.4 Hz, 2H), 9.25 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 431

8-Bromo-2-ethyl-*N*-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (320)



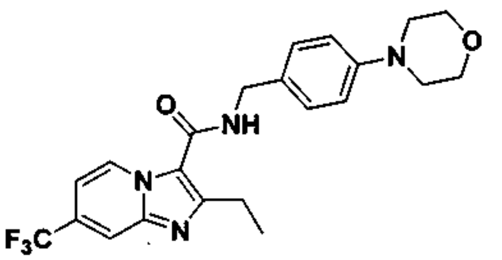
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7. 6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 3.15 (t, J = 4.8 Hz, 4H), 3.85 (t, J = 4.8 Hz, 4H), 4.60 (d, J = 5.2 Hz, 2H), 6.06 (brs, 1H), 6.77 (dd, J = 7.2 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.56 (dd, J = 0.8 Hz, 7.2 Hz, 1H), 9.37 (dd, J = 0.8 Hz, 7.2 Hz, 1H).; LCMS (electrospray) m/z $(M+H)^+$ 445.

2-Ethyl-*N*-(4-morpholinobenzyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamide (321)



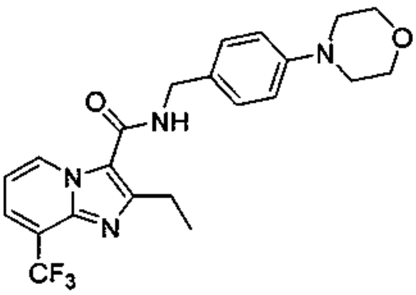
White solid; mp = 207.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, J = 7.2 Hz, 3H), 2.94 (q, J = 7.2 Hz, 2H), 3.13 – 3.15 (m, 4H), 3.83 - 3.85 (m, 4H), 4.60 (d, J = 5.2 Hz, 2H), 6.10 (brs, 1H), 6.89 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 9.2 Hz, 1H), 7.65 (d, J = 9.2 Hz, 1H), 9.82 (s, 1H).

2-Ethyl-N-(4-morpholinobenzyl)-7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamide (322)



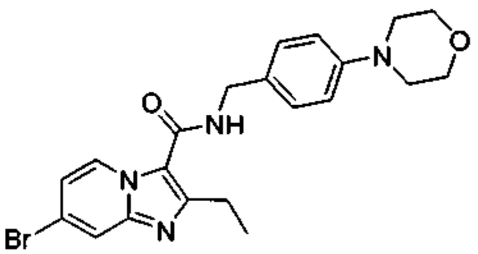
White solid; mp = 174.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 3.16 (t, J = 4.8 Hz, 4H), 3.86 (t, J = 4.8 Hz, 4H), 4.62 (d, J = 5.6 Hz, 2H), 6.09 – 6.11 (m, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.07 (dd, J = 2.0, 7.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.88 – 7.90 (m, 1H), 9.50 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 433

2-Ethyl-*N*-(4-morpholinobenzyl)-8-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamide (323)



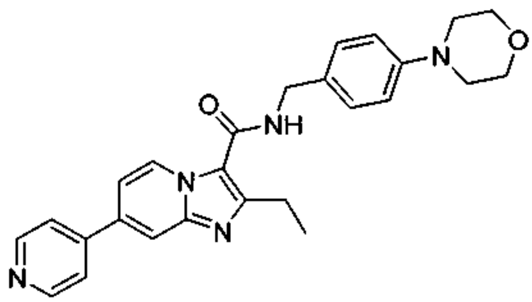
White solid; mp = 200.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.34 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 3.14 – 3.16 (m, 4H), 3.83 – 3.86 (m, 4H), 4.60 (d, J = 5.6 Hz, 2H), 6.11 (brt, J = 5.6 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.93 (dd, J = 6.8, 6.8 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 6.8 Hz, 1H), 9.54 (d, J = 6.8 Hz, 1H).

7-Bromo-2-ethyl-*N*-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (324)



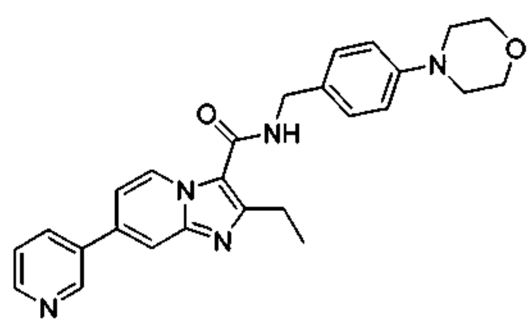
Pale gray solid; mp = 202.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.34 (t, J = 7.6 Hz, 3H), 2.90 (q, J = 7.6 Hz, 2H), 3.13 – 3.15 (m, 4H), 3.83 – 3.86 (m, 4H), 4.58 (d, J = 5.6 Hz, 2H), 6.05 (brt, J = 5.6 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.97 (dd, J = 2.0, 7.2 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 2.0 Hz, 1H), 9.25 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.5, 43.2, 49.3, 67.0, 115.1, 116.0, 117.0, 119.1, 121.1, 128.5, 128.9, 129.2, 143.6, 151.0, 151.4, 161.2; LCMS (electrospray) m/z 443, 445 $(M+H)^+$ (Br^- isotope pattern).

2-Ethyl-*N*-(4-morpholinobenzyl)-7-(pyridin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (325)



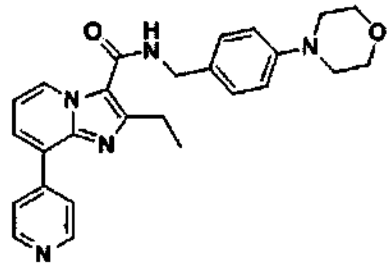
Yellow solid; mp = 210.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, J = 7.6 Hz, 3H), 2.94 (q, J = 7.6 Hz, 2H), 3.12 – 3.15 (m, 4H), 3.82 – 3.85 (m, 4H), 4.60 (d, J = 5.2 Hz, 2H), 6.16 (brt, J = 5.2 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.16 (dd, J = 2.0, 7.2 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 6.0 Hz, 2H), 7.85 (d, J = 2.0 Hz, 1H), 8.68 (d, J = 6.0 Hz, 2H), 9.44 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.6, 43.2, 49.3, 66.9, 111.8, 114.3, 115.3, 116.0, 121.2, 128.6, 128.9, 129.2, 136.3, 145.5, 146.1, 150.7, 151.0, 151.9, 161.2; LCMS (electrospray) m/z 442 $(M+H)^+$.

2-Ethyl-*N*-(4-morpholinobenzyl)-7-(pyridin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide (326)



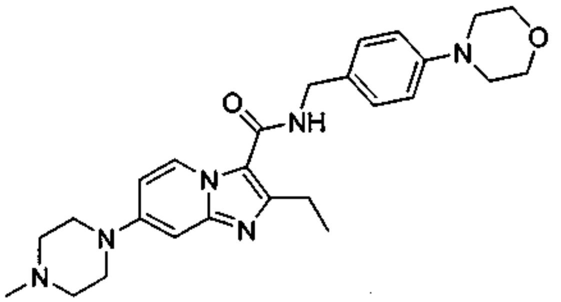
Yellow solid; mp = 208.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36 (t, J = 7.2 Hz, 3H), 2.93 (q, J = 7.2 Hz, 2H), 3.12 – 3.15 (m, 4H), 3.82 – 3.85 (m, 4H), 4.59 (d, J = 4.8 Hz, 2H), 6.21 (brs, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 6.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.37 (dd, J = 5.6, 6.0 Hz, 1H), 7.77 (brs, 1H), 7.90 (d, J = 7.2 Hz, 1H), 8.60 (brs, 1H), 8.88 (brs, 1H), 9.41 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.5, 43.2, 49.3, 66.9, 112.2, 113.8, 115.0, 116.0, 123.9, 128.5, 128.9, 129.3, 134.0, 134.2, 136.2, 146.3, 148.0, 149.6, 150.9, 151.7, 161.3; LCMS (electrospray) m/z 442 $(M+H)^+$.

2-Ethyl-*N*-(4-morpholinobenzyl)-8-(pyridin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (327)



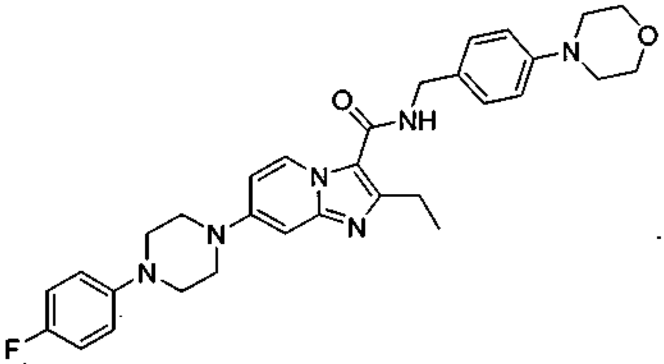
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7. 6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 3.16 (t, J = 4.8 Hz, 4H), 3.86 (t, J = 4.8 Hz, 4H), 4.63 (d, J = 5.6 Hz, 2H), 6.07 (brs, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.02 (dd, J = 6.8 Hz, 6.8 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.54 (dd, J = 1.2 Hz, 7.2 Hz, 1H), 7.99 (d, J = 6.0 Hz, 2H), 8.72 (d, J = 5.2 Hz, 2H), 9.47 (dd, J = 1.2 Hz, 5.6 Hz, 1H).; LCMS (electrospray) m/z $(M+H)^+$ 442.

2-Ethyl-7-(4-methylpiperazin-1-yl)-*N*-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (328)



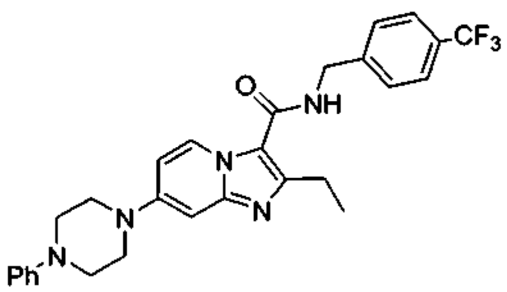
White solid; mp = 204.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.33 (t, J = 7.6 Hz, 3H), 2.33 (s, 3H), 2.54 – 2.56 (m, 4H), 2.85 (q, J = 7.6 Hz, 2H), 3.12 – 3.15 (m, 4H), 3.27 – 3.30 (m, 4H), 3.83 – 3.85 (m, 4H), 4.57 (d, J = 5.6 Hz, 2H), 5.91 (brt, J = 5.6 Hz, 1H), 6.62 (dd, J = 2.4, 8.0 Hz, 1H), 6.5 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 9.16 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.6, 43.1, 46.2, 47.8, 49.4, 54.7, 67.0, 96.4, 105.9, 113.2, 116.0, 128.3, 128.8, 129.8, 148.5, 150.0, 150.9, 151.2, 161.7; LCMS (electrospray) m/z 463 $(M+H)^+$.

2-Ethyl-7-(4-(4-fluorophenyl)piperazin-1-yl)-*N*-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide(329)



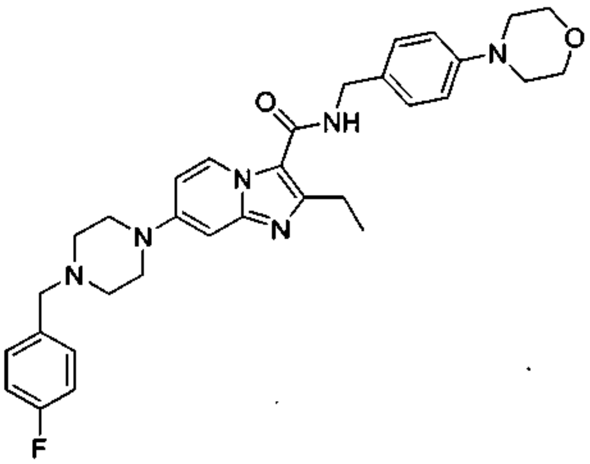
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.34 (t, J = 7.6 Hz, 3H), 2.87 (q, J = 7.6 Hz, 2H), 3.13 – 3.15 (m, 4H), 3.22 – 3.25 (m, 4H), 3.41 – 3.43 (m, 4H), 3.83 – 3.86 (m, 4H), 4.58 (d, J = 5.2 Hz, 2H), 5.99 (brt, J = 5.2 Hz, 1H), 6.67 (dd, J = 2.4, 8.0 Hz, 1H), 6.81 (d, J = 2.4 Hz, 1H), 6.88 – 6.93 (m, 4H), 6.96 (dd, J = 8.4, 8.8 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 9.19 (d, J = 8.0 Hz, 1H); LCMS (electrospray) m/z 543 $(M+H)^+$.

2-Ethyl-7-(4-phenylpiperazin-1-yl)-*N*-(4-(trifluoromethyl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (330)



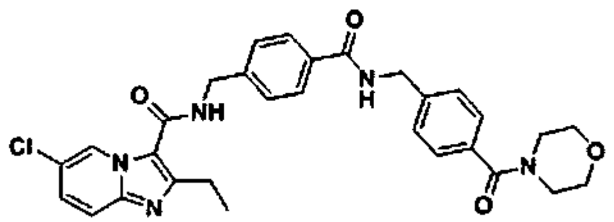
Pale yellow solid; mp = 235.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.40 (t, J = 7.2 Hz, 3H), 2.93 (q, J = 7.2 Hz, 2H), 3.34 – 3.36 (m, 4H), 3.44 – 3.48 (m, 4H), 4.74 (d, J = 6.0 Hz, H), 6.07 (brt, J = 6.0 Hz, 1H), 6.70 (dd, J = 2.4, 7.6 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 7.2, 7.6 Hz, 1H), 6.97 (d, J = 8.4 Hz, 2H), 7.28 – 7.32 (m, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 9.22 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z 508 $(M+H)^+$.

2-Ethyl-7-(4-(4-fluorobenzyl)piperazin-1-yl)-*N*-(4-morpholinobenzyl)imidazo[1,2-a]pyridine-3-carboxamide (331)



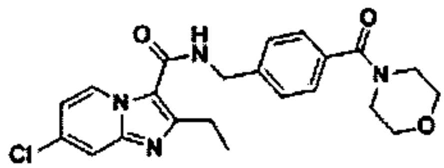
White solid; mp = 212.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.33 (t, J = 7.6 Hz, 3H), 2.56 – 2.58 (m, 4H), 2.85 (q, J = 7.6 Hz, 2H), 3.13 – 3.15 (m, 4H), 3.26 – 3.29 (m, 4H), 3.51 (s, 2H), 3.83 – 3.86 (m, 4H), 4.57 (d, J = 5.6 Hz, 2H), 5.93 (brt, J = 5.6 Hz, 1H), 6.62 (dd, J = 2.4, 7.6 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.98 – 7.03 (m, 2H), 7.26 – 7.31 (m, 4H), 9.15 (d, J = 7.6 Hz, 1H).

6-Chloro-2-ethyl-*N*-(4-((4-(morpholine-4-carbonyl)benzyl)carbamoyl)benzyl) imidazo[1,2-a]pyridine-3-carboxamide (332)



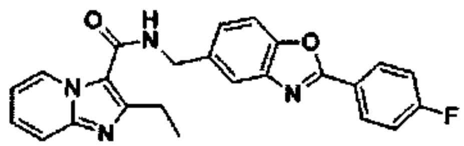
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7. 6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 3.72 (m, 8H), 4.65 (d, J = 6.0 Hz, 2H), 4.73 (d, J = 6.0 Hz, 2H), 6.29 (brs, 1H), 6.62 (brs, 1H), 7.31 (dd, J = 2.0 Hz, 9.6 Hz, 1H), 7.36 (s, 4H), 7.43 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 9.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 9.49 (s, 1H).; LCMS (electrospray) m/z $(M+H)^+$ 560.

7-Chloro-2-ethyl-*N*-(4-(morpholine-4-carbonyl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (333)



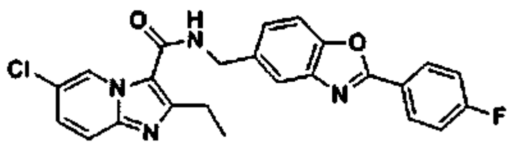
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7. 6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 3.70 - 3.71 (m, 8H), 4.72 (d, J = 6.0 Hz, 2H), 6.17 (brs, 1H), 7.31 (dd, J = 2.0 Hz, 9.2 Hz, 1H), 7.42 (s, 4H), 7.55 (dd, J = 0.8 Hz, 9.6 Hz, 1H), 9.53 (dd, J = 0.8 Hz, 2.0 Hz, 1H).; LCMS (electrospray) m/z $(M+H)^+$ 427.

2-Ethyl-*N*-((2-(4-fluorophenyl)benzo[d]oxazol-5-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (334)



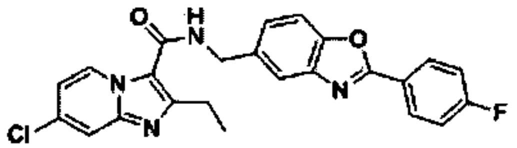
White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (t, J = 7. 6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.65 (d, J = 6.0 Hz, 2H), 6.99 (dd, J = 7.2 Hz, 1H), 7.36 (dd, J = 6.8 Hz, 1H), 7.42 (s, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 9.2 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.77 (s, 1H), 8.23 (dd, J = 5.2 Hz, 8.8 Hz, 2H), 8.47 (t, J = 6.0 Hz, 1H), 8.97 (d, J = 6.8 Hz, 1H).; LCMS (electrospray) m/z $(M+H)^+$ 415.

6-Chloro-2-ethyl-*N*-((2-(4-fluorophenyl)benzo[d]oxazol-5-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (335)



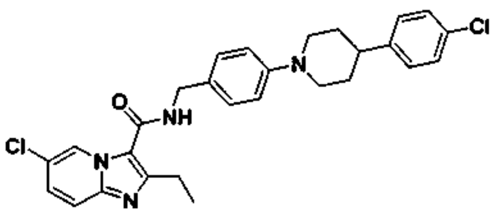
White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (t, J = 7. 6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 4.65 (d, J = 5.6 Hz, 2H), 7.41 – 7.46 (m, 4H), 7.64 (d, J = 9.6 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 8.21 – 8.25 (m, 2H), 8.54 (t, J = 5.6 Hz, 1H), 9.08 (d, J = 2.0 Hz, 1H).; LCMS (electrospray) m/z $(M+H)^+$ 449.

7-Chloro-2-ethyl-*N*-((2-(4-fluorophenyl)benzo[d]oxazol-5-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (336)



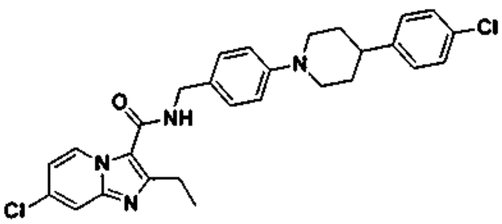
White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (t, J = 7. 2 Hz, 3H), 2.98 (q, J = 7.2 Hz, 2H), 4.64 (d, J = 5.6 Hz, 2H), 7.07 (d, J = 7.6 Hz, 1H), 7.42 – 7.46 (m, 3H), 7.75 (d, J = 8.4 Hz, 2H), 7.77 (s, 1H), 8.23 (d, J = 8.4 Hz, 2H), 8.55 (brs, 1H), 8.96 (d, J = 7.2 Hz, 1H).; LCMS (electrospray) m/z $(M+H)^+$ 449.

6-Chloro-N-(4-(4-(4-chlorophenyl)piperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (337)



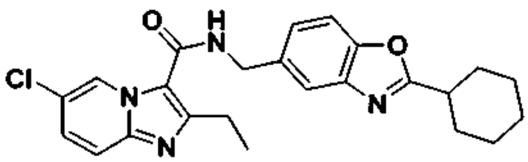
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.6 Hz, 3H), 1.80 – 1.96 (m, 4H), 2.60 – 2.68 (m, 1H), 2.92 - 2.98 (m, 4H), 2.95 (q, J = 7.6 Hz, 2H), 3.79 – 3.83 (m, 2H), 4.61 (q, J = 5.2 Hz, 2H), 5.99 – 6.01 (m, 1H), 6.90 (dd, J = 2.2, 7.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.26 – 7.29 (m, 4H), 7.59 (d, J = 2.0 Hz, 1H), 9.30 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z $(M+H)^+$ 507

7-Chloro-N-(4-(4-(4-chlorophenyl)piperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (338)



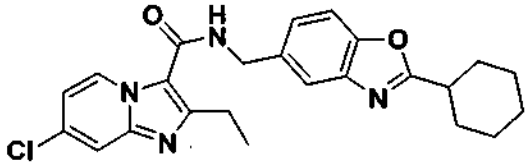
Pale yellow solid; mp = 177.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.4 Hz, 3H), 1.80 – 1.96 (m, 4H), 2.60 – 2.67 (m, 1H), 2.79 - 2.86 (m, 4H), 2.96 (q, *J* = 7.4 Hz, 2H), 3.80 – 3.83 (m, 2H), 4.62 (q, *J* = 5.2 Hz, 2H), 6.00 – 6.02 (m, 1H), 6.98 (dd, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.31 (m, 4H), 7.54 (d, *J* = 9.6 Hz, 2H), 9.30 (d, *J* = 7.6 Hz, 1H).

6-Chloro-*N*-((2-cyclohexylbenzo[d]oxazol-5-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (339)



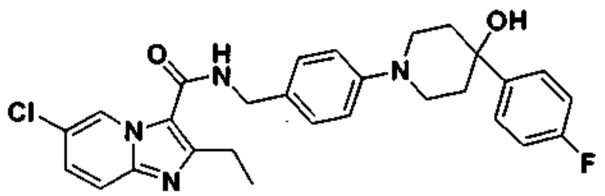
White solid; mp = 169.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 – 1.44 (m, 4H), 1.59 – 1.88 (m, 8H), 2.16 (d, *J* = 10.8 Hz, 2H), 2.96 (q, *J* = 7.6 Hz, 2H), 4.78 (d, *J* = 5.6 Hz, 2H), 6.19 (brs, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.30 – 7.34 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 7.67 (s, 1H), 9.53 (d, *J* = 2.4 Hz, 1H).; LCMS (electrospray) m/z $(M+H)^+$ 437.

7-Chloro-*N*-((2-cyclohexylbenzo[d]oxazol-5-yl)methyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (340)



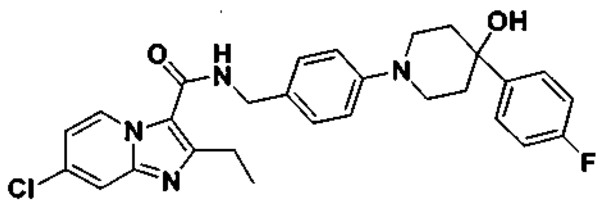
White solid; mp = 163.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 – 1.46 (m, 6H), 1.60 – 1.73 (m, 4H), 1.86 (d, *J* = 13.2 Hz, 2H), 2.15 (d, *J* = 13.2 Hz, 2H), 2.95 (q, *J* = 7.2 Hz, 2H), 4.77 (d, *J* = 5.6 Hz, 2H), 6.12 (brs, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.67 (s, 1H), 9.36 (d, *J* = 7.2 Hz, 1H). ; LCMS (electrospray) m/z $(M+H)^+$ 437.

6-Chloro-2-ethyl-*N*-(4-(4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (341)



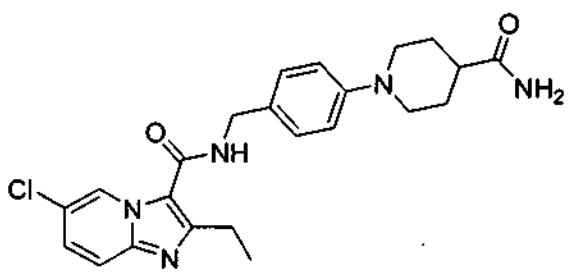
White solid; mp = 173.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7.6 Hz, 3H), 1.66 (s, 1H), 1.85 (d, J = 12.0 Hz, 2H), 2.18 – 2.26 (m, 2H), 2.91 (q, J = 7.6 Hz, 2H), 3.21 – 3.26 (dd, J = 10.4 Hz, 12.0 Hz, 2H), 3.58 (d, J = 11.6 Hz, 2H), 4.60 (d, J = 5.6 Hz, 2H), 6.00 (brs, 1H), 6.89 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 7.04 (dd, J = 8.8 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.48 (dd, J = 5.2 Hz, 8.8 Hz, 2H), 7.56 (d, J = 2.0 Hz, 1H), 9.35 (d, J = 7.6 Hz, 1H). ; LCMS (electrospray) m/z $(M+H)^+$ 507.

7-Chloro-2-ethyl-*N*-(4-(4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (342)



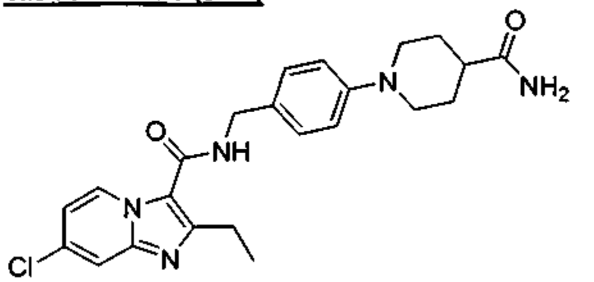
White solid; mp = 199.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 1.6 (s, 1H), 1.86 (dd, J = 2.8 Hz, 14.0Hz, 2H), 2.19 – 2.26 (m, 2H), 2.95 (q, J = 7.6 Hz, 2H), 3.20 – 3.27 (m, 2H), 3.59 (dd, J = 2.4 Hz, 10.0 Hz, 2H), 4.61 (d, J = 5.6 Hz, 2H), 6.02 (s, 1H), 6.98 – 7.06 (m, 4H), 7.27 (d, J = 8.8 Hz, 2H), 7.29 (s, 1H), 7.46 – 7.51 (m, 2H), 7.53 (s, 1H), 9.52 (d, J = 2.4 Hz, 1H). ; LCMS (electrospray) m/z $(M+H)^+$ 507.

***N*-(4-(4-Carbamoylpiperidin-1-yl)benzyl)-6-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (343)**



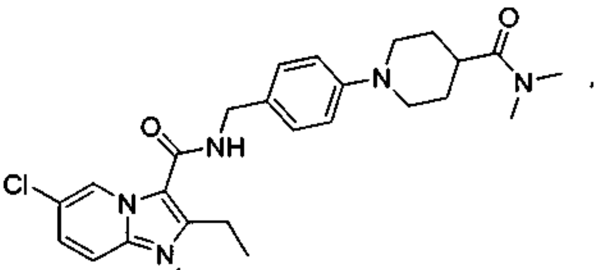
White solid; mp = 257.5 °C; ^{1}H NMR (400 MHz, DMSO-d^6); δ 1.23 (t, J = 7.2 Hz, 3H), 1.57 – 1.66 (m, 2H), 1.74 – 1.76 (m, 2H), 2.19 – 2.45 (m, 1H), 2.59 – 2.66 (m, 2H), 2.94 (q, J = 7.2 Hz, 2H), 3.65 – 3.69 (m, 2H), 4.41 (d, J = 6.0 Hz, 2H), 6.75 (brs, 1H), 6.90 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.26 (brs, 1H), 7.43 (dd, J = 2.4, 9.6 Hz, 1H), 7.67 (d, J = 9.6 Hz, 1H), 8.38 (brt, J = 6.0 Hz, 1H), 9.06 (d, J = 2.4 Hz, 1H); LCMS (electrospray) m/z 440 $(M+H)^+$.

<u>*N*-(4-(4-Carbamoylpiperidin-1-yl)benzyl)-7-chloro-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (344)</u>



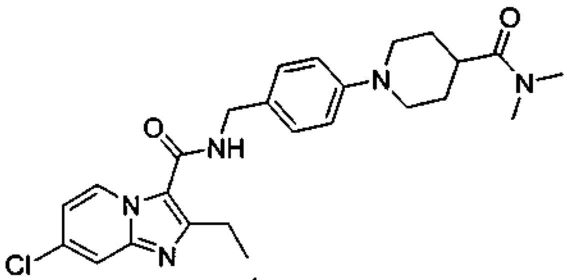
White solid; mp = 244 °C; ^{1}H NMR (400 MHz, DMSO-d^6); δ 1.23 (t, J = 7.2 Hz, 3H), 1.56 – 1.66 (m, 2H), 1.74 – 1.76 (m, 2H), 2.18 – 2.24 (m, 1H), 2.59 – 2.66 (m, 2H), 2.92 (q, J = 7.2 Hz, 2H), 3.65 – 3.68 (m, 2H), 4.40 (d, J = 5.6 Hz, 2H), 6.75 (brs, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.07 (dd, J = 2.0, 7.6 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.25 (brs, 1H), 7.77 (d, J = 2.0 Hz, 1H), 8.36 (brt, J = 5.6 Hz, 1H), 8.93 (d, J = 7.6 Hz, 1H); LCMS (electrospray) m/z 440 $(M+H)^+$.

<u>6-Chloro-*N*-(4-(4-(dimethylcarbamoyl)piperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (345)</u>



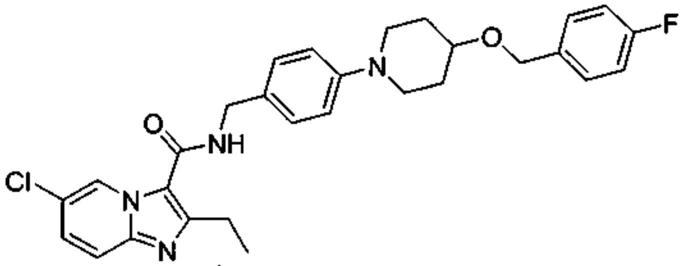
White solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, J = 7.6 Hz, 3H), 1.78 – 1.81 (m, 2H), 1.90 – 2.00 (m, 2H), 2.59 – 2.67 (m, 1H), 2.71 – 7.78 (m, 2H), 2.91 – 2.97 (m, 5H), 3.07 (s, 3H), 3.73 – 3.76 (m, 2H), 4.57 (d, J = 5.2 Hz, 2H), 6.03 (brt, J = 5.2 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 7.23 – 7.28 (m, 3H), 7.50 (d, J = 9.6 Hz, 1H), 9.50 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.6, 28.4, 35.8, 37.2, 38.7, 43.3, 49.3, 115.4, 116.7, 117.0, 121.5, 126.3, 128.2, 128.5, 128.9, 144.5, 151.3, 151.4, 161.1, 174.7; LCMS (electrospray) m/z 468 $(M+H)^+$.

<u>7-Chloro-*N*-(4-(4-(dimethylcarbamoyl)piperidin-1-yl)benzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (346)</u>



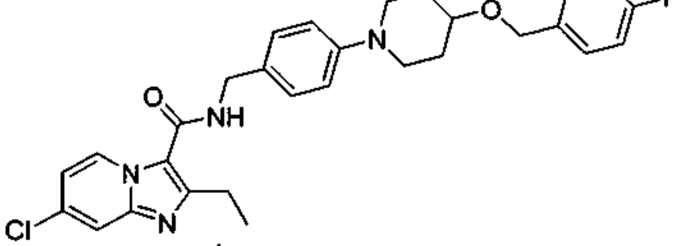
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.33 (t, *J* = 7.2 Hz, 3H), 1.77 – 1.80 (m, 2H), 1.88 – 1.99 (m, 2H), 2.58 – 2.66 (m, 1H), 2.70 – 2.77 (m, 2H), 2.89 – 2.95 (m, 5H), 3.06 (s, 3H), 3.71 – 3.74 (m, 2H), 4.56 (d, *J* = 5.2 Hz, 2H), 6.07 (brs, 1H), 6.84 (dd, *J* = 1.6, 7.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 1.6 Hz, 1H), 9.30 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.5, 28.4, 35.8, 37.2, 38.7, 43.3, 49.3, 114.6, 115.1, 115.7, 116.7, 128.5, 128.6, 128.8, 133.5, 146.1, 151.2, 151.6, 161.2, 174.7; LCMS (electrospray) m/z 468 $(M+H)^+$.

6-Chloro-2-ethyl-*N*-(4-(4-(4-fluorobenzyloxy)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (347)



Pale pink solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, *J* = 7.6 Hz, 3H), 1.73 – 1.82 (m, 2H), 2.00 – 2.04 (m, 2H), 2.91 – 2.98 (m, 4H), 3.50 – 3.59 (m, 3H), 4.53 (s, 2H), 4.58 (d, *J* = 5.2 Hz, 2H), 6.00 (brt, *J* = 5.2 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.99 – 7.04 (m, 2H), 7.23 – 7.35 (m, 5H), 7.50 (d, *J* = 9.6 Hz, 1H), 9.51 (d, *J* = 2.0 Hz, 1H); LCMS (electrospray) m/z 521 $(M+H)^+$.

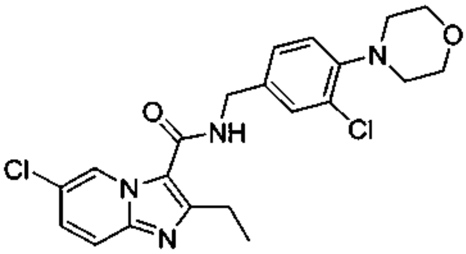
7-Chloro-2-ethyl-*N*-(4-(4-(4-fluorobenzyloxy)piperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (348)



Pale pink solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.34 (t, *J* = 7.2 Hz, 3H), 1.73 – 1.82 (m, 2H), 1.96 – 2.07 (m, 2H), 2.91 – 2.95 (m, 4H), 3.49 – 3.59 (m, 3H), 4.52 (s, 2H), 4.56 (d, *J* = 5.6

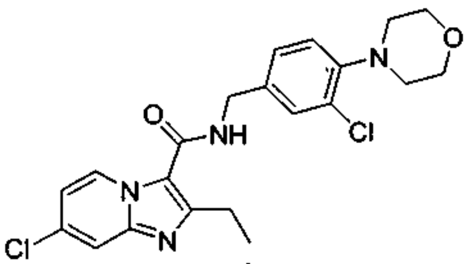
Hz, 2H), 5.99 (brt, J = 5.6 Hz, 1H), 6.86 – 6.92 (m, 3H), 6.99 – 7.03 (m, 2H), 7.22 – 7.32 (m, 4H), 7.55 (d, J = 1.6 Hz, 1H), 9.32 (d, J = 7.2 Hz, 1H); LCMS (electrospray) m/z 521 $(M+H)^+$.

6-Chloro-*N*-(3-chloro-4-morpholinobenzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (349)



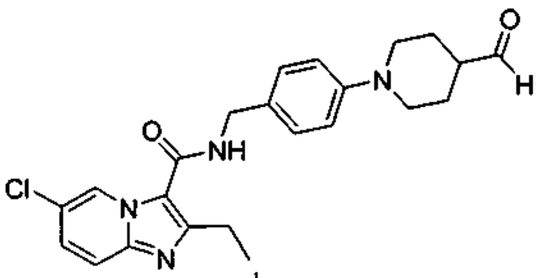
White solid; mp = 175.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.37 (t, J = 7.6 Hz, 3H), 2.94 (q, J = 7.6 Hz, 2H), 2.99 – 3.03 (m, 4H), 3.83 – 3.85 (m, 4H), 4.58 (d, J = 6.0 Hz, 2H), 6.15 (brt, J = 6.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 7.21 (dd, J = 1.6, 8.0 Hz, 1H), 7.26 – 7.28 (m, 1H), 7.36 (d, J = 1.6 Hz, 1H), 7.49 (d, J = 9.2 Hz, 1H), 9.47 (d, J = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.7, 42.7, 51.8, 67.2, 115.1, 117.0, 120.7, 121.7, 126.3, 127.0, 128.4, 129.2, 130.1, 134.0, 144.6, 148.6, 151.6, 161.2; LCMS (electrospray) m/z 433 $(M+H)^+$.

7-Chloro-*N*-(3-chloro-4-morpholinobenzyl)-2-ethylimidazo[1,2-a]pyridine-3-carboxamide (350)



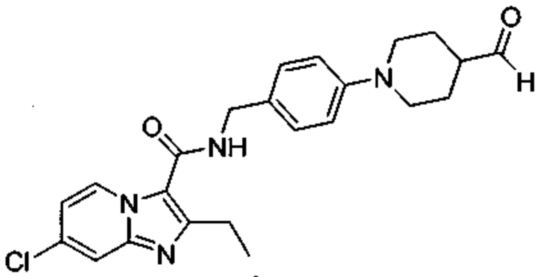
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.38 (t, J = 7.6 Hz, 3H), 2.94 (q, J = 7.6 Hz, 2H), 3.02 – 3.05 (m, 4H), 3.85 – 3.87 (m, 4H), 4.59 (d, J = 5.6 Hz, 2H), 6.09 (brt, J = 5.6 Hz, 1H), 6.88 (dd, J = 2.0, 7.2 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 7.22 (dd, J = 1.6, 8.0 Hz, 1H), 7.37 (d, J = 1.6 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 9.32 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.7, 42.7, 51.8, 67.3, 114.9, 115.8, 120.7, 127.1, 128.6, 129.2, 130.1, 133.8, 134.0, 146.3, 148.7, 151.9, 161.3 (hidden 1 carbon); LCMS (electrospray) m/z 433 $(M+H)^+$.

6-Chloro-2-ethyl-*N*-(4-(4-formylpiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (351)



Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.36 (t, J = 7.6 Hz, 3H), 1.74 – 1.84 (m, 2H), 2.01 – 2.05 (m, 2H), 2.37 – 2.44 (m, 1H), 2.84 – 2.91 (m, 2H), 2.92 (q, J = 7.6 Hz, 2H), 3.60 – 3.65 (m, 2H), 4.59 (d, J = 5.6 Hz, 2H), 5.99 (brt, J = 5.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.27 (dd, J = 2.4, 9.6 Hz, 1H), 7.52 (d, J = 9.6 Hz, 1H), 9.52 (d, J = 2.4 Hz, 1H), 9.70 (s, 1H); LCMS (electrospray) m/z 425 $(M+H)^+$.

7-Chloro-2-ethyl-N-(4-(4-formylpiperidin-1-yl)benzyl)imidazo[1,2-a]pyridine-3-carboxamide (352)



Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.35 (t, J = 7.6 Hz, 3H), 1.74 – 1.84 (m, 2H), 2.01 – 2.05 (m, 2H), 2.38 – 2.44 (m, 1H), 2.84 – 2.90 (m, 2H), 2.91 (q, J = 7.6 Hz, 2H), 3.59 – 3.64 (m, 2H), 4.58 (d, J = 5.2 Hz, 2H), 5.98 (brt, J = 5.2 Hz, 1H), 6.88 (dd, J = 2.0, 7.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 2.0 Hz, 1H), 9.34 (d, J = 7.6 Hz, 1H), 9.70 (s, 1H); LCMS (electrospray) m/z 425 $(M+H)^+$.

Example 3: Additional studies on imidazopyridine compounds

Kinetics of inhibition and bactericidal activity

Mycobacterium tuberculosis H37Rv was incubated at an initial inoculum of $2x10^6$ bacteria/ml in Middlebrook 7H9 media containing an increasing concentration of representative compound 47 or 54. Culture samples were collected over a 14 day period. Serial dilutions of the bacterial suspension were performed and plated on 7H10 medium. Colonies were counted for the different dilutions after 3 weeks incubation at 37°C under 5% CO_2 and compared to that obtained for the DMSO negative and PA-824 positive controls. PA-824 (Stover *et al.*,

2000) is a TB Alliance small chemical compound currently in phase II clinical trials for the treatment of tuberculosis. PA-824 possibly acts via generation of radicals having non-specific toxic effects. However, the durg has been shown to inhibit mycolic acid and protein biosynthesis. In addition, PA-824 demonstrates anaerobic activity.

Bactericidal activity was demonstrated by the decrease in colongy forming unit (CFU) number after incubation with various concentrations of either compound 47 or 54. DMSO control showed no decrease in CFU numbers (Figure 2). The activity of both compounds was quite potent and reached 100% growth inhibition around the same time as the reference compound PA-824. These data demonstrate the therapeutic usefulness of this scaffold for the treatment of tuberculosis.

Activity against MDR strains

MIC of representative compounds 47 and 54, along with the reference compounds isioniazid (INH) and moxifloxacin (MFX), were determined by the Alamar blue method for 10 multi-drug resitstant (MDR) clinical isolates that exhibit different antibiotic resistance profiles and 1 *M. tuberculosis* drug sensitive strain (lab strain H37Rv). Briefly, bacterial suspensions were incubated for 14 days in 7H9 medium containing increasing concentrations of compound. Resazurin was added to a 0.01% final concentration and fluorescence was measured to assess bacterial viability after a 24h-incubation period. MIC was determined as the first concentration giving 80% bacterial growth inhibition compared to DMSO control.

All MDR tested strains showed an MIC lower than or equal to 1.25 μM for compound 47 and 0.625 for compound 54, while INH resistance was confirmed for all these strains (Table 2). These values are similar to that obtained for the *M. tuberculosis* drug sensitive strain (1.25 μM and 0.625 μM, respectively). Both compound 47 and compound 54 showed levels of activity comparable to or better than MFX. These data clearly show that this scaffold has therapeutic applicability for the treatment of tuberculosis and in particular multi-drug resistant strains of the disease.

In Vivo activity in a murine model

The effect of compounds 177 and 185 on the bacterial load of TB-infected mice was compared to that of the reference compound Isoniazid (INH). 8-week old female BalbC mice were infected with $6x10^5$ *M. tuberculosis* H37Rv via intranasal instillation. Mice were sacrificed at day 1 to control the number of CFU in the lungs. In the acute model of infection, mice were treated for 4 weeks, starting at day 1. Compounds were freshly dissolved in a 0.5% methylcellulose solution and administered by oral gavage 5 times/week. Bacterial load was assessed in lungs and spleen after homogenizing the organs in 1X PBS. Serial dilutions of organs homogenates were spread on Middlebrook 7H11 plates and CFU were determined after 3 weeks incubation at 37°C under 5% CO2.

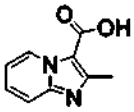
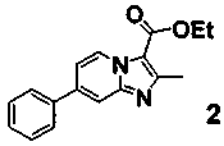
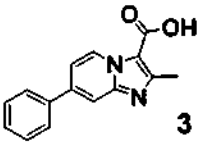
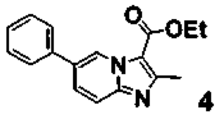
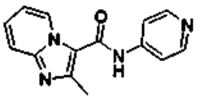
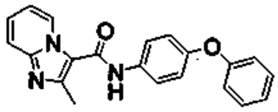
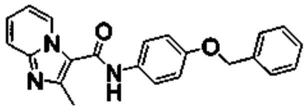
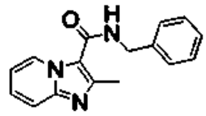
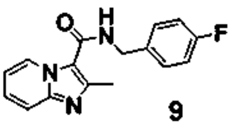
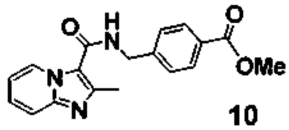
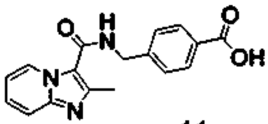
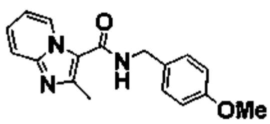
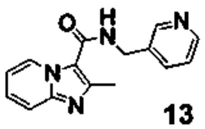
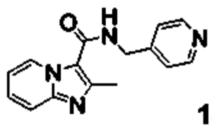
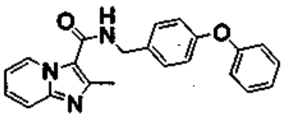
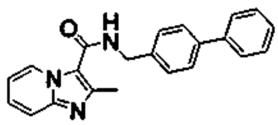
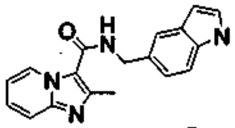
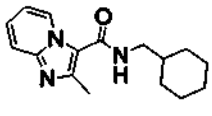
In the acute model of infection (after 4 weeks of treatment; Figure 3), a reduction of ~2 log CFU compared to untreated mice was observed in the lungs of mice treated with 50 mg/kg of either compound 177 or compound 185 administered orally (Figure 3A). No CFU were detected in the spleen of those same mice, while the infection control mice presented an average of $2.5x10^4$ CFU/ spleen (Figure 3B). No CFU were recovered from either lungs or spleen from mice treated with 25 mg/kg of INH. Overall both compound 177 and compound 185, demonstrated a significant effect in the acute mouse model of infection.

One of the current challenges for TB drug discovery is the identification of compounds that are active against persistent bacteria. Although the location and state of latent bacteria remains a matter of debate, one commonly shared hypothesis for mycobacterial persistence is that *M. tuberculosis* bacilli are able to survive in macrophages for prolonged periods of time and, unlike other bacteria, are able to actively replicate. The intraphagosomal profile of *M. tuberculosis* is complex; a large variety of genes are over-expressed and timely regulated and are also dependent on environmental factors. Altogether, this makes the identification of one specific tubercle factor that could be selected as the ideal target difficult. Consequently, non-target cell-based assays are a critical tool in the search of intracellular *M. tuberculosis* inhibitors.

Investigation of bacillus growth inhibitors within macrophages has long been limited due to cumbersome CFU plating, slow bacillus growth, safety requirements and difficulties in setting-up appropriate infection conditions. As a consequence, this approach was always used as a secondary assay after the initial selection of compounds that are active on *in vitro* extracellular growth. With the advent of automated confocal microscopy, the above mentioned limitations could be readdressed and the methodology employed herein demonstrates the feasibility of large scale compound screening.

Obviously compounds found to be active against both intracellular and *in vitro M. tuberculosis* growth are the most promising. The best inhibitors isolated from this library have an inhibitory activity within the same range as INH and/or PA-824. Further structure activity relationship studies will contribute to determine if their activity can be additionally improved. Taken together, the above results show that monitoring *M. tuberculosis* growth with automated fluorescence microscopy is highly robust and reliable and that this method enables fast selection of potent anti-TB compounds.

Table 1

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 1	+	+	 2	+	+
 3	+	+	 4	+	+
 5	+	+	 6	+	+
 7	+	+	 8	+	++
 9	+	+	 10	++	+
 11	+	+	 12	++	++
 13	+	+	 14	+	+
 15	++	+++	 16	+++	+++
 17	++	++	 18	+	+

Activity range: +++ indicates < 1 uM; ++ indicates between 1-20 uM, + indicates > 20 uM

Table 1 continued

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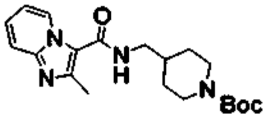
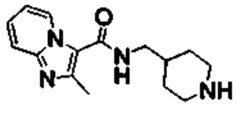
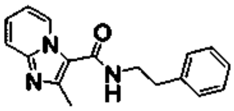
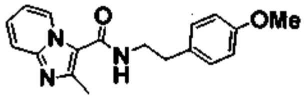
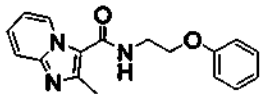
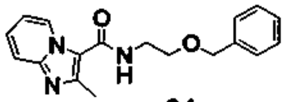
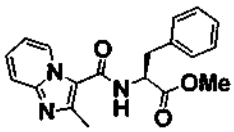
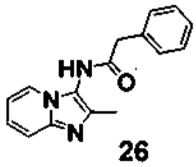
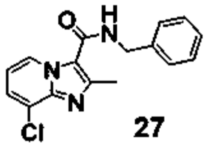
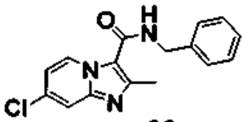
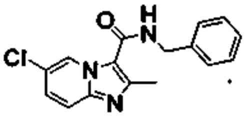
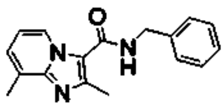
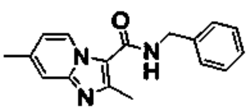
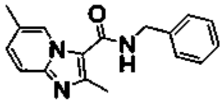
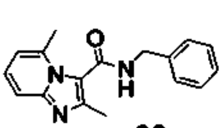
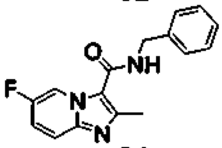
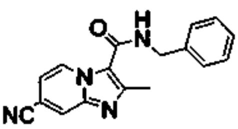
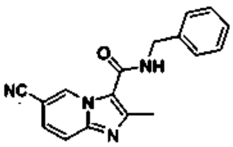
 19	+	+	 20	+	+
 21	+	+	 22	+	+
 23	++	++	 24	+	+
 25	+	+	 26	+	+
 27	+	+	 28	+	++
 29	++	++	 30	+	+
 31	++	+++	 32	+++	+++
 33	+	+	 34	++	++
 35	+	+	 36	+	+

Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM

Table 1 continued

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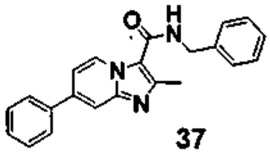
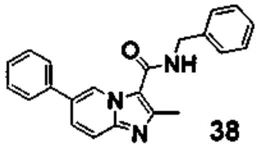
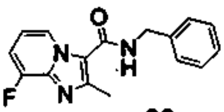
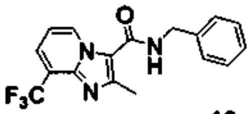
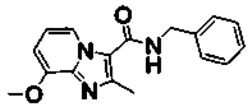
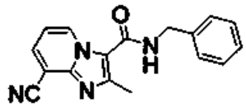
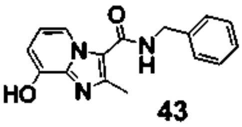
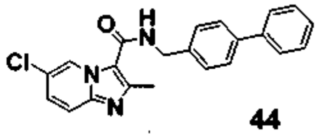
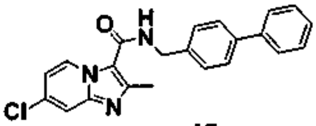
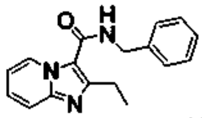
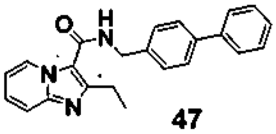
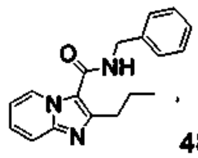
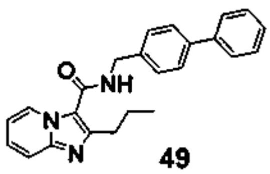
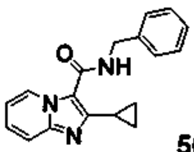
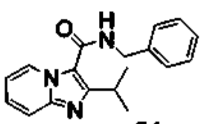
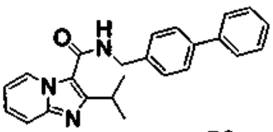
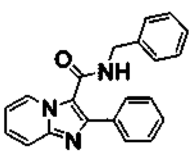
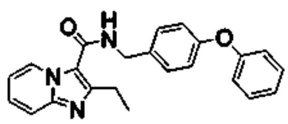
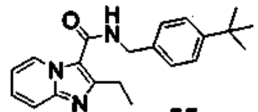
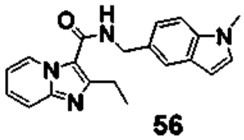
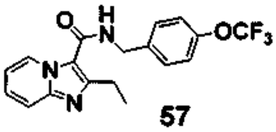
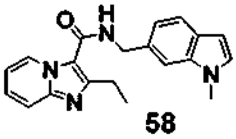
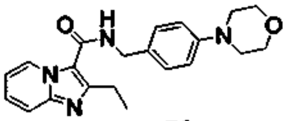
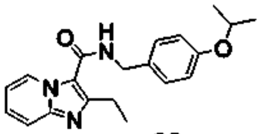
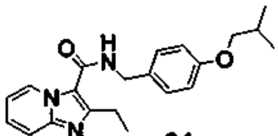
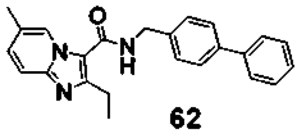
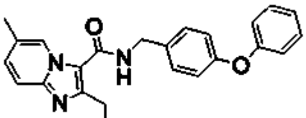
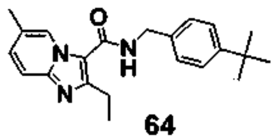
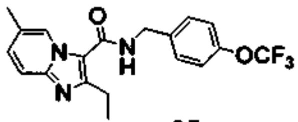
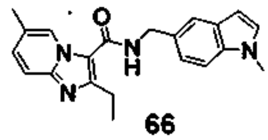
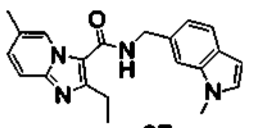
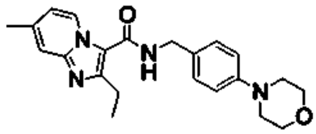
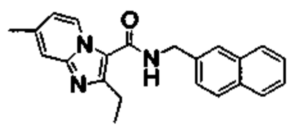
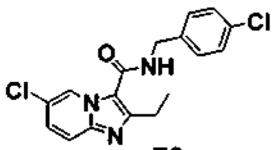
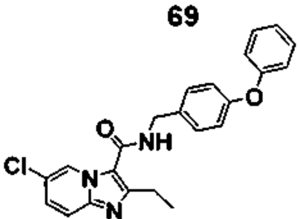
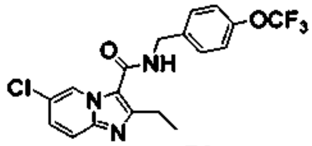
 37	+	+	 38	+	+
 39	++	++	 40	+	+
 41	+	+	 42	+	+
 43	+	+	 44	+++	+++
 45	+++	+++	 46	++	++
 47	+++	+++	 48	++	+
 49	+++	+++	 50	++	++
 51	+	+	 52	++	++
 53	+	+	 54	+++	+++

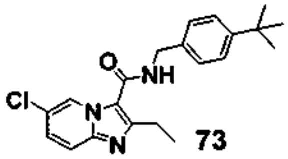
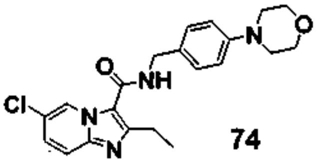
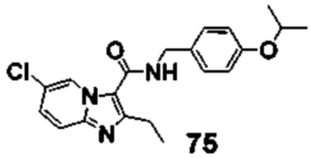
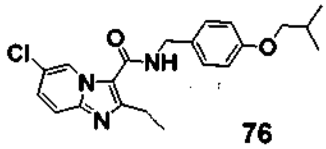
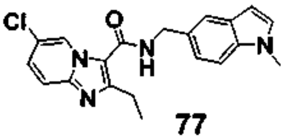
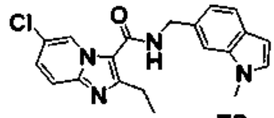
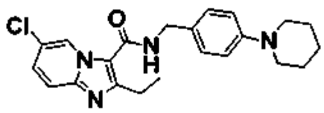
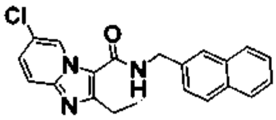
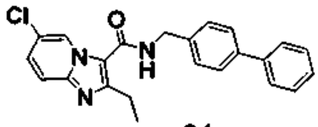
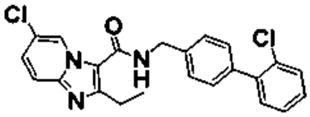
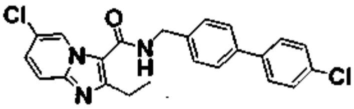
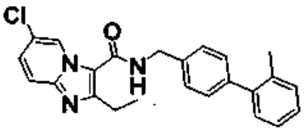
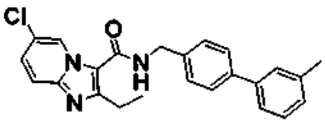
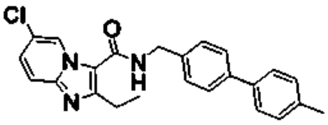
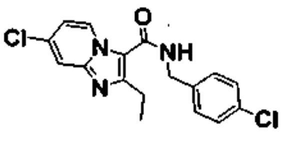
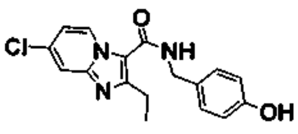
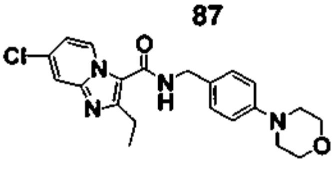
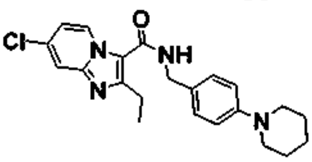
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 55	+++	+++	 56	+++	+++
 57	+++	+++	 58	++	++
 59	++	++	 60	+++	+++
 61	+++	+++	 62	+++	+++
 63	+++	+++	 64	+++	+++
 65	+++	+++	 66	+++	+++
 67	+++	+++	 68	++	+++
 69	++	+++	 70	+++	+++
 71	+++	+++	 72	+++	+++

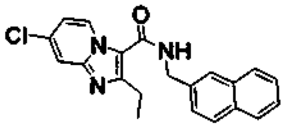
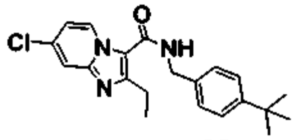
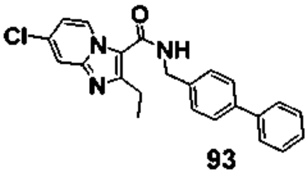
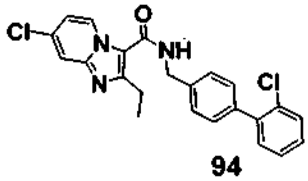
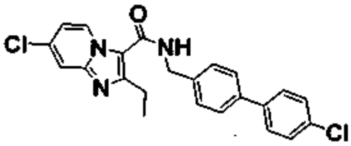
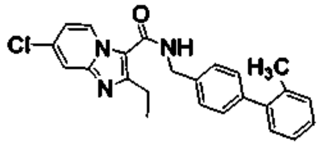
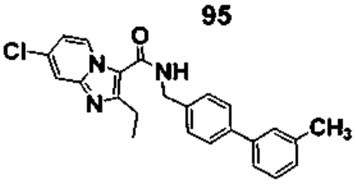
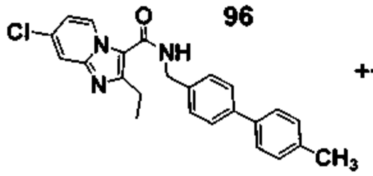
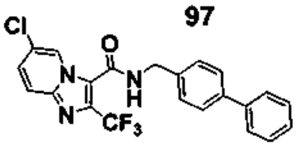
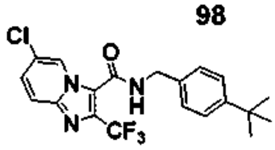
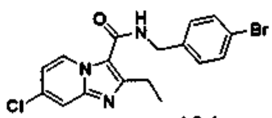
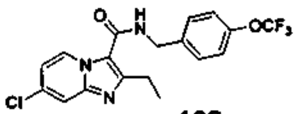
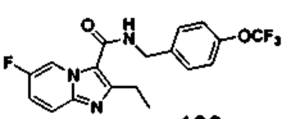
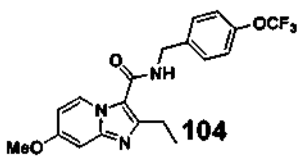
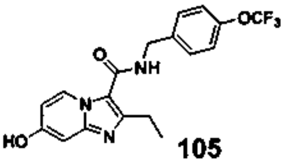
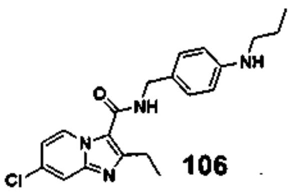
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 73	+++	+++	 74	+++	+++
 75	+++	+++	 76	+++	+++
 77	+++	+++	 78	+++	+++
 79	+++	+++	 80	+++	+++
 81	+++	+++	 82	+++	+++
 83	+++	+++	 84	+++	+++
 85	+++	+++	 86	+++	+++
 87	+++	+++	 88	++	++
 89	+++	++	 90	+++	+++

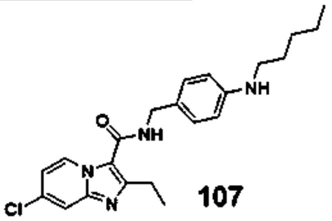
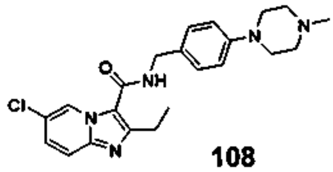
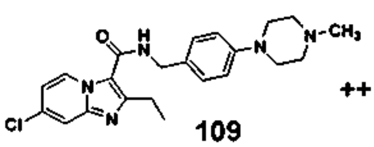
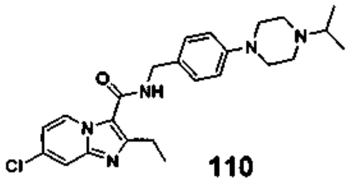
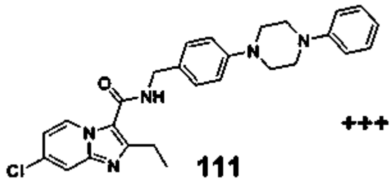
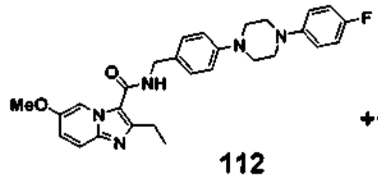
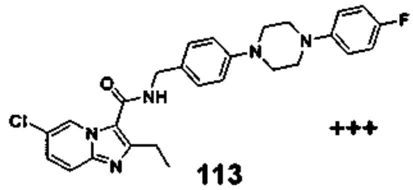
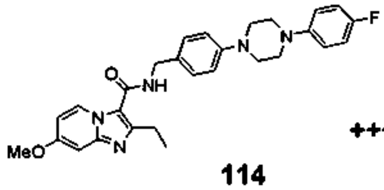
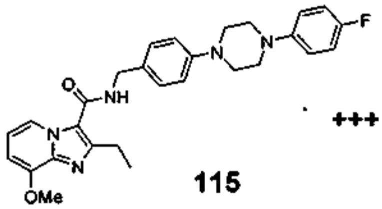
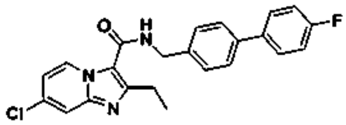
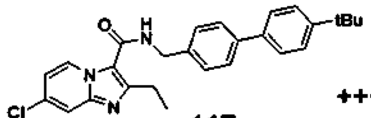
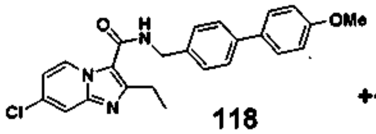
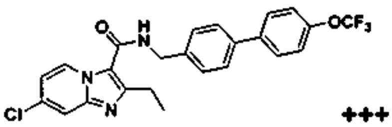
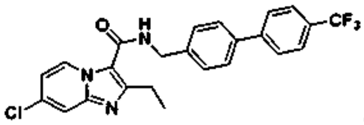
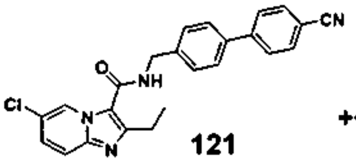
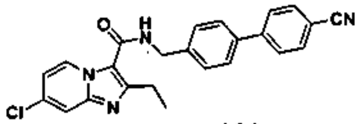
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 91	+++	++	 92	+++	+++
 93	+++	+++	 94	+++	+++
 95	+++	+++	 96	+++	+++
 97	+++	+++	 98	+++	+++
 99	+++	+++	 100	+++	+++
 101	++	+++	 102	+++	++
 103	++	+++	 104	+	++
 105	+	+	 106	+++	++

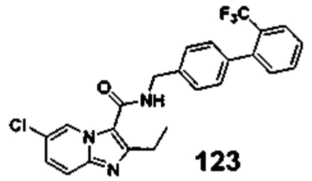
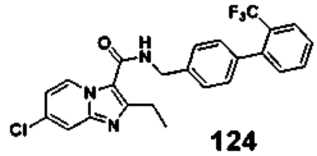
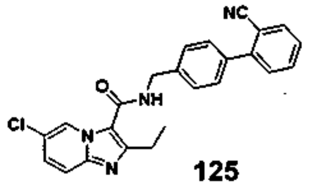
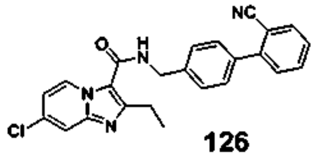
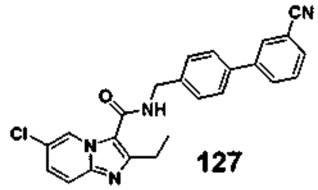
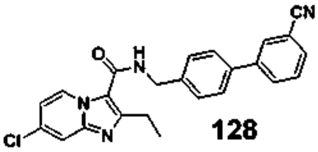
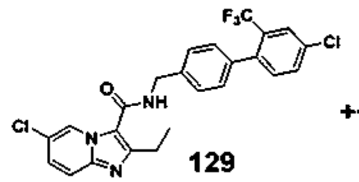
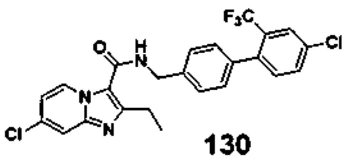
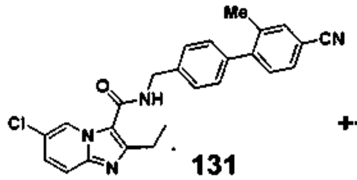
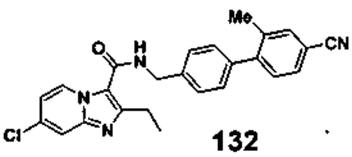
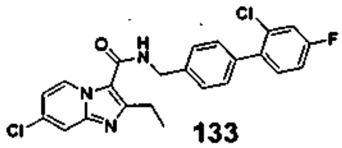
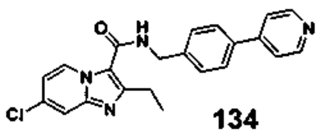
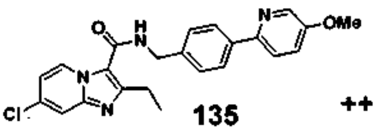
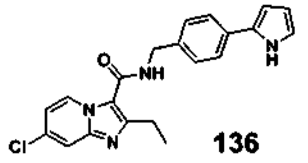
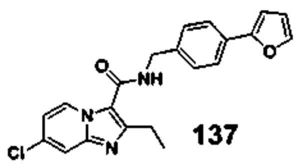
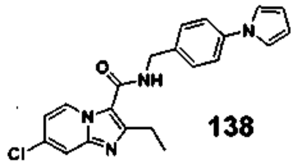
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 107	+++	+++	 108	++	++
 109	++	++	 110	++	+++
 111	+++	+++	 112	+++	nd
 113	+++	+++	 114	+++	nd
 115	+++	nd	 116	+++	+++
 117	+++	+++	 118	+++	+++
 119	+++	+++	 120	+++	+++
 121	+++	+++	 122	+++	+++

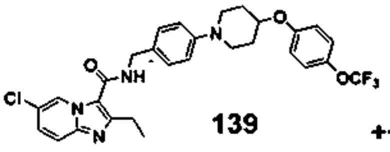
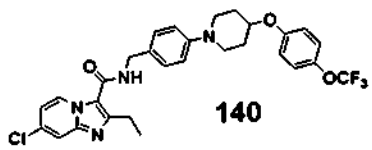
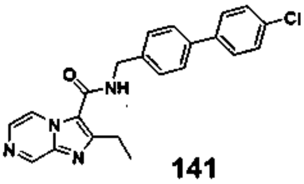
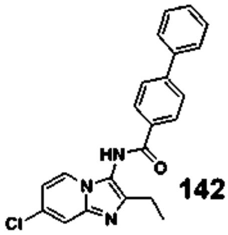
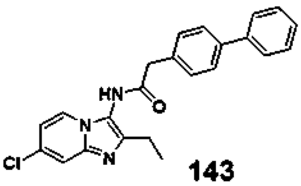
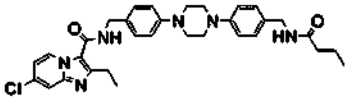
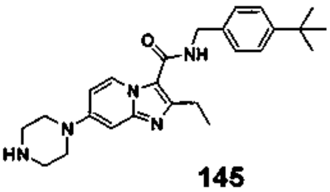
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 123	++	+++	 124	++	+++
 125	+++	++	 126	+++	++
 127	+	+++	 128	+	+++
 129	+++	+++	 130	++	+++
 131	+++	+++	 132	+++	+++
 133	+++	+++	 134	++	+++
 135	++	+++	 136	++	++
 137	++	+++	 138	+++	+++

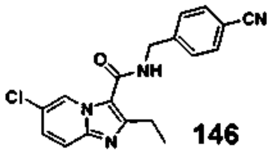
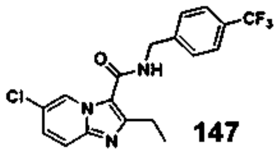
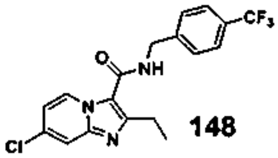
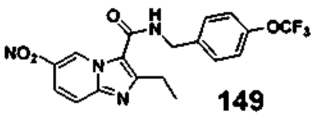
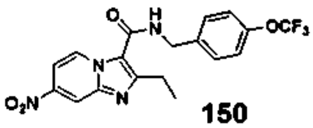
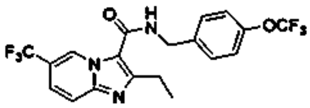
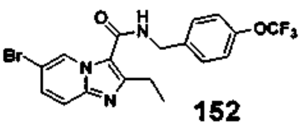
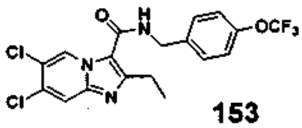
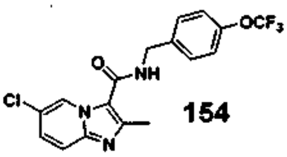
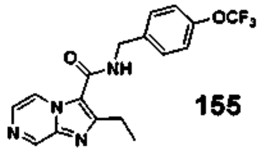
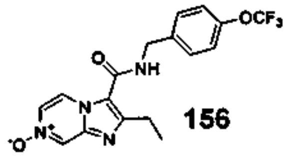
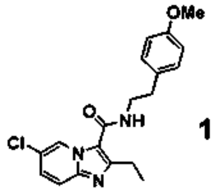
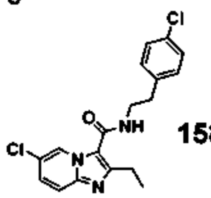
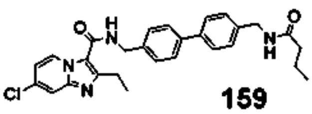
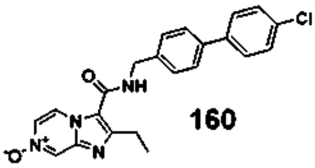
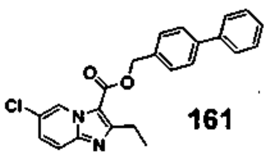
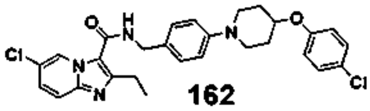
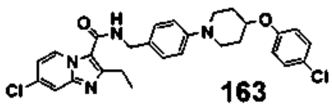
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 139	+++	+++	 140	+++	+++
 141	+++	+++	 142	+	+
 143	++	+++	 144	+++	+++
 145	+	+			

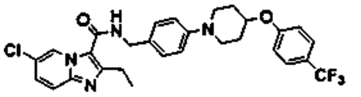
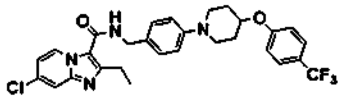
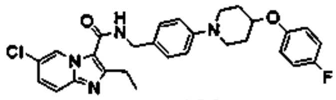
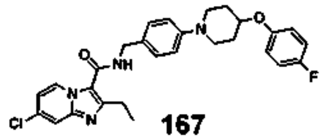
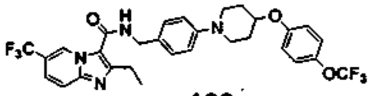
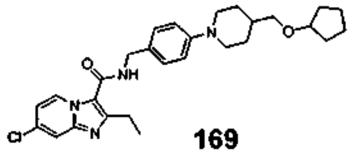
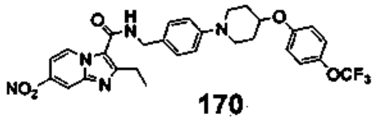
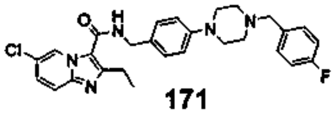
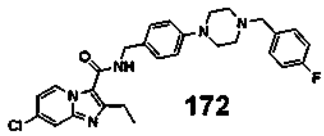
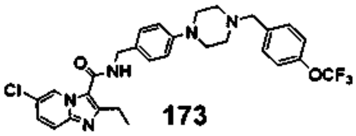
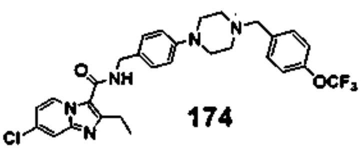
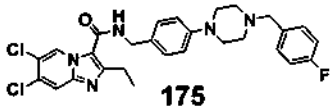
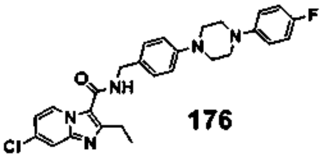
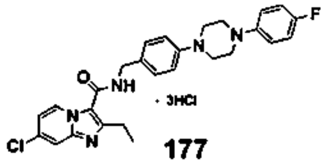
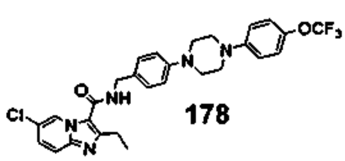
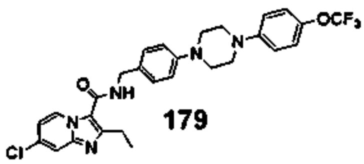
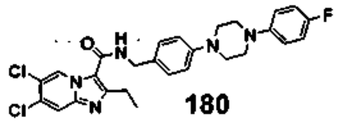
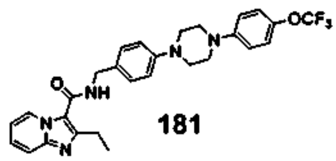
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 146	+	++	 147	+++	+++
 148	+++	+++	 149	+	+
 150	+	+	 151	++	+
 152	+++	+++	 153	++	+
 154	+++	++	 155	+	+
 156	+	+	 157	+++	+++
 158	+++	+++	 159	+++	+++
 160	+	+	 161	+++	+++
 162	+++	+++	 163	+++	+++

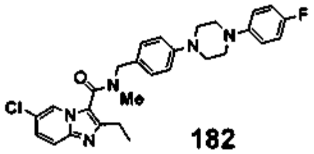
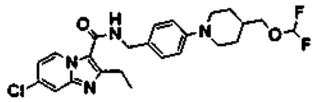
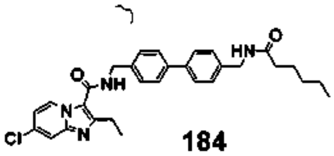
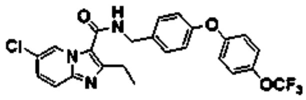
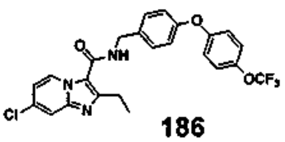
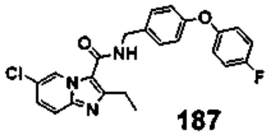
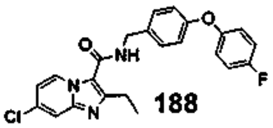
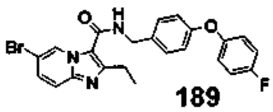
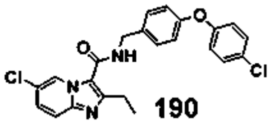
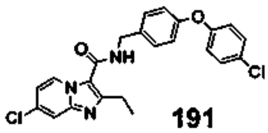
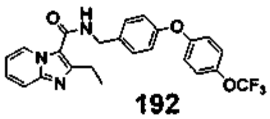
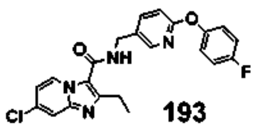
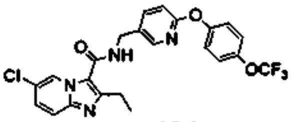
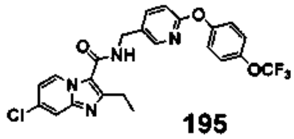
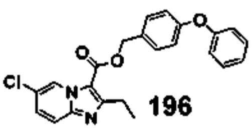
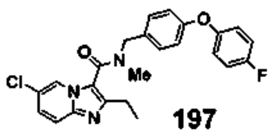
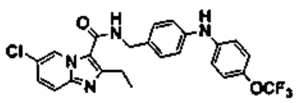
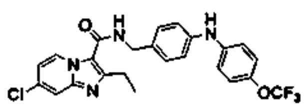
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 164	+++	+++	 165	+++	+++
 166	+++	+++	 167	+++	+++
 168	++	++	 169	+++	nd
 170	++	++	 171	+++	+++
 172	+++	+++	 173	+++	+++
 174	+++	+++	 175	+	+++
 176	+++	+++	 177	+++	+++
 178	+++	+++	 179	+++	+++
 180	+++	+++	 181	+++	+++

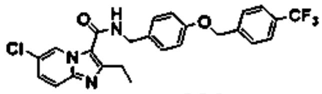
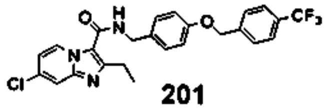
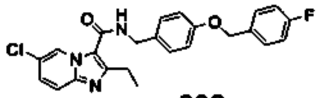
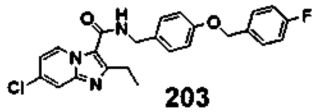
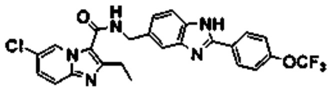
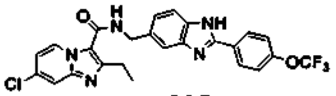
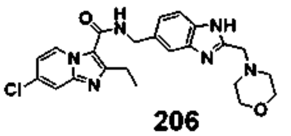
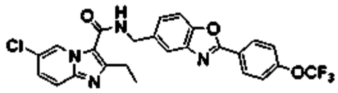
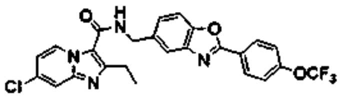
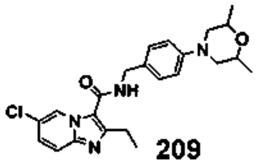
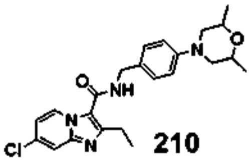
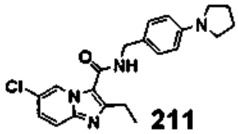
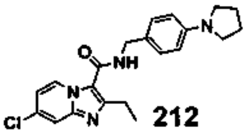
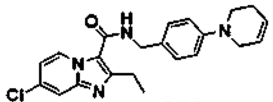
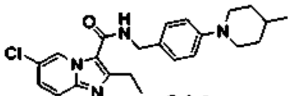
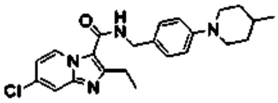
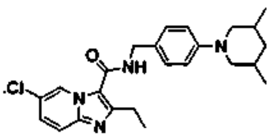
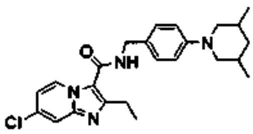
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 182	+++	++	 183	+++	nd
 184	+++	+++	 185	+++	+++
 186	+++	+++	 187	+++	+++
 188	+++	+++	 189	+++	+++
 190	+++	+++	 191	+++	+++
 192	+++	+++	 193	+++	+++
 194	++	+++	 195	++	++
 196	++	+++	 197	++	++
 198	++	+++	 199	+++	+++

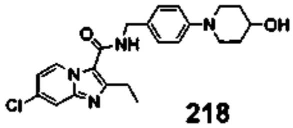
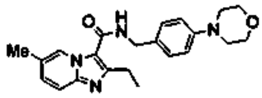
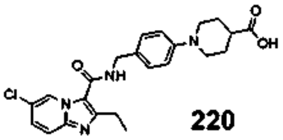
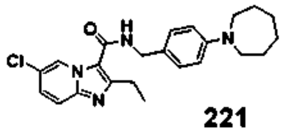
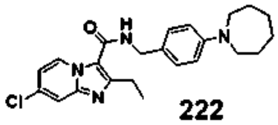
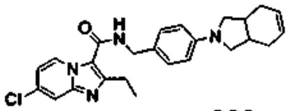
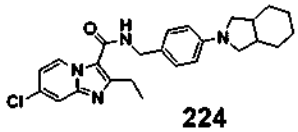
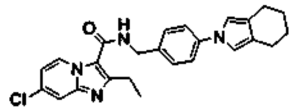
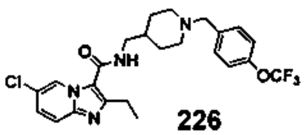
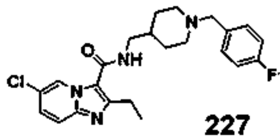
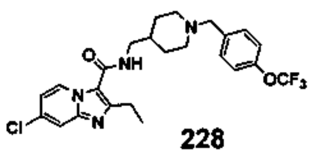
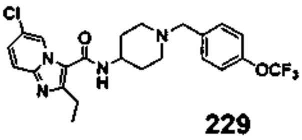
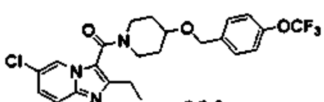
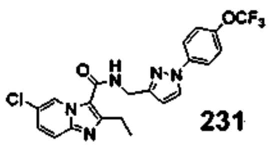
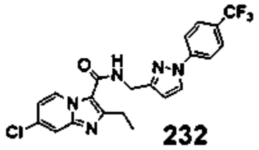
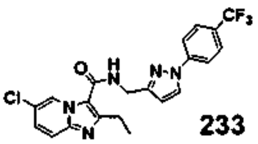
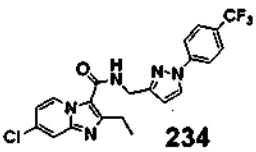
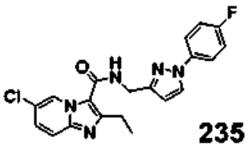
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 200	+++	+++	 201	+++	+++
 202	+++	+++	 203	++	++
 204	+	+	 205	+	+
 206	+	+	 207	+++	+++
 208	+++	+++	 209	+++	+++
 210	++	+++	 211	+++	+++
 212	+++	+++	 213	+++	++
 214	+++	+++	 215	+++	+++
 216	+++	+++	 217	+++	+++

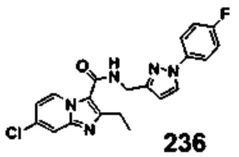
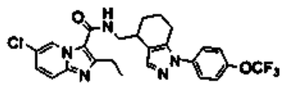
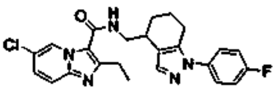
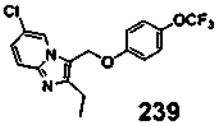
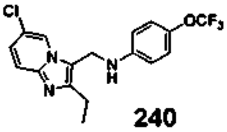
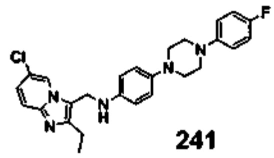
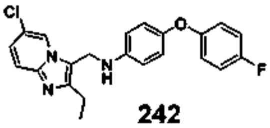
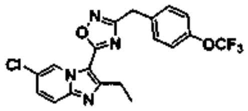
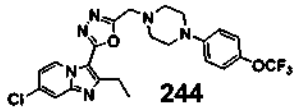
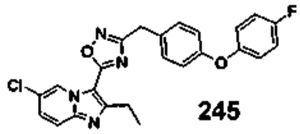
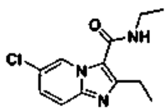
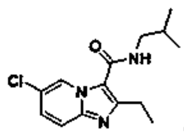
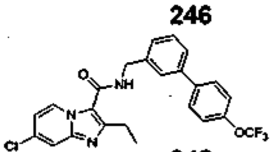
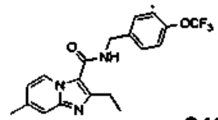
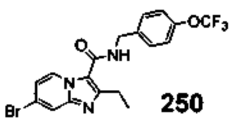
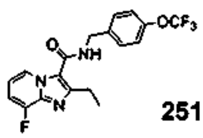
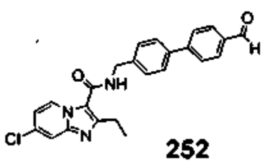
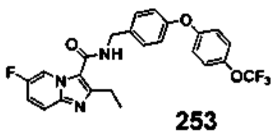
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 218	+++	+	 219	+++	nd
 220	+++	nd	 221	+++	+++
 222	+++	+++	 223	+++	nd
 224	+++	nd	 225	+++	nd
 226	+++	+++	 227	++	+++
 228	+	+	 229	+	+
 230	+	+	 231	+++	+++
 232	++	++	 233	+	+
 234	++	++	 235	++	++

Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

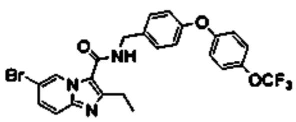
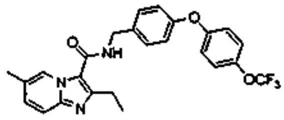
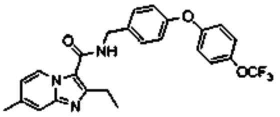
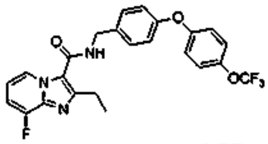
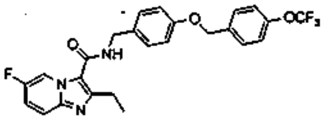
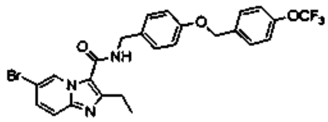
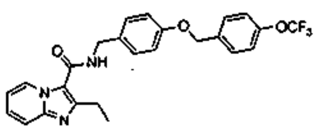
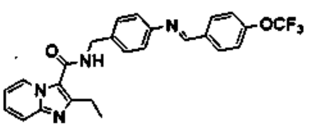
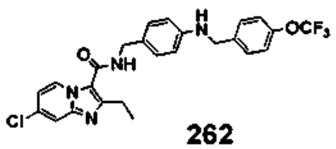
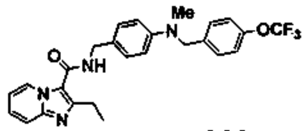
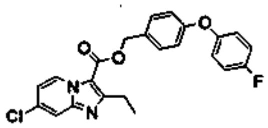
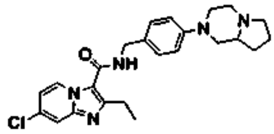
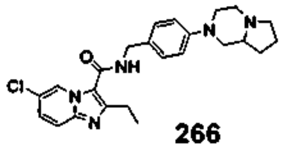
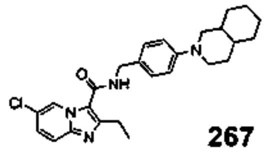
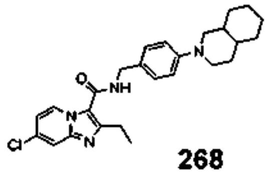
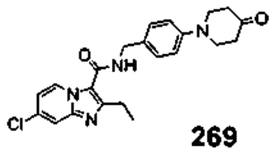
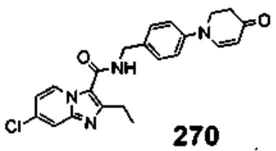
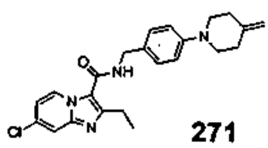
Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 236	++	+	 237	+	+
 238	+	+	 239	+	+
 240	+	+	 241	+	+
 242	+	+	 243	+	+
 244	++	++	 245	++	nd
 246	+	nd	 247	+	nd
 248	+++	nd	 249	+++	nd
 250	+++	nd	 251	+++	nd
 252	+++	nd	 253	+++	nd

Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM

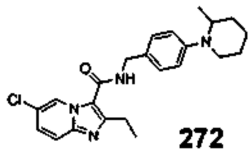
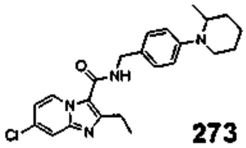
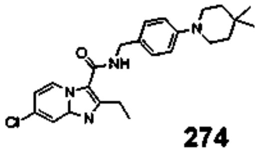
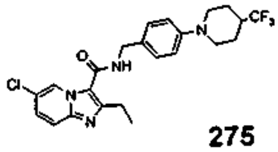
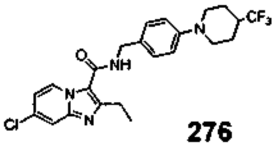
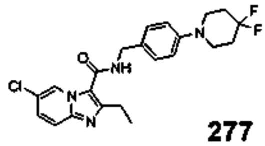
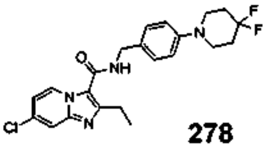
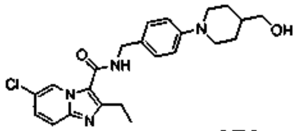
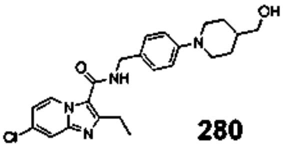
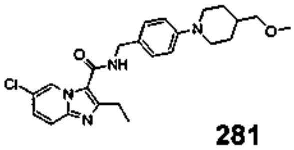
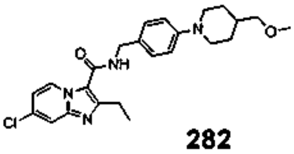
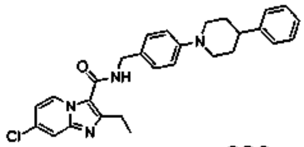
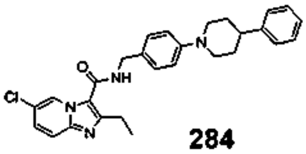
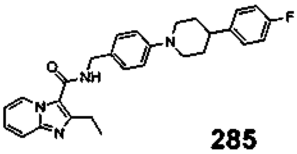
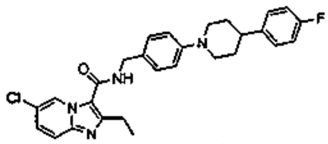
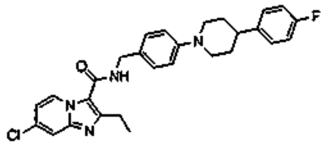
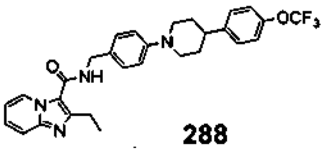
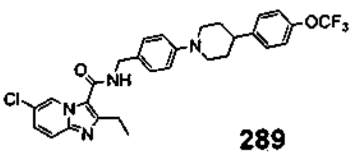
nd : not determined

Table 1 continued

Compound	QUM (µM)	QIM (µM)	Compound	QUM (µM)	QIM (µM)
 254	+++	nd	 255	+++	nd
 256	+++	nd	 257	+++	nd
 258	+++	+++	 259	+++	nd
 260	+++	nd	 261	+	+
 262	+++	+++	 263	+++	+++
 264	+++	nd	 265	+	nd
 266	+	nd	 267	+++	+++
 268	+++	nd	 269	+++	++
 270	+	+	 271	+++	nd

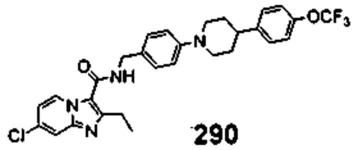
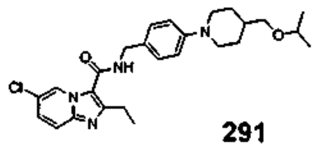
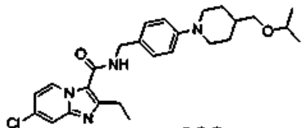
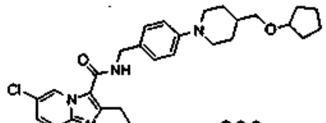
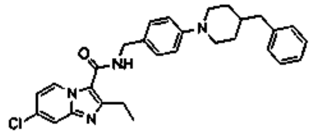
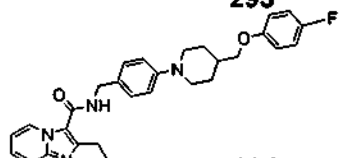
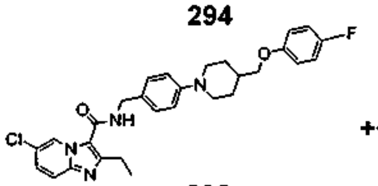
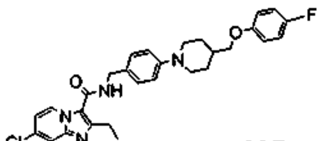
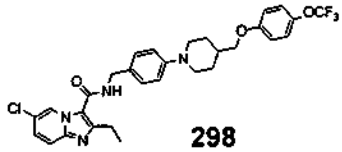
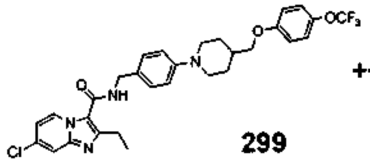
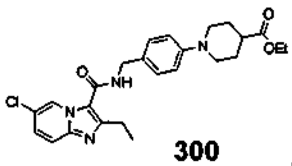
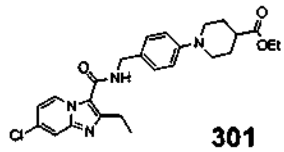
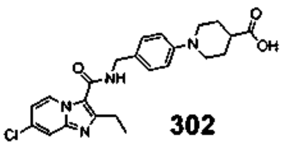
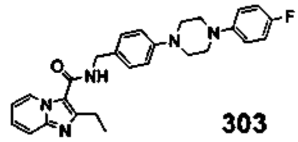
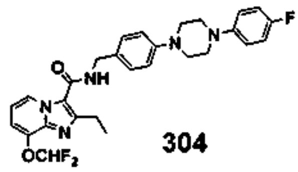
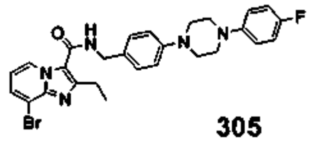
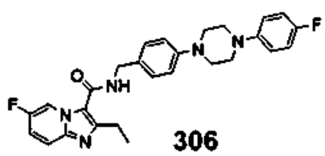
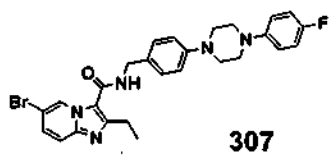
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 272	+++	+++	 273	+++	+++
 274	+++	nd	 275	++	nd
 276	+	nd	 277	++	nd
 278	++	nd	 279	+	nd
 280	+++	nd	 281	+++	+++
 282	+++	+++	 283	+++	nd
 284	+++	nd	 285	+++	nd
 286	+++	+++	 287	+++	+++
 288	+++	nd	 289	+++	nd

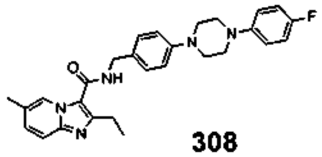
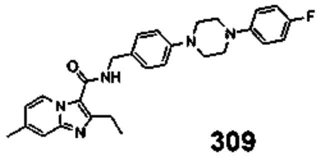
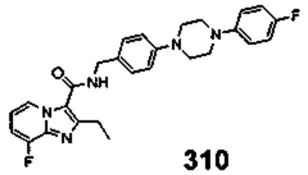
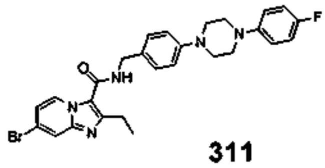
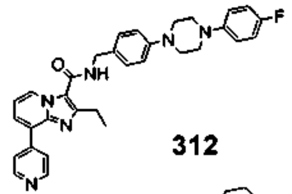
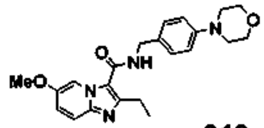
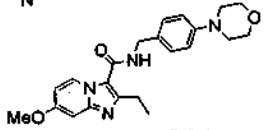
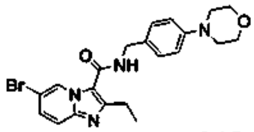
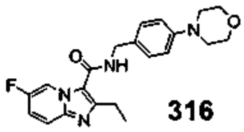
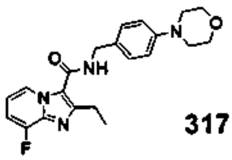
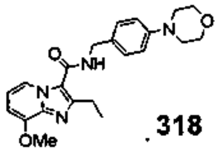
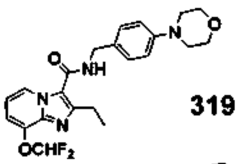
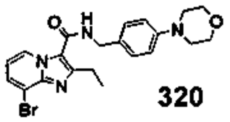
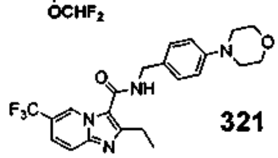
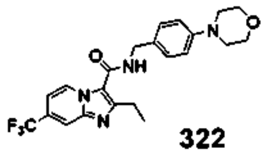
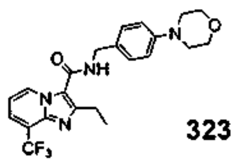
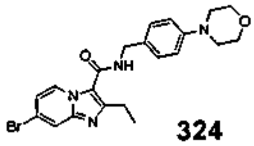
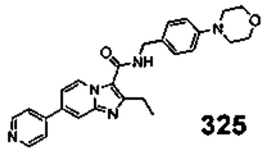
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 290	+++	nd	 291	+++	+++
 292	+++	+++	 293	+++	nd
 294	++	nd	 295	+++	+++
 296	+++	+++	 297	+++	+++
 298	+++	nd	 299	+++	nd
 300	+++	nd	 301	+++	nd
 302	+++	nd	 303	+++	+++
 304	+++	nd	 305	+++	nd
 306	+++	+++	 307	+++	+++

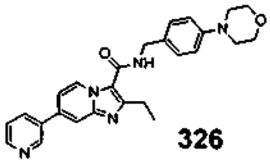
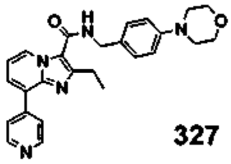
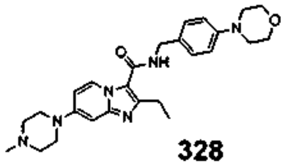
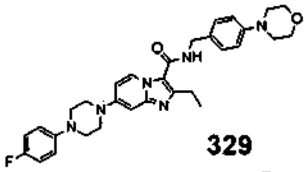
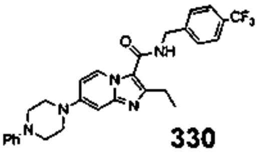
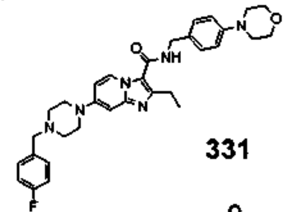
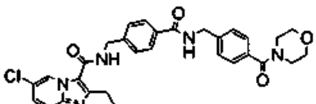
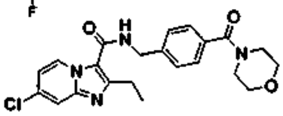
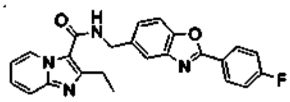
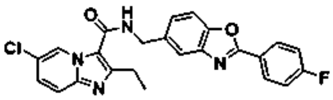
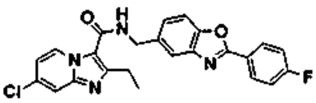
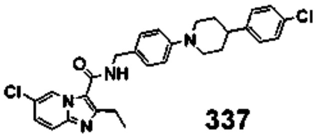
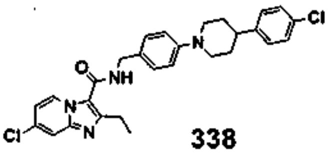
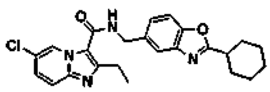
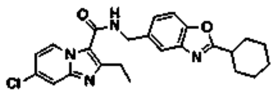
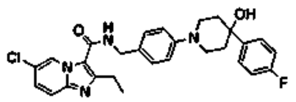
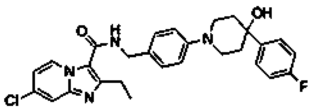
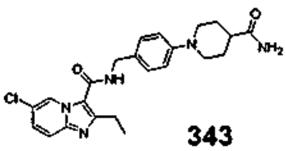
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 308	+++	nd	 309	+++	+++
 310	+++	+++	 311	+++	+++
 312	+++	nd	 313	+++	nd
 314	+++	nd	 315	+++	+++
 316	++	++	 317	+++	+++
 318	+++	nd	 319	++	nd
 320	+++	nd	 321	+++	nd
 322	++	nd	 323	++	nd
 324	+++	+++	 325	+	+

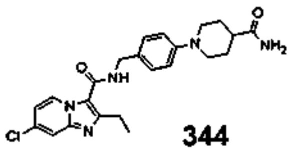
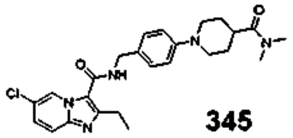
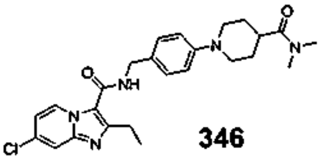
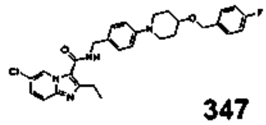
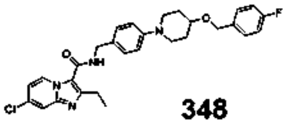
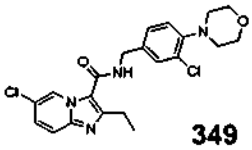
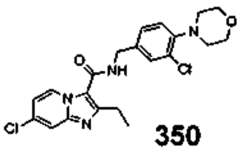
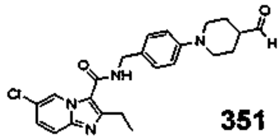
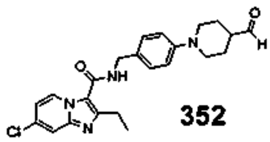
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 326	+	+	 327	+	nd
 328	+	+	 329	+	+
 330	+	+++	 331	+	+
 332	+	nd	 333	+	nd
 334	+++	nd	 335	+++	nd
 336	+++	nd	 337	+++	nd
 338	+++	nd	 339	+++	nd
 340	+++	nd	 341	+++	nd
 342	+++	nd	 343	+++	nd

Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

Table 1 continued

Compound	QUM (μM)	QIM (μM)	Compound	QUM (μM)	QIM (μM)
 344	++	nd	 345	+++	nd
 346	+++	nd	 347	+++	nd
 348	++	nd	 349	+++	nd
 350	+++	nd	 351	+++	nd
 352	+++	nd			

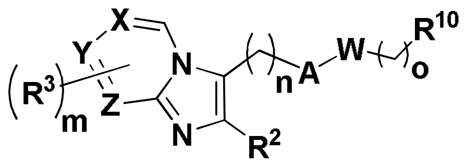
Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM
nd : not determined

Table 2

	MIC_{80} (µM)										
	MDR isolates										Sensitive Strain
Compound	#13	#33	#48	#61	#80	#125	#137	#143	#146	#171	H37Rv
47	0.3125	0.3125	0.3125	0.3125	0.3125	0.625	1.25	1.25	0.1562 5	1.25	1.25
54	0.15625	0.15625	0.15625	0.15625	0.15625	0.3125	0.625	0.3125	0.3125	0.3125	0.625
INH	5	10	10	20	5	10	20	10	20	5	1.25
MFX	0.15625	0.3125	0.3125	0.3125	0.625	0.625	0.625	1.25	0.625	0.625	1.25

We claim:

1. A compound having the general formula Ib:



Ib

wherein

X, Y and Z are CH**;**

o is 0; n is 0; m is 0, 1, 2, 3 or 4;

A is C=O

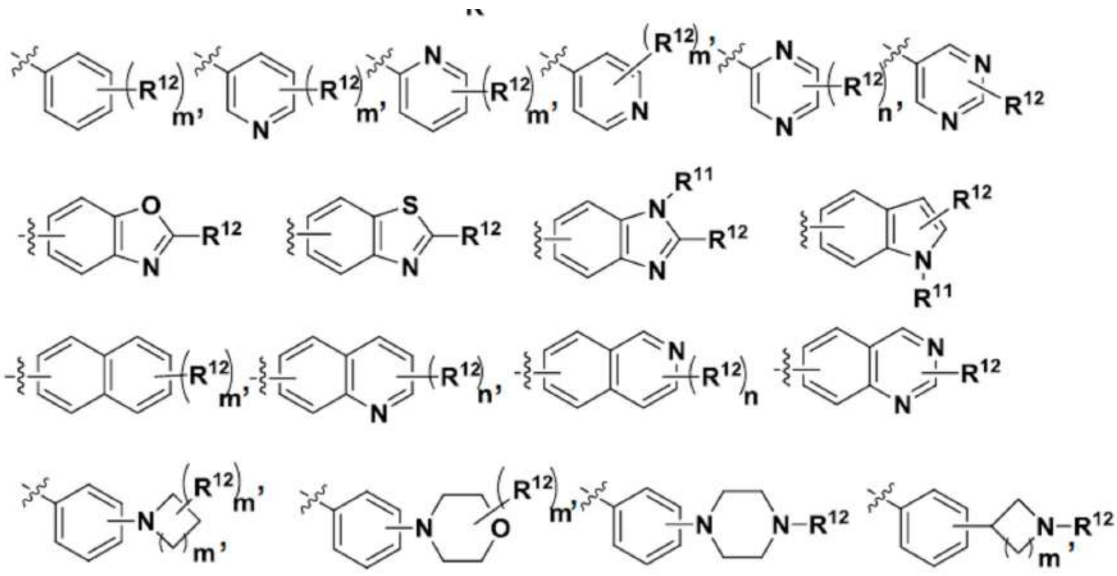
W is NH;

R^2 is, at each occurrence, independently selected from the group consisting of hydrogen, halogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, -OH, -OR^5, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkoxy, C_3-C_{15} cycloalkylalkoxy, C_3-C_{15} cycloalkylalkyl, -CN, -NO_2, -NH_2, -$N(R^5)_2$, -$C(O)R^5$, -$C(O)OR^5$, -$C(O)N(R^5)_2$, -SR^5, -$S(O)R^5$, -$S(O)_2R^5$, -$S(O)_2N(R^5)_2$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl;

R^3 is, at each occurrence, independently selected from the group consisting of hydrogen, halogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, hydroxyl, -OR^6, -CN, -NO_2, -NH_2, -$N(R^6)C(O)R^6$, -$C(O)R^6$, -$C(O)OR^6$, -$C(O)N(R^6)_2$, -$S(O)R^6$, -$S(O)_2R^6$, -$S(O)_2N(R^6)_2$, aryl, e.g. phenyl, benzyl, heteroaryl, heterocyclyl, any of which is optionally substituted, or two groups of R^3 are connected to each other to make five or six membered cyclic and heterocyclic rings;

R^5 and R^6 are, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl;

R^{10} is a moiety selected from the group consisting of



wherein m' is 0, 1, 2, 3 or 4 and n' is 0, 1, 2, or 3;

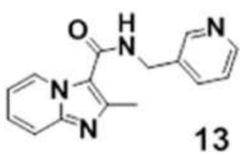
R^{11} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, -OH, -OR^{13}, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkoxy, C_3-C_{15} cycloalkylalkoxy, C_3-C_{15} cycloalkylalkyl, -NH_2, -$N(R^{13})_2$, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$C(O)N(R^{13})_2$, -$S(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{13})_2$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl,;

R^{12} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, hydroxyl, -OR^{14}, -$C(O)R^{14}$, -$C(O)OR^{14}$, -CN, -NO_2, -NH_2, -$N(R^{14})_2$, -$C(O)N(R^{14})_2$, -$S(O)R^{14}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})_2$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl;

R^{13} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl; and

R^{14} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_8 alkyl optionally substituted with at least one hydroxyl or halogen; C_3-C_7 cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, aryl, e.g. phenyl, benzyl, heteroaryl and heterocyclyl.

2. The compound as claimed in claim 1, having one of the formulae 1-352,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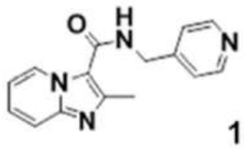
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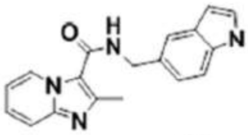
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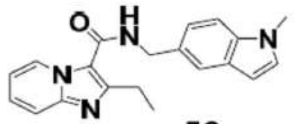
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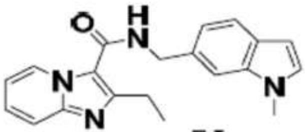
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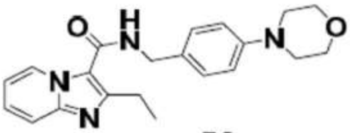
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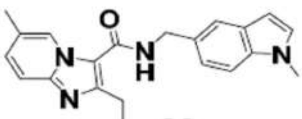
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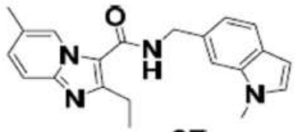
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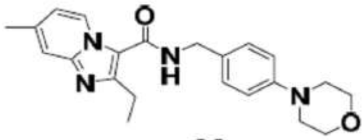
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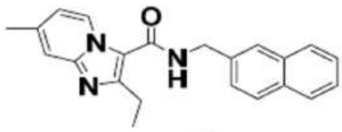
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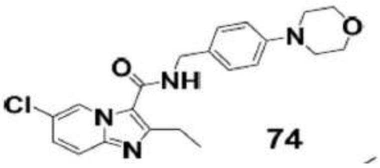
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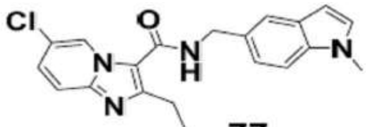
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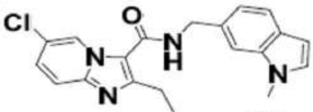
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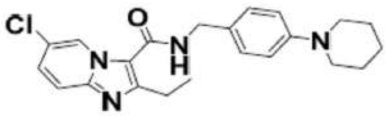
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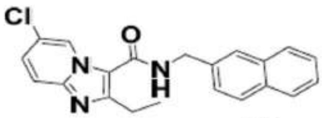
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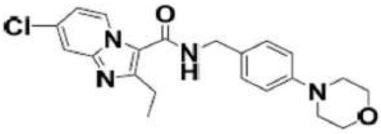
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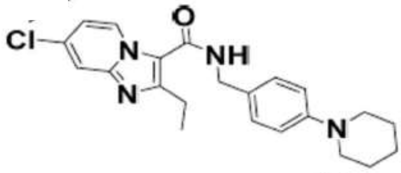
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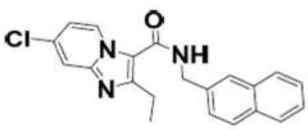

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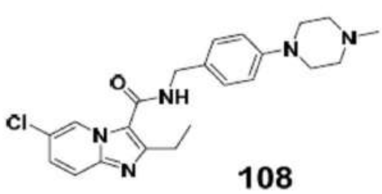

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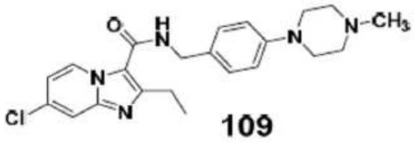

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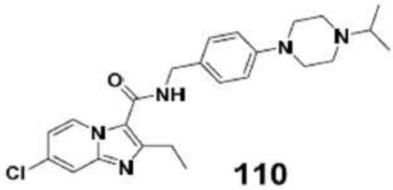

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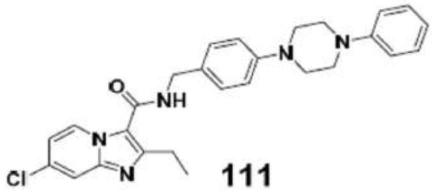

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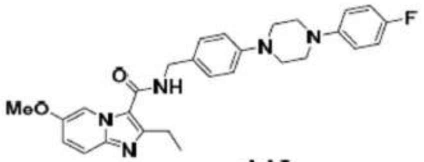

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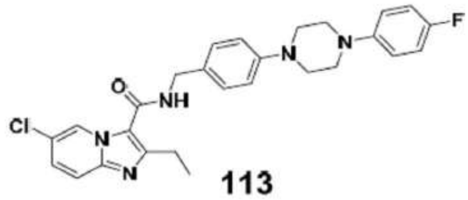

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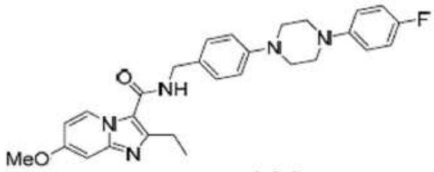

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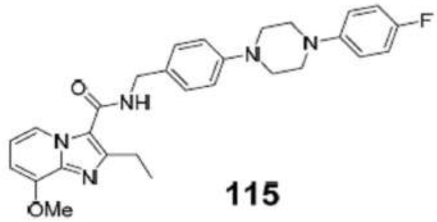

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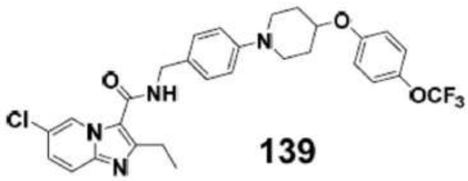

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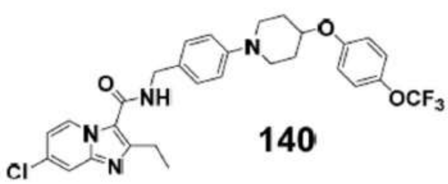

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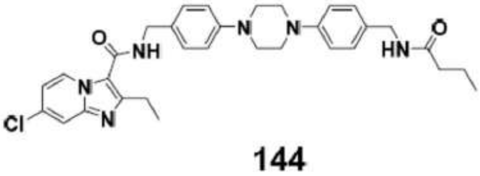

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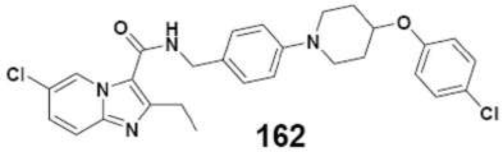

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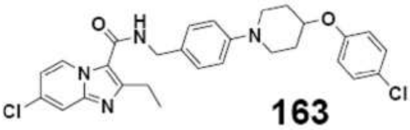

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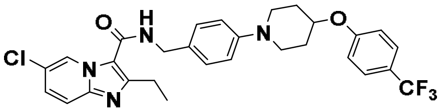

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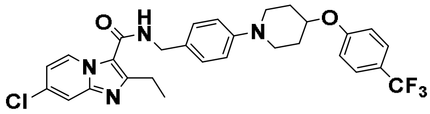

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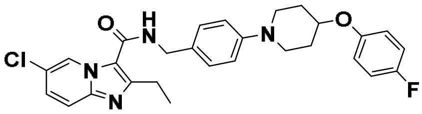

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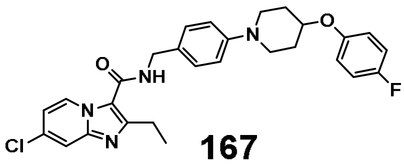

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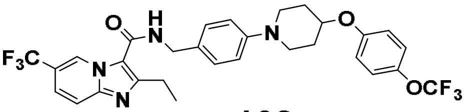

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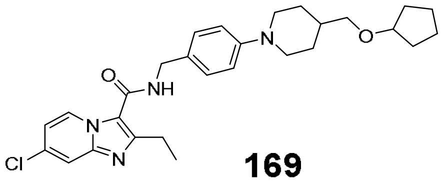

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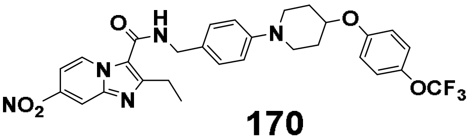

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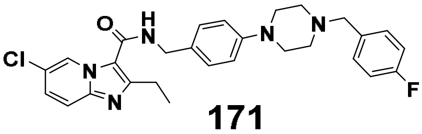

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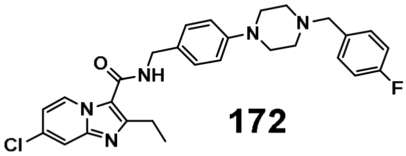

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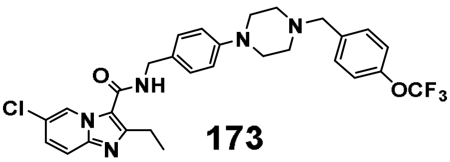

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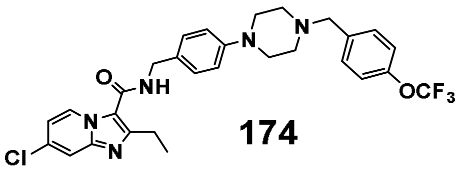

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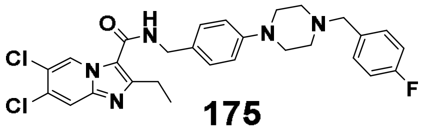

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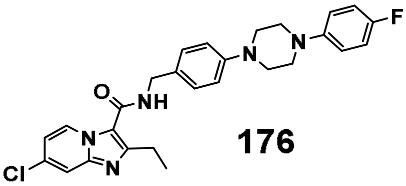

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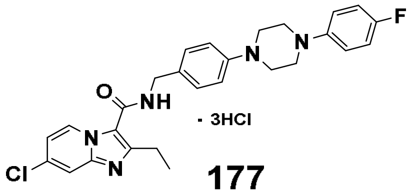

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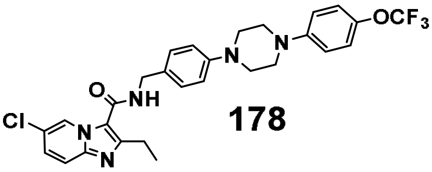

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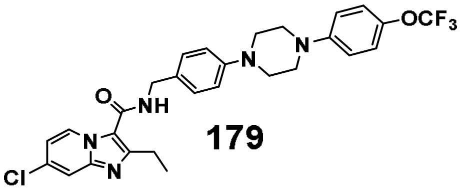

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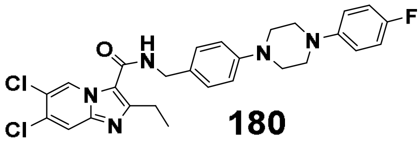

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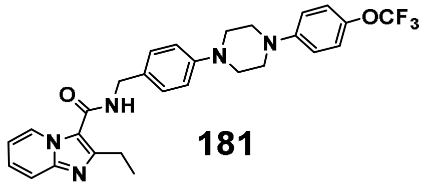

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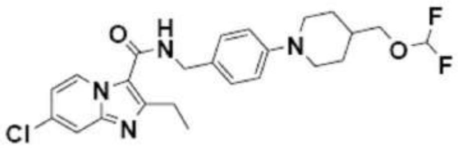

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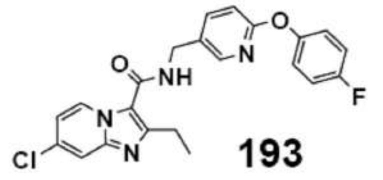

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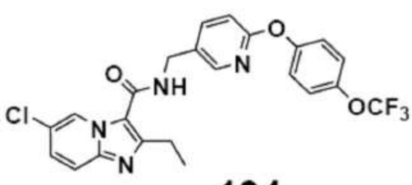

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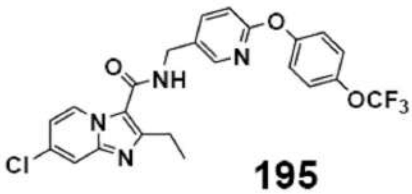

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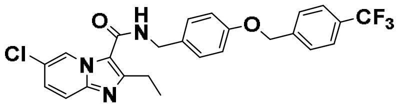

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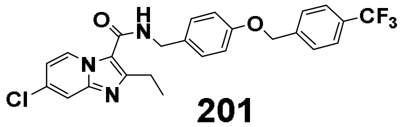

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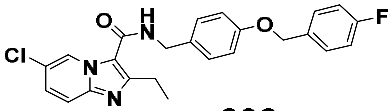

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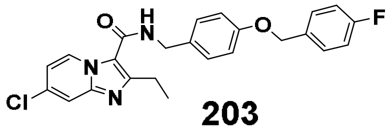

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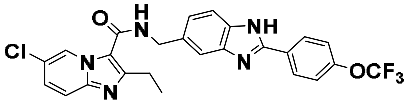

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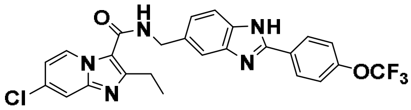

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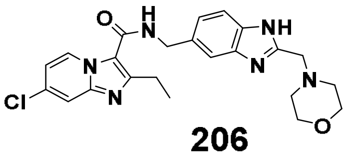

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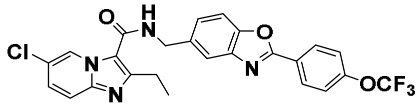

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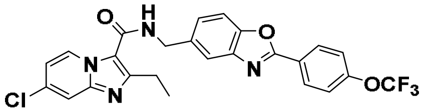

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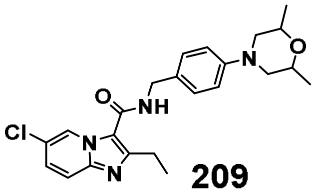

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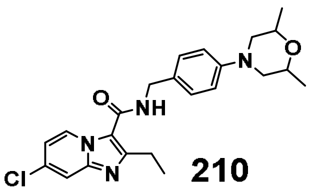

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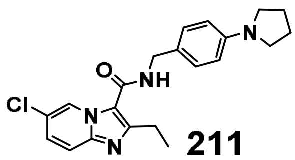

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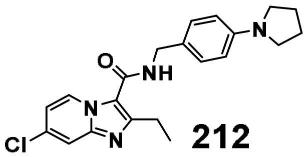

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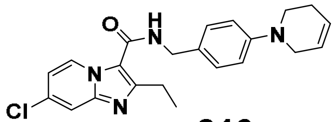

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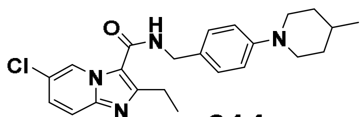

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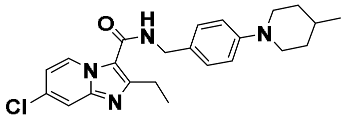

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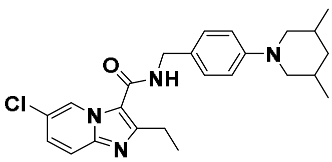

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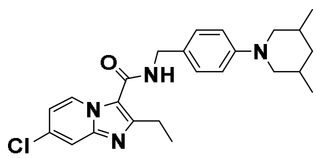

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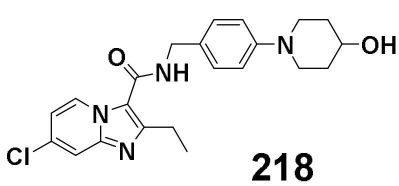

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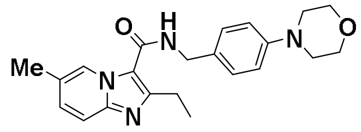

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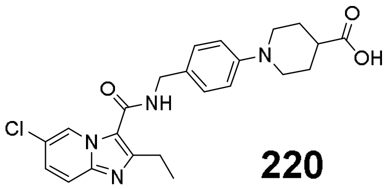

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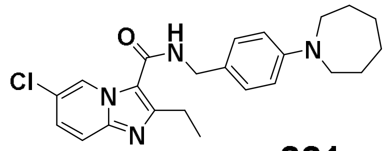

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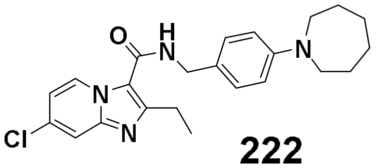

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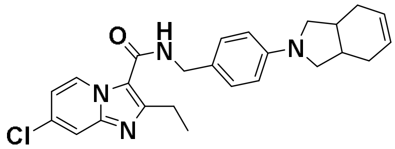

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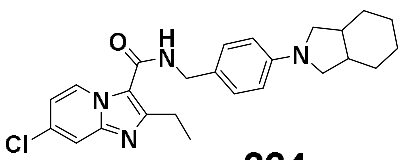

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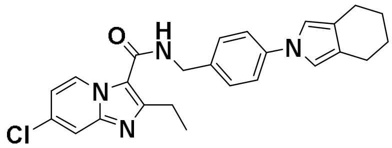

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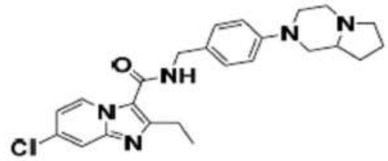

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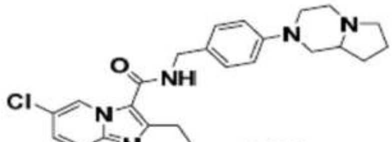

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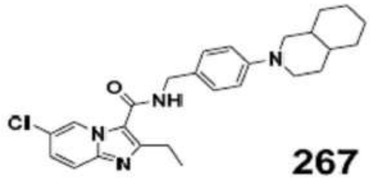

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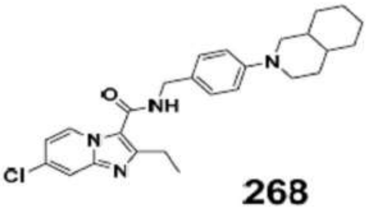

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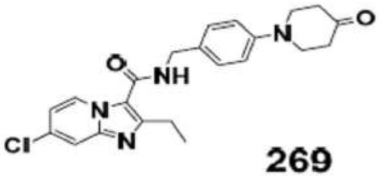

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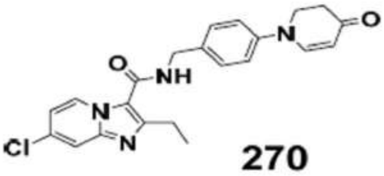

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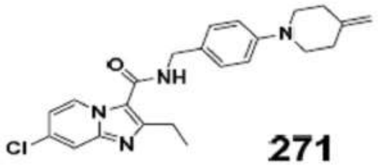

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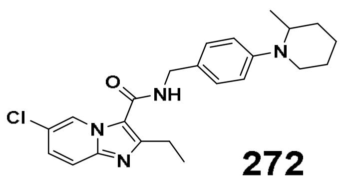

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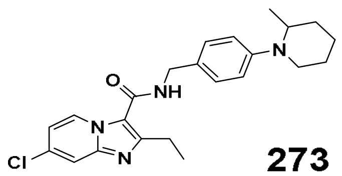

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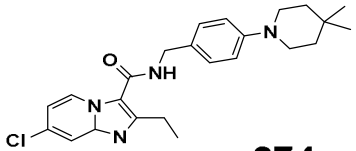

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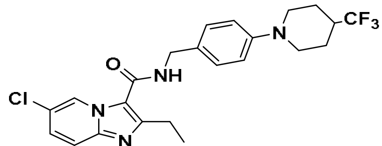

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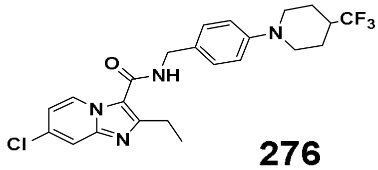

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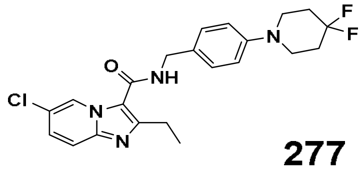

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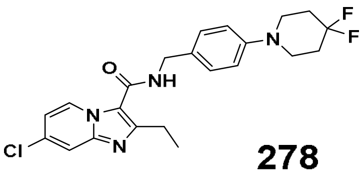

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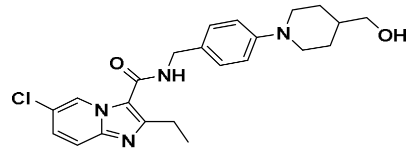

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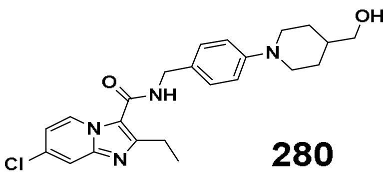

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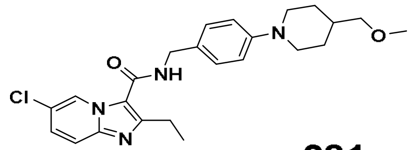

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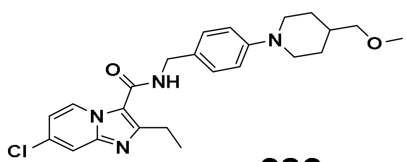

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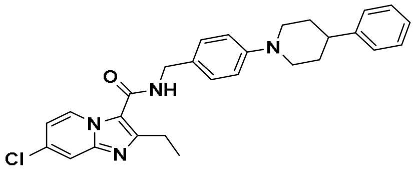

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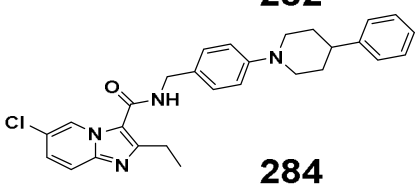

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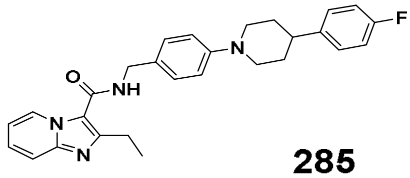

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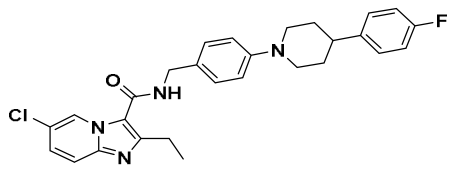

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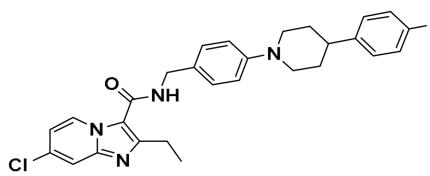

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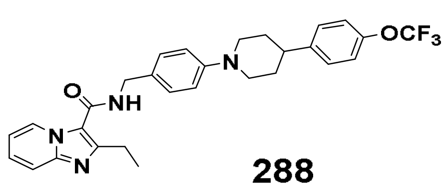

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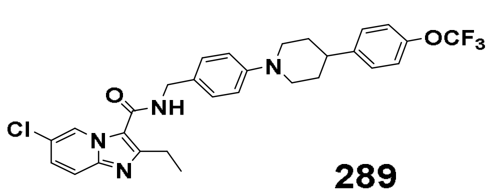

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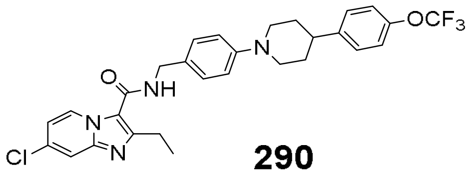

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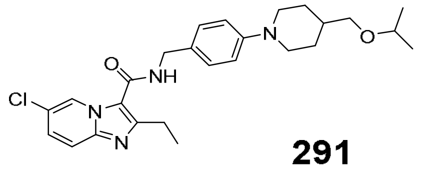

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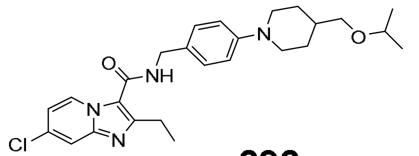

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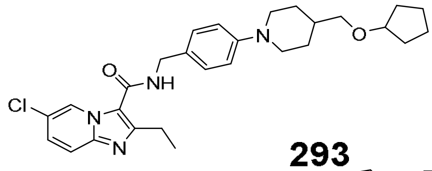

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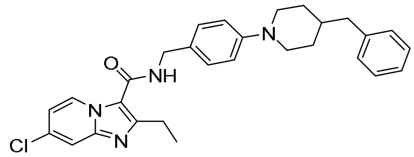

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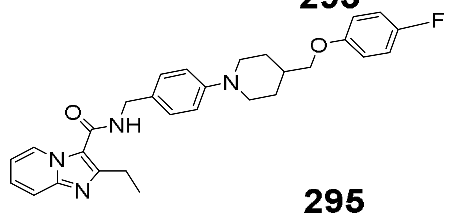

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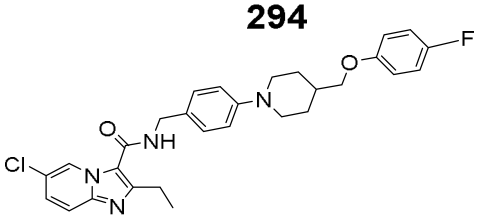

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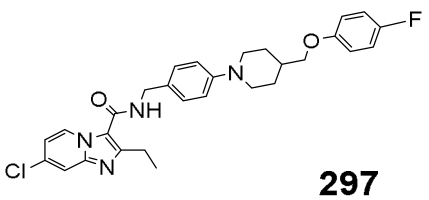

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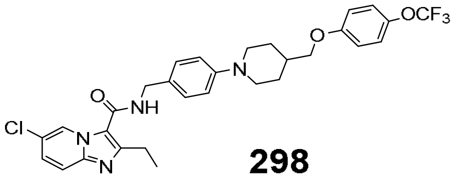

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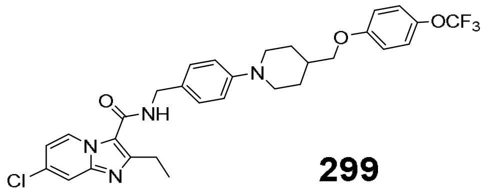

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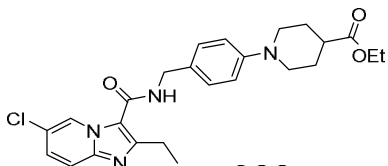

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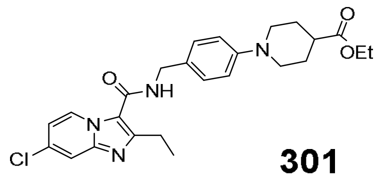

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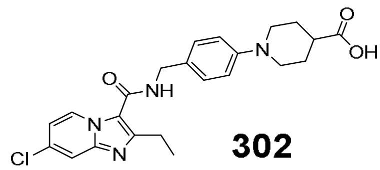

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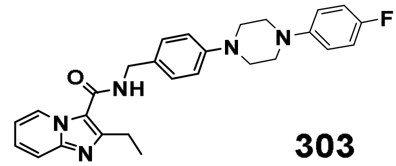

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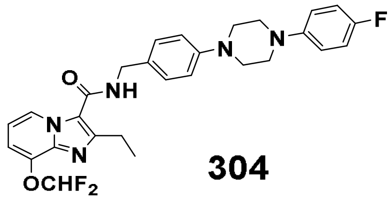

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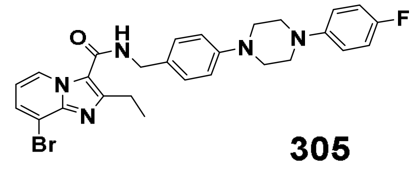

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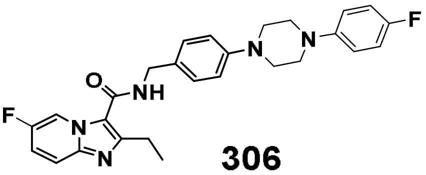

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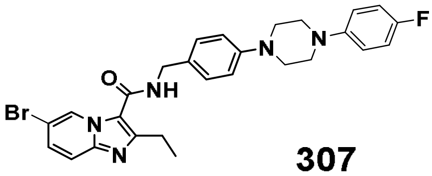

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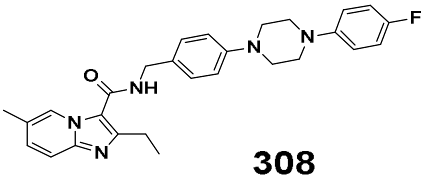

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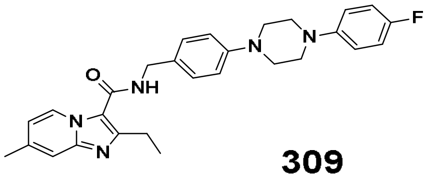

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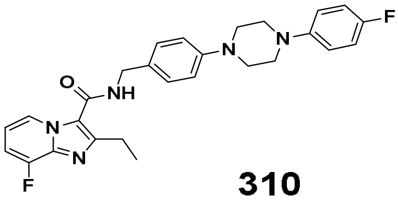

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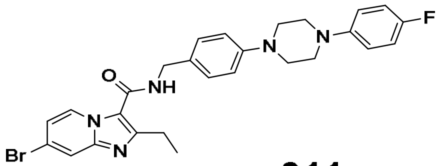

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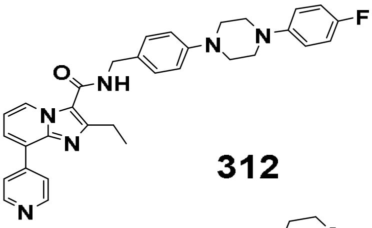

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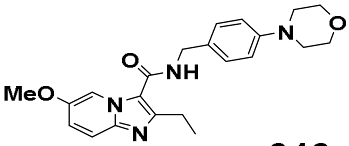

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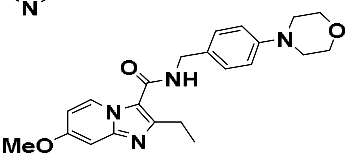

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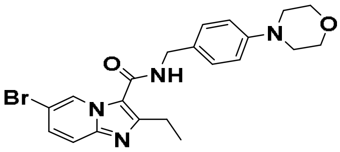

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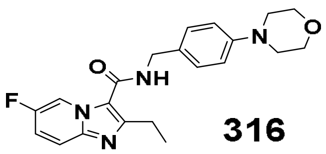

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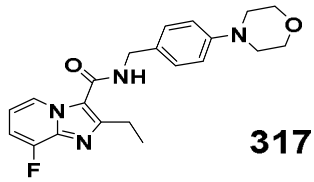

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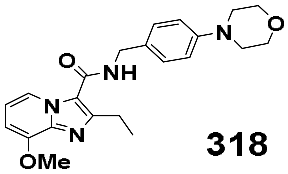

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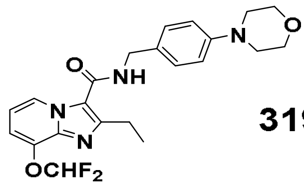

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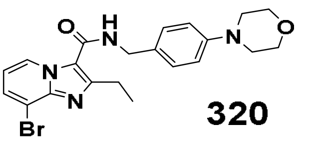

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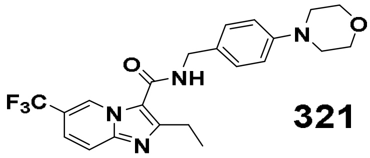

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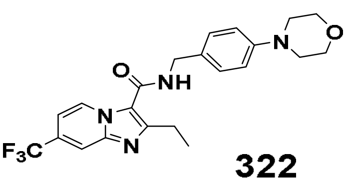

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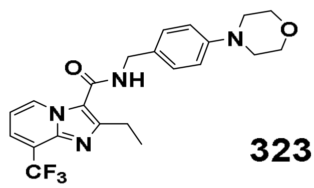

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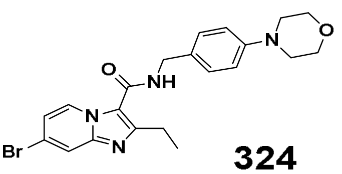

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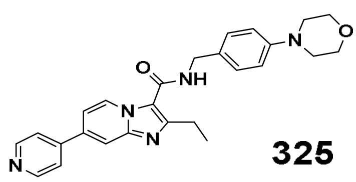

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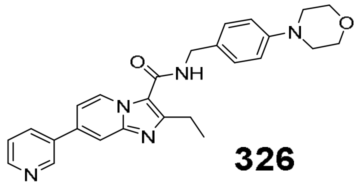

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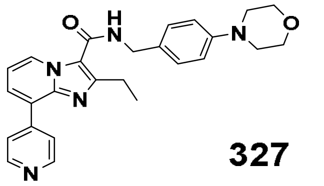

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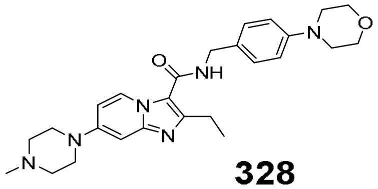

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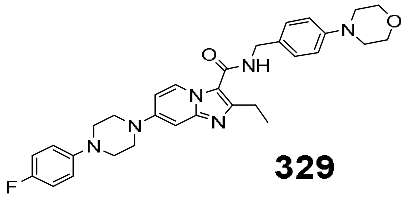

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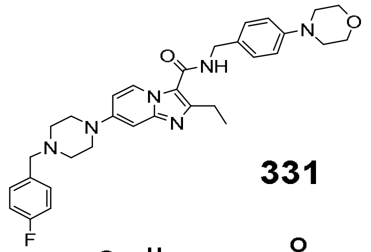

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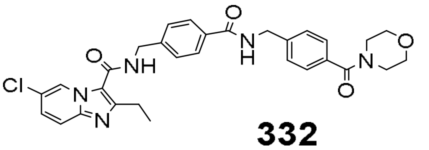

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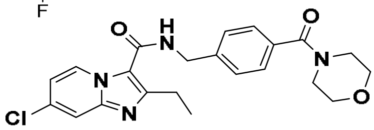

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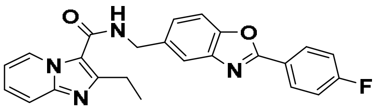

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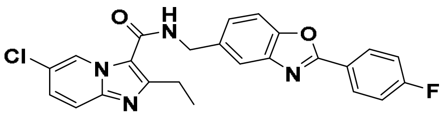

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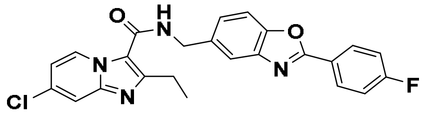

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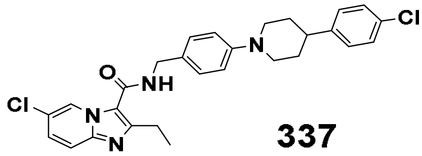

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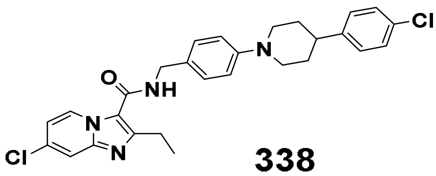

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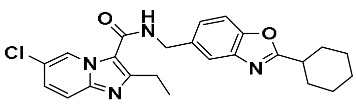

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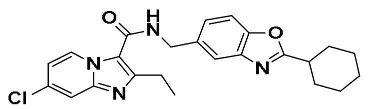

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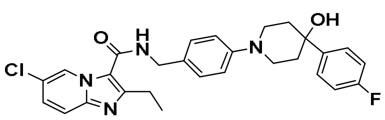

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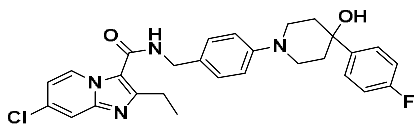

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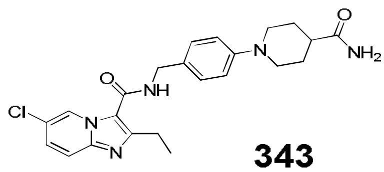

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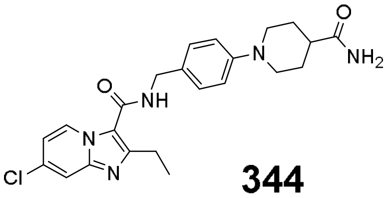

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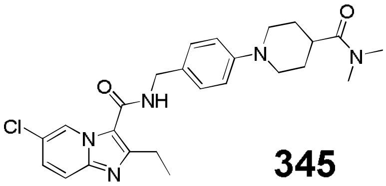

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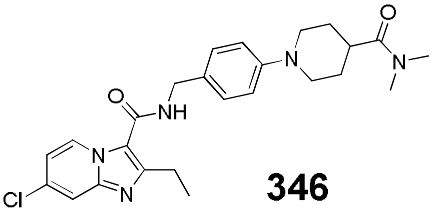

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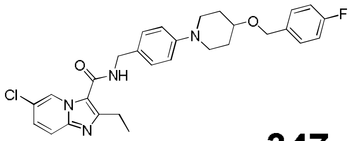

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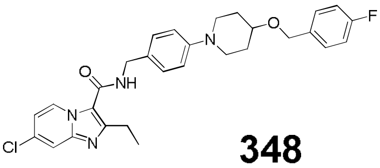

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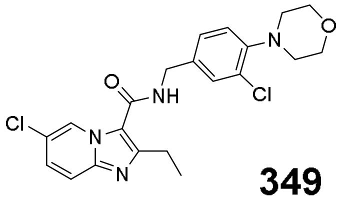

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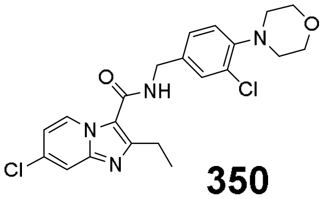

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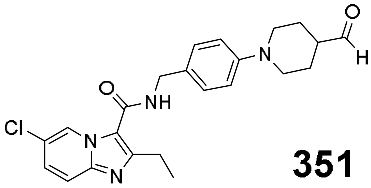

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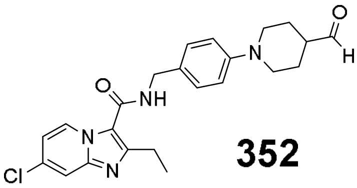

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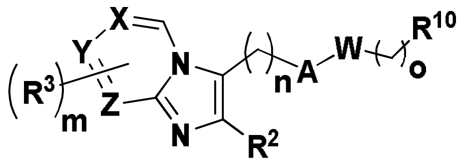
preferably one of the formulae, 56, 66-69, 74, 77-80, 89-91, 110, 111, 113, 139, 140, 144, 162-167, 171-182, 193, 209-218, 221-225, 267-269, 271-274, 280-293, 295-315, 317-318, 320-321, and 324.

3. A compound having one of the formulae 17, 56, 58, 59, 66-69, 74, 77-80, 89-91, 108-115, 139, 140, 144, 162-181, 183, 193-195, 204-225, 265-329, and 331-352 as shown in claim 2, preferably one of the formulae 56, 66-69, 74, 77-80, 89-91, 110, 111, 113, 139, 140, 144, 162-167, 171-181, 193, 209-218, 221-225, 267-269, 271-274, 280-293, 295-315, 317-318, 320-321, and 324.

4. The compound as claimed in claim 1, having formula 177.

5. A compound having the general formula Ib:



Ib

wherein

X, Y and Z are CH;

o is 1; n is 0; m is 1, 2, 3 or 4;

A is C=O;

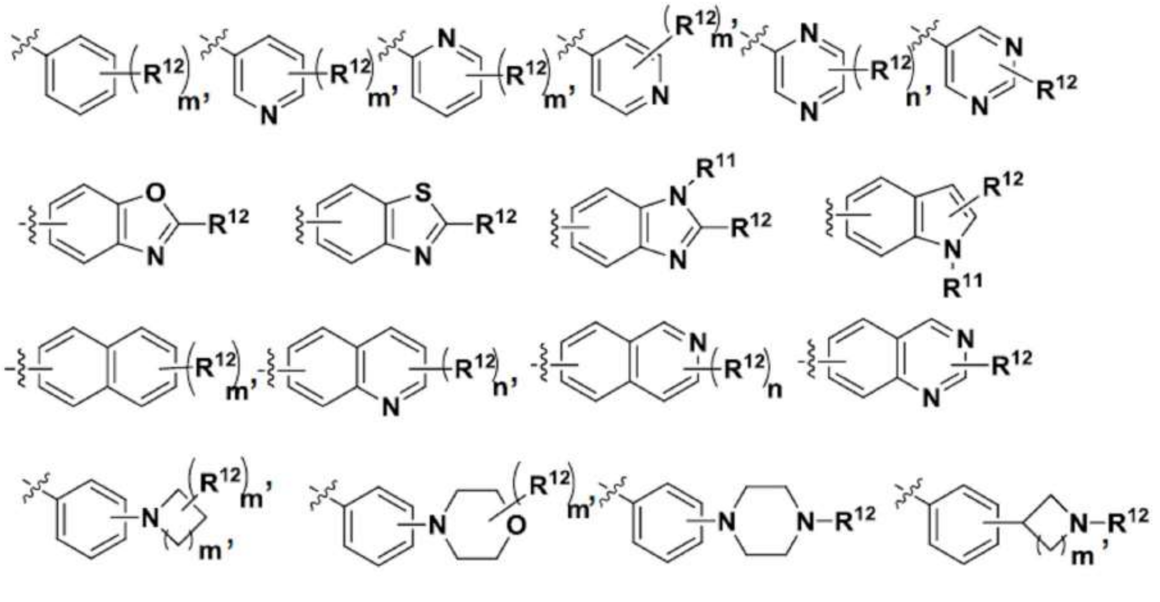
W is NH;

R^2 is, at each occurrence, independently selected from the group consisting of hydrogen, halogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, $-OR^5$, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkoxy, C_3-C_{15} cycloalkylalkoxy, C_3-C_{15} cycloalkylalkyl, -CN, $-NO_2$, $-NH_2$, $-N(R^5)_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-SR^5$, $-S(O)R^5$, $-S(O)_2R^5$, $-S(O)_2N(R^5)_2$, aryl, e.g. phenyl, benzyl, and heterocyclyl;

R^3 is, at each occurrence, independently selected from the group consisting of halogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, hydroxyl, $-OR^6$, -CN, $-NO_2$, $-NH_2$, $-N(R^6)C(O)R^6$, $-C(O)R^6$, -C(O)N(R^6)$_{2,}$ $-S(O)R^6$, $-S(O)_2R^6$, $-S(O)_2N(R^6)_2$, aryl, e.g. phenyl, benzyl, heteroaryl, heterocyclyl, or two groups of R^3 are connected to each other to make five or six membered cyclic and heterocyclic rings,

R^5 and R^6 are, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl;

R^{10} is a moiety selected from the group consisting of



wherein m' is 0, 1, 2, 3 or 4 and n' is 0, 1, 2, or 3;

R^{11} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, -OH, -OR^{13}, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkoxy, C_3-C_{15} cycloalkylalkoxy, C_3-C_{15} cycloalkylalkyl, -NH_2, -$N(R^{13})_2$, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$C(O)N(R^{13})_2$, -$S(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{13})_2$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl;

R^{12} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, hydroxyl, -OR^{14}, -$C(O)R^{14}$, -CN, -NO_2, -NH_2, -$N(R^{14})_2$, -$C(O)N(R^{14})_2$, - -$S(O)R^{14}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})_2$, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl;

R^{13} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl, and

R^{14} is, at each occurrence, independently selected from the group consisting of hydrogen, C_1-C_8 alkyl optionally substituted with at least one hydroxyl or halogen; C_3-C_7 cycloalkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, aryl, e.g. phenyl, benzyl, heteroaryl and heterocyclyl.

6. A pharmaceutical composition comprising a compound as claimed in any of claims 1 –5, and a pharmaceutically acceptable carrier.

Dated 10th day of July, 2019

Arora

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AGENT FOR THE APPLICANT(S)
IN/PA-2160

D1

IMIDAZO[1,2-a]PYRIDINE COMPOUNDS, SYNTHESIS THEREOF, AND METHODS OF USING SAME

Government Interests

[0001] This invention was made with Government support under Grant R01 AI 054193 awarded by the National Institutes of Health. The Government has certain rights in the invention.

Cross-Reference to Related Application

[0002] The present application claims priority to U. S. Provisional Patent Application No. 61/258,549, filed November 5, 2009, entitled IMIDAZO[1,2-a] PYRIDINE COMPOUNDS, SYNTHESIS THEREOF, AND METHODS OF USING SAME, the disclosure of which is hereby incorporated by reference in its entirety.

Technical Field

[0003] Embodiments herein relate to the field of chemistry and biochemistry, and, more specifically, to imidazo[1,2-a]pyridine compounds, synthesis thereof, and methods of using same.

Background

[0004] Worldwide, over two billion people are infected with tuberculosis (TB), and an estimated 14,400,000 people have active cases of TB. Of these active cases, 83% are located in Africa, South-East Asia and the Western Pacific region. The global impact of TB is enormous: each year, TB kills 1.5 million HIV-negative people and 0.2 million HIV-positive people. New drug resistant strains emerge each year.

[0005] The current treatment for active, drug-susceptible TB includes a carefully-monitored regimen of a cocktail of rifampin, isoniazid, pyrazinamide and ethambutol for two months, followed by an additional four months of rifampin and isoniazid. Multi-drug resistant TB infection requires a lengthy course of therapy lasting two years or more with drugs that are expensive and poorly tolerated. Because of their length, complexity, and expense, these regimens represent inadequate therapies for most TB cases. New therapeutics are urgently needed to combat TB infection, yet no new drugs have been approved to treat TB in over 40 years.

[0006] In addition, in a different technical area, a large number of fungi are known to grow at the expense of commercially important plants that are essential to human survival. A number of fungicides have been developed for use in protecting both ornamental plants and food crops from pathogenic fungi. While many safe and effective fungicides are currently in use, the evolution of pathogenic fungi and the ever-increasing pressure to use lower levels of fungicides create the need for new fungicides. Effective antifungal treatments are urgently needed to treat damaging fungal infections in plant species.

Brief Description of the Drawings

[0007] Embodiments will be readily understood by the following detailed description in conjunction with the accompanying drawings. Embodiments are illustrated by way of example and not by way of limitation in the figures of the accompanying drawings.

[0008] **Figure 1** illustrates the low cost of treatment with high- and low-dose imidazo[1,2-a]pyridine therapy for TB.

[0009] **Figure 2** shows the SAR of particular imidazo[1,2-a]pyridine agents and some trends observed from screening the compounds in an anti-TB assay.

[0010] **Figure 3** shows the SAR of particular imidazo[1,2-a]pyridine agents and some trends observed from screening the compounds in an antifungal assay.

[0011] **Figure 4** shows the structures of particular imidazo[1,2-a]pyridine agents screened in Figures 2 and 3.

Detailed Description of Disclosed Embodiments

[0012] In the following detailed description, reference is made to the accompanying drawings which form a part hereof, and in which are shown by way of illustration embodiments that may be practiced. It is to be understood that other embodiments may be utilized and structural or logical changes may be made without departing from the scope. Therefore, the following detailed description is not to be taken in a limiting sense, and the scope of embodiments is defined by the appended claims and their equivalents.

[0013] Various operations may be described as multiple discrete operations in turn, in a manner that may be helpful in understanding embodiments; however, the order of description should not be construed to imply that these operations are order dependent.

[0014] For the purposes of the description, a phrase in the form "A/B" or in the form "A and/or B" means (A), (B), or (A and B). For the purposes of the description, a phrase in the form "at least one of A, B, and C" means (A), (B), (C), (A and B), (A and C), (B and C), or (A, B and C). For the purposes of the description, a phrase in the form "(A)B" means (B) or (AB) that is, A is an optional element.

[0015] The description may use the terms "embodiment" or "embodiments," which may each refer to one or more of the same or different embodiments. Furthermore, the terms "comprising," "including," "having," and the like, as used with respect to embodiments, are synonymous.

[0016] As used herein, the term "halogen" refers to fluoro, bromo, chloro, and iodo substituents.

[0017] As used herein, the term "alkyl" refers to a cyclic, branched, or straight chain alkyl group containing only carbon and hydrogen, and unless otherwise mentioned contains one to twelve carbon atoms. This term may be further exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, isobutyl, t-butyl, pentyl, pivalyl, heptyl, adamantyl, and cyclopentyl. Alkyl groups can either be unsubstituted or substituted with one or more substituents, for instance, halogen, alkyl, alkoxy, alkylthio, trifluoromethyl, acyloxy, hydroxy, mercapto, carboxy, aryloxy, aryloxy, aryl, arylalkyl, heteroaryl, amino, alkylamino, dialkylamino, morpholino, piperidino, pyrrolidin-1-yl, piperazin-1-yl, or other functionality to form a "functionalized alkyl."

[0018] As used herein, the term "substituted alkyl" refers to an alkyl moiety including 1-4 substituents selected from halogen, het, cycloalkyl, cycloalkenyl, aryl, amino, cyano, nitro, $-OQ_{10}$, $-SQ_{10}$, $-S(O)_2Q_{10}$, -S(O)Q10, $-OS(O)_2Q_{10}$, $-C(=NQ_{10})Q_{10}$, $-C(=NOQ_{10})Q_{10}$, $-S(O)_2-N=S(O)(Q_{10})_2$, $-S(O)_2-N=S(Q_{10})_2$, $-NQ_{10}Q_{10}$, $-C(O)Q_{10}$, $-C(S)Q_{10}$, $-C(O)OQ_{10}$, $-OC(O)Q_{10}$, $-C(O)NQ_{10}Q_{10}$, $-C(S)NQ_{10}Q_{10}$, $-N(Q_{10})C(S)NQ_{10}Q_{10}$, $-C(O)NQ_{10}Q_{10}$, $-C(S)NQ_{10}Q_{10}$, $-C(O)C(Q_{16})_2OC(O)Q_{10}$, -CN, =S, $-NQ_{10}C(O)Q_{10}$, $-NQ_{10}C(O)NQ_{10}Q_{10}$, $-S(O)_2NQ_{10}Q_{10}$, $-NQ_{10}S(O)_2Q_{10}$, $-NQ_{10}S(O)Q_{10}$, $-NQ_{10}SQ_{10}$, and $-SNQ_{10}Q_{10}$. Each of the het, cycloalkyl, cycloalkenyl, and aryl being optionally substituted with 1-4 substituents independently selected from halogen and Q_{15}.

[0019] As used herein, the term "cycloalkyl" refers to a cyclic alkyl moiety. Unless otherwise stated, cycloalkyl moieties include between 3 and 8 carbon atoms.

[0020] As used herein, the term "alkene" refers to a hydrocarbon molecule with the general formula C_nH_{2n} that contains one or more double bonds.

[0021] As used herein, the term "alkyne" refers to a moiety having the general formula C_2H_{2n-2} corresponding to carbon chains with a triple carbon-carbon bond included.

[0022] As used herein, the term "alcohol" refers to any organic compound in which a hydroxyl group (-OH) is bound to a carbon atom of an alkyl or substituted alkyl group. The general formula for simple acyclic alcohols is $C_nH_{2n+1}OH$.

[0023] As used herein, the term "epoxide" refers to any of a class of organic compound, cyclic ethers, having a three-member ring.

[0024] As used herein, the term "ketone" refers to an organic compound containing the carbonyl group, >C=O, to which other carbon atoms are attached.

[0025] As used herein, the term "ester" refers to the product of the reaction between a carboxylic acid and an alcohol.

[0026] As used herein, the term "ether" refers to an organic compound containing the functional group RO-R'.

[0027] As used herein, the term "aldehyde" refers to an organic compound containing a -CHO group.

[0028] As used herein, the term "nitrile" refers to any of a class of organic compounds containing the cyano radical –CN.

[0029] As used herein, the term "thiol" refers to a molecular group that includes a bonded sulfur and hydrogen atom (-SH).

[0030] As used herein, the term "thioester" refers to a compound resulting from the bonding of sulfur with an acyl group with the general formula R-S-CO-R'. Thioesters are the product of esterification between a carboxylic acid and a thiol (as opposed to an alcohol in regular esters).

[0031] As used herein, the term "sulfide" refers to an organic compound containing sulfur bonded to carbon. The term "disulfide" refers to the structural unit composed of a linked pair of sulfur atoms.

[0032] As used herein, the term "sulfone" refers to a chemical compound containing a sulfonyl functional group attached to two carbon atoms. The central sulfur atom is twice double bonded to oxygen and has two further hydrocarbon substituents. The general structural formula is R-S(=O)(=O)-R' where R and R' are the organic groups.

[0033] As used herein, the term "sulfoxide" refers to a chemical compound containing a sulfinyl functional group attached to two carbon atoms. Sulfoxides can be considered oxidized sulfides.

[0034] As used herein, the term "amine" refers to NH_2, NHR, or NR_2. Unless otherwise stated R can be alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, het or aryl.

[0035] As used herein, the term "amide" refers to an organic compound containing the -$CONH_2$- group.

[0036] As used herein, the term "urea" refers to an organic compound with the chemical formula $(NH_2)_2CO$ or RNHCONHR'.

[0037] As used herein, the term "carbamate" refers to any of a group of organic compounds sharing a common functional group with the general structure -NH(CO)O-. Carbamates are esters of carbamic acid, NH_2COOH. Since carbamic acid contains nitrogen attached to a carboxyl group, it is also an amide. Therefore, carbamate esters may have alkyl or aryl groups substituted on the nitrogen, or the amide function. For example, ethyl carbamate is unsubstituted, whereas ethyl N–methylcarbamate has a methyl group attached to the nitrogen.

[0038] As used herein, the term "nitro" refers to NO_2.

[0039] As used herein, the term "aryl" refers to phenyl, substituted phenyl, naphthyl, and substituted naphthyl.

[0040] As used herein, the term "morpholine" refers to an organic chemical compound having the chemical formula $O(CH_2CH_2)_2NH$. This heterocycle features both amine and ether functional groups. Because of the amine, morpholine is a base; its conjugate acid is called morpholinium. For example, when morpholine is neutralized by hydrochloric acid, one obtains the salt morpholinium chloride.

[0041] As used herein, the term "thiomorpholine" refers to C_4H_9NS, and is a heterocyclic compound containing nitrogen and sulfur. It may be considered a thio derivative of morpholine.

[0042] As used herein, the term "piperazine" refers to an organic compound that consists of a six-member ring containing two opposing nitrogen atoms.

[0043] As used herein, the term "piperidine" refers to an organic compound with the molecular formula $(CH_2)_5NH$. This heterocyclic amine consists of a six-member ring containing five methylene units and one nitrogen atom.

[0044] As used herein, the term "acyl" refers to any of a group or radical of the form RCO- where R is an organic group.

[0045] As used herein, the term "furan" refers to any of a class of aromatic heterocyclic compounds containing a ring of four carbon atoms and an oxygen atom; for instance, C_4H_4O. As used herein, the term "nitrofuran" refers to a furan ring with a nitro group.

[0046] As used herein, the term "thiophene" refers to the heterocyclic compound with the formula C_4H_4S. Consisting of a flat five-membered ring, it is aromatic as indicated by its extensive substitution reactions. Related to thiophene are benzothiophene and dibenzothiophene, containing the thiophene ring fused with one and two benzene rings, respectively. Compounds analogous to thiophene include furan (C_4H_4O) and pyrrole (C_4H_4NH).

[0047] As used herein, the term "imidazole" refers to an organic compound with the formula $C_3H_4N_2$. This aromatic heterocyclic is classified as an alkaloid. Imidazole refers to the parent compound whereas imidazoles are a class of heterocycles with similar ring structure but varying substituents. A nitroimidazole is an imidazole derivative that contains a nitro group.

[0048] As used herein, the term "oxazole" refers to a five-member heterocycle having three carbon atoms, one oxygen atom, one nitrogen atom and two double bonds; the 1,3-isomer is aromatic.

[0049] As used herein, the tem "oxazoline" refers to an unsaturated heterocyclic compound containing a five-member ring, two double bonds, one nitrogen and one oxygen atom; and any derivative of this compound.

[0050] As used herein, the term "thiazole" refers to any of a class of unsaturated heterocyclic compounds containing a ring of three carbon atoms, a sulfur and an nitrogen atom; for instance the simplest one, C_3H_3SN.

[0051] As used herein, the term "thiazoline" refers to an unsaturated heterocyclic compound containing a five-member ring, two double bonds, one nitrogen and one sulfur atom; and any derivative of this compound.

[0052] As used herein, the term "triazole" refers to either one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, having a five-member ring of two carbon atoms and three nitrogen atoms.

[0053] As used herein, the term "pyridine" refers to any of a class of aromatic heterocyclic compounds containing a ring of five carbon atoms and a nitrogen atom; for instance the simplest one, C_5H_5N.

[0054] As used herein, the term "pyrazine" refers to a diazine in which the two nitrogen atoms are in the para- position.

[0055] As used herein, the term "naphthalene" refers to an aromatic, white, solid hydrocarbon with formula $C_{10}H_8$ and the structure of two fused benzene rings.

[0056] As used herein, the term "diketopiperazine" refers to a class of cyclic organic compounds that result from peptide bonds between two amino acids to form a lactam. They are the smallest possible cyclic peptides.

[0057] As used herein, the term "quinoline" refers to any of a class of aromatic heterocyclic compounds containing a benzene ring fused with a ring of five carbon atoms and a nitrogen atom; for instance the simplest one, C_9H_7N. Isoquinoline, also known as benzo[c]pyridine or 2-benzanine, is a heterocyclic aromatic organic compound. It is a structural isomer of quinoline. Isoquinoline and quinoline are benzopyridines, which are composed of a benzene ring fused to a pyridine ring. In a broader sense, the term isoquinoline is used to make reference to isoquinoline derivatives.

[0058] As used herein, the term "oxazolidinone" refers to a class of heterocyclic organic compounds containing both nitrogen and oxygen in a 5-member ring.

[0059] As used herein, the term "heterocyclic" refers to organic compounds containing at least one atom of carbon, and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure. These structures may comprise either simple aromatic rings or non-aromatic rings. Each mono-cyclic ring may be aromatic, saturated or partially unsaturated. A bi-cyclic ring system may include a mono-cyclic ring containing one or more heteroatom fused with a cycloalkyl or aryl group. A bi-cyclic ring system may also include a mono-cyclic ring containing one or more heteroatom fused with another mono-cyclic ring system.

[0060] Examples of "heterocyclics" include but are not limited to pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazinyl, 3-pyridazinyl, 4-pyridazinyl, 4-oxo-2-imidazolyl, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 4-pyridazinyl, 3-pyrazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 1,2,3-oxathiazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, 2-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1,3,4-oxadiazole, 4-oxo-2-thiazolinyl, 5-methyl-1,3,4-thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, 1,2,4-dithiazolone, phthalimide, quinolinyl, morpholinyl, benzimidazolyl, benzo[d]thiazolyl, benzo[d]oxazolyl, diazinyl, triazinyl, quinolinyl, quinoxalinyl, naphthyridinyl, azetidinyl, pyrrolidinyl, hydantoinyl, oxathiolanyl, dioxolanyl, imidazolidinyl, azabicyclo [2.2.1] heptyl, 2-methyl-1,4-dioxa-8-azaspiro[4.5]decane, 2,3-dimethyl-1,4-dioxa-8-azaspiro[4.5]decane, 3-methyl-1,5-dioxa-9-azaspiro[5.5]undecane, and 2,4-dimethyl-1,5-dioxa-9-azaspiro[5.5]undecane.

[0061] As used herein, the term "heteroaryl" refers to a mono- or bicyclic het in which one or more cyclic ring is aromatic.

[0062] As used herein, the term "substituted heteroaryl" refers to a heteroaryl moiety substituted with one or more functional groups selected from halogen, alkyl, hydroxyl, amino, alkoxy, cyano, and nitro.

[0063] As used herein, the term "substituted aryl" refers to an aryl moiety having 1-3 substituents selected from halogen, het, alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, aryl, cyano, nitro, $-OQ_{10}$, $-SQ_{10}$, $-S(O)_2Q_{10}$, $-S(O)Q_{10}$, $-OS(O)_2Q_{10}$, $-C(=NQ_{10})Q_{10}$, $-C(=NOQ_{10})Q_{10}$, $-S(O)_2-N=S(O)(Q_{10})_2$, $-S(O)_2-N=S(Q_{10})_2$, $-NQ_{10}Q_{10}$, $-C(O)Q_{10}$, $-C(S)Q_{10}$, $-C(O)OQ_{10}$, $-OC(O)Q_{10}$, $-C(O)NQ_{10}Q_{10}$, $-C(S)NQ_{10}Q_{10}$, $-C(O)C(Q_{16})_2OC(O)Q_{10}$, $-NQ_{10}C(O)Q_{10}$, $-N(Q_{10})C(S)NQ_{10}Q_{10}$, $-N(Q_{10})C(S)Q_{10}$, $-NQ_{10}C(O)NQ_{10}Q_{10}$, $-S(O)_2NQ_{10}Q_{10}$, $-NQ_{10}S(O)_2Q_{10}$, $-NQ_{10}S(O)Q_{10}$, $-NQ_{10}SQ_{10}$, and $-SNQ_{10}Q_{10}$. The het, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, and aryl being optionally substituted with 1-3 substituents selected from halogen and Q_{15}.

[0064] Each Q_{10} is independently selected from H, alkyl, cycloalkyl, het, cycloalkenyl, and aryl. The het, cycloalkyl, cycloalkenyl, and aryl being optionally substituted with 1-3 substituents selected from halo and Q_{13}.

[0065] Each Q_{11} is independently selected from H, halogen, alkyl, aryl, cycloalkyl, and het. The alkyl, aryl, cycloalkyl, and het being optionally substituted with 1-3 substituents independently selected from halogen, nitro, cyano, =S, =0, and Q_{14}.

[0066] Each Q_{13} is independently selected from Q_{11}, $-OQ_{11}$, $-SQ_{11}$, $-S(O)_2Q_{11}$, $-S(O)Q_{11}$, $-OS(O)_2Q_{11}$, $-C(=NQ_{11})Q_{11}$, $-S(O)_2-N=S(O)(Q_{11})_2$, $-S(O)_2-N=S(Q_{11})_2$, $-SC(O)Q_{11}$, $-NQ_{11}Q_{11}$, $-C(O)Q_{11}$, $-C(S)Q_{11}$, $-C(O)OQ_{11}$, $-OC(O)Q_{11}$, $-C(O)NQ_{11}Q_{11}$, $-(S)NQ_{11}Q_{11}$, $-C(O)C(Q_{16})_2OC(O)Q_{10}$, -CN, =O, =S, $-NQ_{11}C(O)Q_{11}$, $-NQ_{11}C(S)Q_{11}$, $-NQ_{11}C(O)NQ_{11}Q_{11}$, $-NQ_{11}C(S)NQ_{11}Q_{11}$, $-S(Q)_2NQ_{11}Q_{11}$, $-NQ_{11}S(O)_2Q_{11}$, $-NQ_{11}S(O)Q_{11}$, $-NQ_{11}SQ_{11}$, $-NO_2$, and $-SNQ_{11}Q_{11}$.

[0067] Each Q_{14} is independently selected from H, alkyl, cycloalkyl, phenyl, or naphthyl, each optionally substituted with 1-4 substituents independently selected from F, Cl, Br, I, $-OQ_{16}$, $-SQ_{16}$, $-S(O)_2Q_{16}$, $-S(O)Q_{16}$, $-OS(O)_2Q_{16}$, $-NQ_{16}Q_{16}$, $-C(O)Q_{16}$, $-C(S)Q_{16}$, $-C(O)OQ_{16}$, $-NO_2$, $-C(O)NQ_{16}Q_{16}$, $-C(S)NQ_{16}Q_{16}$, -CN, $-NQ_{16}C(O)Q_{16}$, $-NQ_{16}C(S)Q_{16}$, -

$NQ_{16}C(O)NQ_{16}Q_{16}$, $-NQ_{16}C(S)NQ_{16}Q_{16}$, $-S(O)_2NQ_{16}Q_{16}$, and $-NQ_{16}S(O)_2Q_{16}$. The alkyl, cycloalkyl, and cycloalkenyl being further optionally substituted with =O or =S.

[0068] Each Q_{15} is independently selected from H, alkyl, cycloalkyl, heteroaryl, phenyl, or naphthyl, each optionally substituted with 1-4 substituents independently selected from F, Cl, Br, I, $-OQ_{16}$, $-SQ_{16}$, $-S(O)_2Q_{16}$, $-S(O)Q_{16}$, $-OS(O)_2Q_{16}$, $-C(=NQ_{16})Q_{16}$, $-S(O)_2-N=S(O)(Q_{16})_2$, $-S(O)_2-N=S(Q_{16})_2$, $-SC(O)Q_{16}$, $-NQ_{16}Q_{16}$, $-C(O)Q_{16}$, $-C(S)Q_{16}$, $-C(O)OQ_{16}$, $-OC(O)Q_{16}$, $-C(S)NQ_{16}Q_{16}$, $-C(O)C(Q_{16})_2OC(O)Q_{16}$, -CN, $-NQ_{16}C(O)Q_{16}$, $-NQ_{16}C(S)Q_{16}$, $-NQ_{16}C(O)NQ_{16}Q_{16}$, $-NQ_{16}C(S)NQ_{16}Q_{16}$, $-S(O)_2NQ_{16}Q_{16}$, $-NQ_{16}S(O)_2Q_{16}$, $-NQ_{16}S(O)Q_{16}$, $-NQ_{16}SQ_{16}$, $-NO_2$, and $-SNQ_{16}Q_{16}$. The alkyl, cycloalkyl, and cycloalkenyl being further optionally substituted with =O or =S.

[0069] Each Q_{16} is independently selected from H, alkyl, and cycloalkyl. The alkyl and cycloalkyl optionally including 1-3 halogens.

[0070] Embodiments of the present disclosure provide novel imidazopyridines, for instance imidazo[1,2-a]pyridines. Certain embodiments are directed to compounds and methods for the treatment and prevention of tuberculosis (TB). Other embodiments are directed to compounds and methods for inhibiting fungal growth on plant species. In still other embodiments, methods are provided for the synthesis of the disclosed imidazo[1,2-a]pyridine compounds.

[0071] In embodiments, the imidazo[1,2-a]pyridine compounds of this disclosure may be useful in treating or preventing tuberculosis in a subject. The *in vitro* activity of disclosed compounds may be assessed by standard testing procedures, for instance in H37Rv TB screens.

[0072] In embodiments, the imidazo[1,2-a]pyridine compounds described herein may be useful for treating (for instance, ameliorating or preventing) multi-drug resistant (MDR) and non-MDR TB in a subject. In an embodiment, a compound may be administered to a subject locally or systemically. In embodiments, an imidazo[1,2-a]pyridine compound may be administered parenterally, for instance subcutaneously, intravenously, or intramuscularly, or it may be administered orally or by inhalation. An imidazo[1,2-a]pyridine compound may be used alone or in combination with other anti-tuberculosis agents. In an embodiment, an imidazo[1,2-a]pyridine compound may be administered in varying concentrations depending upon the infection's susceptibility to the compound being administered, the extent of the disease, whether the infection is latent or active, whether the infection is drug-resistant, and the general health of the subject.

[0073] In an embodiment, imidazo[1,2-a]pyridine compounds may be incorporated into a pharmaceutical composition. Embodiments of the present disclosure encompass any racemic, optically-active, polymorphic, tautomeric, or stereoisomeric form or mixture thereof, of a compound of the disclosure, which possesses the useful properties described herein.

[0074] In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, use of the compounds as pharmaceutically acceptable salts may be appropriate. Examples of pharmaceutically acceptable salts within the scope of embodiments herein include organic acid addition salts formed with acids which form a physiological acceptable anion and inorganic salts.

[0075] Pharmaceutical compositions in accordance with embodiments of the disclosure may be prepared by combining the disclosed compounds with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier may be at least one substance that may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds disclosed herein dissolved in water and water-propylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers, and/or thickening agents.

[0076] In an embodiment, a pharmaceutical composition may be provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of one or more active component. In embodiments, the quantity of active component (compound) in a pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound and the desired concentration. In an embodiment, the quantity of active component may range from 0.5% to 90% by weight of the composition.

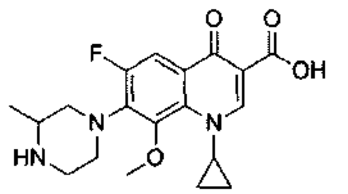
[0077] In embodiments, in therapeutic use for treating, ameliorating, preventing, or combating TB in subjects, the compounds or pharmaceutical compositions thereof may be administered orally, parenterally, and/or by inhalation at a dosage to obtain and maintain a concentration or blood-level of active component in the animal undergoing treatment that is therapeutically effective. In an embodiment, such a therapeutically effective amount/dosage of active component may be in the range of from about 0.1 to about 100 mg/kg, for instance, from about 0.1 to about 10 mg/kg, of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the infection, the particular mycobacterial species, whether the infection is latent or active, the drug resistance of the strain, the duration of the infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose also may be divided into multiple doses for administration, for instance, two to four times per day.

[0078] In an embodiment, an initial imidazo[1,2-a]pyridine compound was provided and tested as an exemplary member of the new imidazo[1,2-a]pyridine class of anti-tuberculosis agents disclosed herein. Such compound is identified below as compound ND-8454, and the compound's structure is shown in Table 1. Imidazo[1,2-a]pyridine is a simple bicyclic compound with a bridgehead nitrogen atom. This class of molecules is unrepresented within the TB literature, and the scaffold is very attractive because of the low cost of starting materials and the ease with which potent (<1 μg/mL) anti-TB compounds are synthesized therefrom.

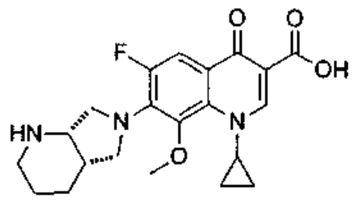
[0079] Many of the existing clinical candidates for TB therapeutics are derivatives of existing scaffolds (for instance, moxifloxacin and gatifloxacin, see Table 1), which results in drugs that are much more prone to emerging resistance. Other clinical candidates are complex compounds that are difficult and costly to manufacture (for example anti-TB candidates TMC207, PA-824, OPC-67683, and LL-3858, see Table 1).

[0080] In contrast, ND-8454, *N*-benzyl-2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamide, the initial "hit" based on the imidazo[1,2-a]pyridine scaffold, has an *in vitro* activity against H37Rv TB comparable to the current clinical candidates (MIC = 0.08 μg/mL or 286 nM) and no observed toxicity to VERO or HeLa cells (>128 and >50 μM, respectively).

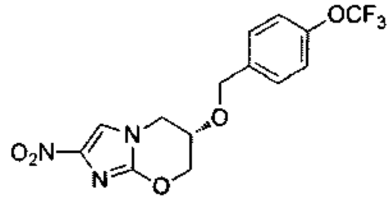
Table 1. Current TB clinical candidates and ND-8454 (initial imidazo[1,2-a]pyridine hit)



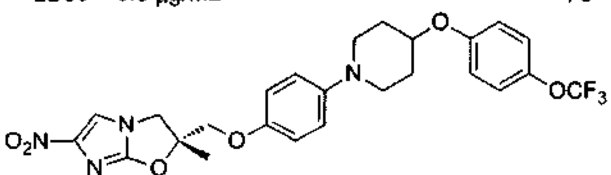
Gatifloxacin (OFLOTUB Consortium)
MIC = 0.03 - 1.56 μg/mL H37Rv TB
MIC = 3.12 μg/mL MDR-TB
LD99 = 0.5 μg/mL



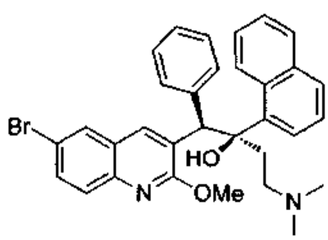
Moxifloxacin (Bayer)
MIC = 0.04 - 0.5 μg/mL H37Rv TB
MIC = 0.5 μg/mL MDR-TB
LD99 = 0.8 μg/mL



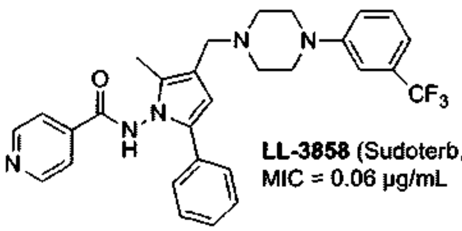
PA-824 (TB Alliance)
MIC of 0.25 – 0.03 μg/mL
vs. H37Rv and MDR-TB



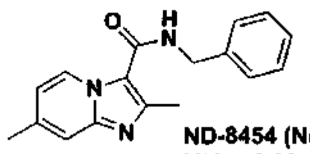
OPC-67683 (Otsuka)
MIC of 0.006 – 0.024 μg/mL
vs. H37Rv and MDR-TB



TMC207 (Diarylquinoline, J&J)
MIC = 0.06 μg/mL vs. H37Rv and MDR-TB



LL-3858 (Sudoterb, Lupin)
MIC = 0.06 μg/mL



ND-8454 (Notre Dame)
MIC = 0.08 μg/mL H37Rv TB
MIC = 0.02 μg/mL MDR-TB
VERO >128 μM

[0081] In accordance with various embodiments, Table 2 illustrates the potency of several exemplary compounds against several individual strains of single drug resistant TB.

Table 2. TB Potency against single drug resistant strains (MIC90 in μM)

Resistance to (μM)	rRMP	rINH	rKM	*rSM*
ND-8454	0.28	0.33	1.07	1.02
ND-9652	1.49	2.03	5.83	5.84
ND-9758	<0.002	0.003	0.01	0.01
ND-9872	0.23	0.28	0.89	0.87
ND-9902	0.74	1.10	2.96	2.95
ND-9903	0.24	0.25	0.59	0.63
ND-9965	0.54	0.57	1.98	2.31
RMP	> 1	0.01	0.02	0.02
INH	0.23	>8	0.43	0.23
MOX	0.10	0.12	0.24	0.15

RMP = Rifampicin; INH – Isoniazid; KM = Kanamycin; SM = Streptomycin

[0082] In accordance with various embodiments, Table 3 illustrates the potency of several exemplary compounds against several strains of multi-drug resistant (MDR) TB.

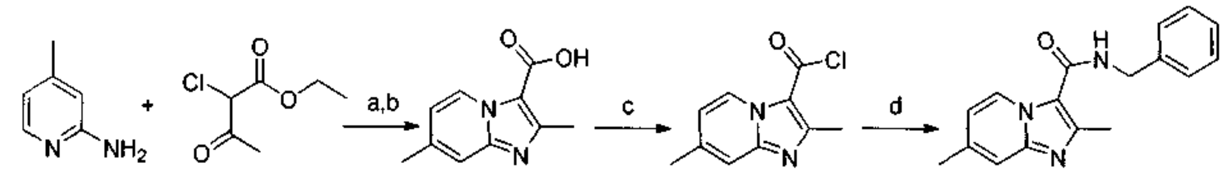
Table 3. MDR-TB Potency (MIC90 in μg/mL)

Resistance to (μg/mL):	HRESP	HREZSP	HCPTh	HREKP	HRERb*	HREZSKPTh	HRERb*	HRERb*	HREZRbTh
ND-8454	0.625	0.3125	0.313	0.078	0.039	0.019	0.039	0.078	0.039
ND-8667	0.3125	0.019	0.039	0.039c	**<=0.0098**	**<=0.0098**	0.01	0.019	0.019
ND-9361	0.078	0.019	NT	0.078	0.039	0.019	0.01	0.078	0.019

Abbreviations: H=Isoniazid, R=Rifampicin, E=Ethambutol, Z=Pyrazinamide, S=Streptomycin, C=Cycloserine, K=Kanamycin, P=*p*-aminosalicylic acid, Rb=rifabutin, Th=thioacetazone, * genetically different strains.

[0083] In embodiments, the exemplary compounds described above may be synthesized according to the following general procedures. ND-8454, for example, can be made in four synthetic steps from readily available, inexpensive reagents. To evaluate the potential availability and affordability of making this compound on a kilogram scale, the cost to scale up ND-8454 using the following exemplary procedure was evaluated (see Scheme 1, below).

Scheme 1. Synthesis of ND-8454



Reagents: (a) 1,2-dimethoxyethane, reflux, 48 hours; (b) 1 N LiOH, EtOH, reflux, 36 hours; (c) oxalyl chloride, CH_2Cl_2, DMF (cat.), room temperature, 4 hours; (d) benzylamine, Et_3N, CH_2Cl_2, reflux, 14 hours

[0084] In this specific example of synthesis of ND-8454, a solution of 2-amino-4-picoline (10.0 g, 91.5 mmol) and ethyl-2-chloroacetoacetate (7.93 g, 45.8 mmol) were dissolved in 92 mL of 1,2-dimethoxyethane (DME) and heated for 36 h at reflux. The reaction mixture was filtered and solids (2-amino-4-picoline hydrochloride salt) was collected and washed with hexanes. The filtrate liquor was concentrated *in vacuo* and residue was dissolved in CH_2Cl_2 and washed with 5% acetic acid solution (2x) and brine. The organic phase was collected, dried over sodium sulfate (Na_2SO_4), filtered and then concentrated *in vacuo*. Crude material obtained was purified by silica gel column chromatography with a 20% ethyl acetate : CH_2Cl_2 solvent system to give 7.8 g (78%) of ethyl 2,7-dimethylimidazo[1,2-a]pyridine-3-carboxylate as a tan solid.mp 59-61°C; ^{1}H NMR (300 MHz, $CDCl_3$) 9.14 δ (d, J = 7.1 Hz, 1H), 7.34 (s, 1H), 6.78 (dd, J = 7.1, 1.7 Hz, 1H), 4.40 (q, J = 7.1, 7.1, 7.1 Hz, 2H), 2.66 (s, 3H), 2.42 (s, 3H), 1.42 (t, J = 7.1, 7.1 Hz, 3H). HRMS (EI), M+1 calcd. for $C_{12}H_{15}N_2O_2$, 219.1155; found 219.1128. Retention time = 1.4 minutes (mobile phase: 60% water : acetonitrile).

The ethyl 2,7-dimethylimidazo[1,2-a]pyridine-3-carboxylate (6.4 g, 29.3 mmol) was dissolved in 75 mL of ethanol (95%), 1M LiOH (60 mL, 60 mmol) was added and reaction was heated to reflux for 36 hours. The resulting solution was concentrated to dryness and then made acidic (pH~2-3) with the addition of 4 N HCl; resulting solids were collected by filtration and rigorously dried to give 4.6 grams (82%) of 2,7-dimethylimidazo[1,2-a]pyridine-3-carboxylic acid, an off-white solid. mp 180- 183°C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.52 (d, J = 7.1 Hz, 1H), 7.73 (td, J = 1.8, 0.9, 0.9 Hz, 1H), 7.48 (dd, J = 7.1, 1.3 Hz, 1H), 2.81 (s, 3H), 2.63 (s, 3H). HRMS (EI), M+1 calcd. for $C_{10}H_{11}N_2O_2$, 191.0815; found 191.0837. Retention time = 0.6 – 0.7 minutes (mobile phase: 60% water : acetonitrile).

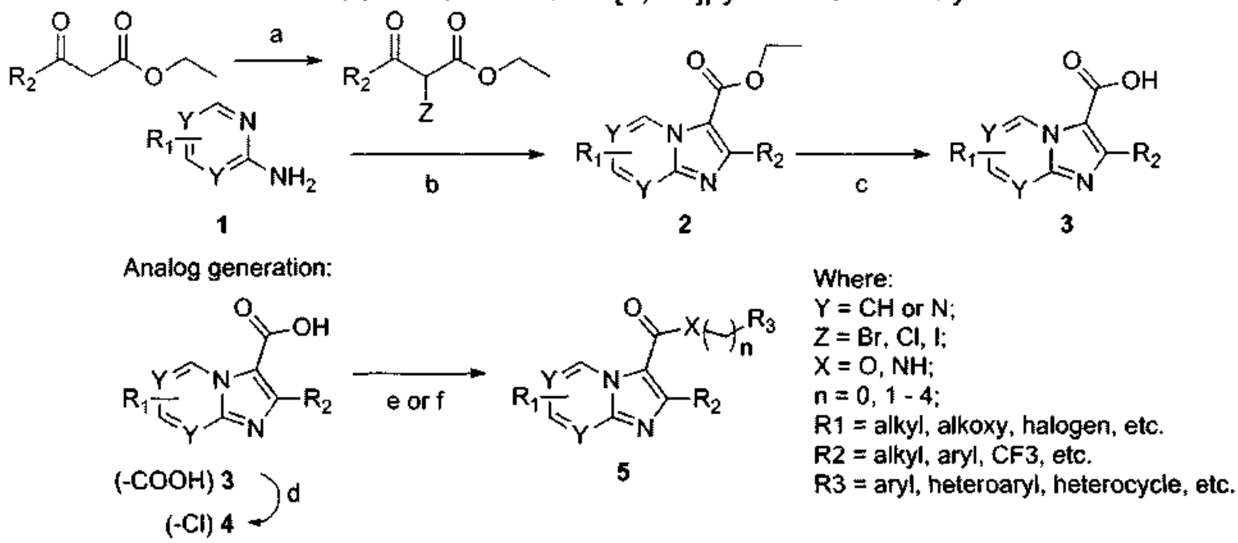
[0085] The 2,7-dimethylimidazo[1,2-a]pyridine-3-carboxylic acid (2.8 grams, 14 mmol) was partly dissolved in 35 mL anhydrous CH_2Cl_2 and oxalyl chloride (3.3 mL, 39 mmol) was added followed by catalytic (20 μL) N'N-dimethylforamide (DMF).

[0086] The reaction was stirred under argon at room temperature for 4 hours. The clear, orange solution was concentrated to dryness and the resulting acid chloride (3.6 grams, 14 mmol, yellow solid) was dissolved in 35 mL anhydrous CH_2Cl_2. Triethylamine (5.9 mL, 41.9 mmol) and benzylamine (1.8 mL, 16.7 mmol) were added slowly. The reaction was heated to 50°C under argon for 16 hours. The reaction was then concentrated to dryness and the resulting solid was dissolved in ethyl acetate (EtOAc) and washed with saturated sodium bicarbonate solution (2x) and brine washed.

[0087] The organics were collected and dried over Na_2SO_4, the drying agent was filtered off, and the organics were concentrated down to an oil which crystallized upon standing. The solid was purified through a silica gel column eluting with a gradient of 1:10 (EtOAc : CH_2Cl_2) to 10:1 (EtOAc : CH_2Cl_2). 2.75 grams of *N*-benzyl-2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamide (ND-8454, 70%) was obtained as an off-white solid. mp 166 - 167°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (d, *J* = 7.1 Hz, 1H), 7.39-7.28 (m, 5H), 7.25 (s, 1H), 6.75 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.05 (bs, 1H, NH), 4.69 (d, *J* = 5.7 Hz, 2H), 2.65 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.52, 146.54, 145.36, 138.30, 128.84, 127.67, 127.61, 127.35, 127.31, 115.72, 115.05, 43.42, 21.34, 16.83. HRMS (EI), M+1 calcd. for $C_{17}H_{18}N_3O$, 280.1444; found 280.1480. Retention time = 0.8 – 1.1 minutes (mobile phase: 60% water : acetonitrile).

[0088] In another embodiment, imidazo[1,2-a]pyridine compounds may be synthesized according to the general procedures shown in Scheme 2, below.

Scheme 2: Imidazo[1,2-a]pyridine Chemistry



Reagents: (a) N-Z-succinimide, DMSO, room temperature, 4 hours, where Z=Bromo, Chloro, or Iodo; (b) 1,2-dimethoxyethane, reflux, 48 hours; (c) 1 N LiOH, EtOH, reflux, 36 hours; (d) oxalyl chloride, CH_2Cl_2, DMF (cat.), room temperature, 4 hours; (e) R-NH_2 or R-OH, EDC-HCl, DMAP, CH_3CN, 16 hours; when chloride (f) R-NH_2 or R-OH, Et_3N, CH_2Cl_2, 16 hours.

[0089] Figure 1 shows that ND-8454 may be made from readily available materials using the process described above. The active pharmaceutical ingredient may be obtained at a $300-1000/kg price range on commercial scale. This translates to a remarkably low cost of only $0.03-$0.1/day at a 100 mg daily dose. Therefore, ND-8454 and similar imidazo[1,2-a]pyridine agents are very inexpensive to manufacture and may be made readily accessible to populations in need.

[0090] Embodiments of the present disclosure also provide methods for treating or preventing TB infection in a subject using compounds described herein. As used herein, the terms "tuberculosis" and "TB" refer to mycobacterial infection, a common and often deadly infectious disease usually caused by *Mycobacterium tuberculosis.* Tuberculosis usually attacks the lungs (as pulmonary TB), but can also affect the central nervous system, the lymphatic system, the circulatory system, the genitourinary system, the gastrointestinal system, bones, joints, and even the skin. Other mycobacteria such as *Mycobacterium bovis, Mycobacterium africanum, Mycobacterium canetti*, and *Mycobacterium microti* also cause tuberculosis, but these species are less common in humans.

[0091] The classic symptoms of tuberculosis are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. Infection of other organs causes a wide range of symptoms. In some embodiments, a tuberculosis diagnosis may be made by radiology (commonly chest X-rays), a tuberculin skin test, and blood tests, as well as microscopic examination and microbiological culture of bodily fluids. Tuberculosis treatment is difficult and normally requires long courses of multiple antibiotics, and antibiotic resistance is a growing problem.

[0092] Approximately one third of the world's population is infected with *M. tuberculosis*. However, most of these cases will not develop the full-blown disease; asymptomatic, latent infection is most common. About one in ten of these latent infections will eventually progress to active disease, which, if left untreated, kills more than half of its victims. In 2004, mortality and morbidity statistics included 14.6 million chronic active cases, 8.9 million new cases, and 1.6 million deaths, mostly in developing countries. In addition, a rising number of people in the developed world are contracting tuberculosis because of compromised immune systems from immunosuppressive drugs, substance abuse, or AIDS. The distribution of tuberculosis is not uniform worldwide, with about 80% of the population in many Asian and African countries testing positive in tuberculin tests, while only 5-10% of the US population tests positive. It is estimated that the US has 25,000 new cases of tuberculosis each year, 40% of which occur in immigrants from countries where tuberculosis is endemic.

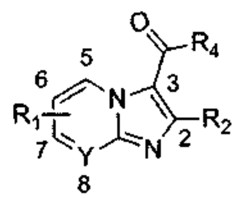
[0093] An estimated 75% of active TB cases involve pulmonary TB. Symptoms include chest pain, coughing up blood, a productive, prolonged cough for more than three weeks, fever, chills, night sweats, appetite loss, weight loss, pallor, and often a tendency to fatigue very easily. In the other 25% of active cases, the infection moves from the lungs, causing extrapulmonary tuberculosis. This occurs more commonly in immunosuppressed persons and young children. Extrapulmonary infection sites include the pleura in tuberculosis pleurisy, the central nervous system in meningitis, the lymphatic system in scrofula of the neck, the genitourinary system in urogenital tuberculosis, and bones and joints in Pott's disease of the spine. An especially serious form is disseminated TB, more commonly known as miliary tuberculosis. Although extrapulmonary TB is not contagious, it may co-exist with pulmonary TB, which is contagious.

[0094] The primary cause of TB, *Mycobacterium tuberculosis*, is an aerobic, Gram-positive bacterium. In addition, the *M. tuberculosis complex* includes three other TB-causing mycobacteria: *M. bovis, M. africanum* and *M. microti*. *M. africanum* is not widespread, but in parts of Africa it is a significant cause of tuberculosis. *M. bovis* was once a common cause of tuberculosis, but the introduction of milk pasteurization has largely eliminated this as a public health problem in developed countries. *M. microti* is mostly seen in immunodeficient people, although it is possible that the prevalence of this pathogen has been underestimated.

[0095] Other known pathogenic mycobacteria include *Mycobacterium leprae*, *Mycobacterium avium* and *M. kansasii*. The last two are part of the non-tuberculous mycobacteria (NTM) group. Nontuberculous mycobacteria cause neither TB nor leprosy, but they do cause pulmonary diseases resembling TB.

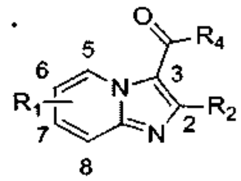
[0096] Specific gene polymorphisms in IL12B have been linked to tuberculosis susceptibility. Additionally, patients with diabetes mellitus are at increased risk of contracting tuberculosis, and they have a poorer response to treatment, possibly due to poorer drug absorption. Other conditions that increase risk include IV drug abuse; recent TB infection or a history of inadequately treated TB; chest X-ray suggestive of previous TB, showing fibrotic lesions and nodules; silicosis; prolonged corticosteroid therapy and other immunosuppressive therapy; head and neck cancers; hematologic and reticuloendothelial diseases, such as leukemia and Hodgkin's disease; end-stage kidney disease; intestinal bypass or gastrectomy; chronic malabsorption syndromes; vitamin D deficiency; and low body weight. Furthermore, some drugs, including rheumatoid arthritis drugs that work by blocking tumor necrosis factor-alpha, raise the risk of activating a latent infection due to the importance of this cytokine in the immune defense against TB. In embodiments, a subject having one or more of these risk factors may be a suitable candidate for effective therapies that treat or prevent TB.

[0097] As discussed above, compounds in accordance with embodiments of the present disclosure are designed to exhibit anti-TB activity. Methods are provided, in some embodiments, for treating or preventing tuberculosis in a subject. Briefly, the method includes selecting a subject in need of treatment and administering to the subject a therapeutically effective amount of at least one compound having the formula:



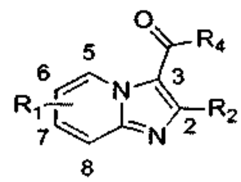
or a pharmaceutically acceptable salt thereof. According to embodiments, R_1 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or heterocylic, wherein R_1 is mono or polysubstituted; R_2 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or heterocylic, wherein R_2 is mono or polysubstituted; R_3 = H, alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, acyl, substituted acyl, haloacyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or heterocylic, wherein R_3 is mono or polysubstituted, wherein R_3 is not a methyl ester, ethyl ester, t-butyl ester, or thiazoline; and Y = CH or N anywhere on positions 5, 6, 7 or 8.

[0098] In an embodiment, a further compound may have the formula:



or a pharmaceutically acceptable salt thereof. According to embodiments, R_1 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or heterocylic, wherein R_1 is mono or polysubstituted; R_2 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, wherein R_2 is mono or polysubstituted; Y = CH or N anywhere on positions 5, 6, 7 or 8; and $R_4 = OR_1$, NHR_1, NR_1R_2, $NHNR_1$, or $NHOR_1$.

[0099] In specific, non-limiting examples, the compounds may have the formula:



wherein:

(a) R_1 = 7-CH_3, R_2 = CH_3, R_4 = (3-chloro-5-(trifluoromethyl)pyridin-2-yl)methanamine (ND-9902);

(b) R_1 = 7-CH_3, R_2 = CH_3, R_4 = 4-(4-(trifluoromethyl)phenoxy)aniline (ND-9903);

(c) R_1 = 7-CH_3, R_2 = CH_3, R_4 = 4-(4-fluorophenoxy)benzylamino (ND-9758);

(d) R_1 = 7-CH_3, R_2 = CH_3, R_4 = (3-ethoxy)benzylamino (ND-9906);

(e) R_1 = 7-CH_3, R_2 = CH_3, R_4 = (3- isopropoxy)benzylamino (ND-9872); or

(f) R_1 = 6-CH_3, R_2 = CH_3, R_4 = (4-methylsulfonyl)benzylamino (ND-9965).

[00100] In embodiments, when screened *in vitro,* it was apparent that the imidazo[1,2-a]pyridines had advantages over the other anti-TB heterocycles evaluated previously. For instance, while levels of potency of the ester analogs (notably, benzyl and ethyl) were good in various heterocyclic series (oxazolines, oxazoles, thiazolines, thiazoles and imidazo[1,2-a]pyridines), these esters were metabolically labile. While the corresponding amides were anticipated to be more stable, their anti-TB activity was dramatically decreased, except for the imidazo[1,2-a]pyridine benzyl amides ($NHCH_2Ph$), which were more potent. In addition, the stability of the imidazo[1,2-a]pyridine analogs in rat, dog and human microsomes were vastly improved (>80% remained after a 15 minute incubation). Furthermore, unlike the other heterocyclic scaffolds, the imidazo[1,2-a]pyridines were remarkably metabolically stable in a simulated gastric juice assay (>90% remaining after a 15-minute incubation).

[00101] In other embodiments, imidazo[1,2-a]pyridine analogs were generated and optimized using *in vitro* SAR studies to improve potency, metabolism, organism selectivity and formulation. Briefly, a set of imidazo[1,2-a]pyridine analogs were prepared and subjected to metabolism and organism selectivity profiling. Figure 2 shows the SAR of particular imidazo[1,2-a]pyridine agents and some trends observed from screening the compounds. (See Figure 4 for the structures of the compounds referenced in Figure 2.) The VERO assay is a toxicity assay that measures the viability of African Green Monkey epithelial kidney cells when treated with the compounds being studied. The other assays include three H37Rv TB screens that differ only in the media used: GAS for glycerol-alanine-salts with ferric ammonium citrate, GAST for glycerol-alanine-salts with Tween 80 instead of ferric ammonium citrate, and 7H12, which is a non-glycerol containing medium. The microsomes were derived from male Sprague-Dawley rats and contained drug-metabolizing enzymes, such as cytochrome P450, flavin monooxygenases, and UDP glucuronyl transferases. The simulated gastric juices assay contained pepsins, and was run at pH~1.2.

[00102] In embodiments, compounds ND-8448, ND-8451 and ND-8454 were all screened against a panel of diverse organisms which included four Gram-positive strains (*Bacillus subtilis*, *Staphylococcus aureus*, MRSA *Staphylococcus aureus*, *VRE Enterococcus Faecalis*), two Gram-negative strains (*E. coli*, *Pseudomonas aeruginosa*), a yeast (*Sporobolomyces salmonicolor*) and fungi (*Candida albicans* and *Penicillium notatum*), as well as five cancer cell lines (Huvec, K-562, HeLa, PC-3 and MCF-7) and the VERO cell line to check for mammalian toxicity. Remarkably, these three compounds were inactive against all of the control organisms studied.

[00103] In an embodiment, an evaluation may involve screening of the imidazo[1,2-a]pyridines against H37Rv TB in at least two different assay media, for instance, the GAST (glycerol-alanine-salts with Tween 80) and 7H12 (non-glycerol containing medium), to ensure that potency is not adversely affected by either glycerol or Tween and is not carbon source dependant. Compounds that have MIC's less than 5 µM are then screened in the VERO cellular toxicity and LORA TB recovery assay (an assay designed to simulate the latent TB state). The most impressive compounds that have outstanding potency (MIC <1 μM) and a large therapeutic window (IC50 >128 μM in the VERO assay) are then evaluated in rat microsomes and simulated gastric juices.

[00104] In an embodiment, compounds ND-8454, ND-8667, and ND-9361 were all screened against a panel of extreme drug-resistant TB strains HRESPOCTh, HREPKOTh, HRESPO, and then cross screened against *M. smegmatis*. As illustrated below in Table 4, all three drugs were effective against the extreme drug-resistant (XDR) strains.

Table 4: XDR-TB activity of imidazopyridine agents (MIC90 values in μg/mL)

Resistance to (μg/mL):	HRESPOCTh	HREPKOTh	HRESPO	*M. smegmatis*
ND-8454	0.02	0.02	0.039	>=5
ND-8667	0.01	0.0049	0.0049	>=5
ND-9361	0.02	0.01	0.01	>=5

Abbreviations: H=Isoniazid, R=Rifampicin, E=Ethambutol, Z=Pyrazinamide, S=Streptomycin, C=Cycloserine, Th=Ethionamide, K=Kanamycin, P=*p*-aminosalicylic acid, Rb=Rifabutin, Th=Thioacetazone, O=Ofloxacin.

[00105] In another embodiment, compounds ND-8454, ND-9652, ND-9758, ND-9872, ND-9902, ND-9903, and ND-9965 were screened against several non-tubercular mycobacteria (NTM). As illustrated below in Table 5, all seven drugs were effective against *M. avium, M. bovis BCG and M. kansasii* and other non-tubercular mycobacterial strains to a lesser extent, indicating that the imidazo[1,2-a]pyridines are selective anti-mycobacterial agents.

Table 5: NTM activity of imidazopyridine agents (MIC90 in μM)

	M. chelonae	*M. marinum*	*M. avium*	*M. kansasii*	*M. bovis BCG*
ND-8454	> 50	> 50	1.32	1.32	0.33
ND-9652	> 50	> 50	12.00	12.00	2.78
ND-9758	6.07	5.21	< 0.195	< 0.195	< 0.195
ND-9872	> 50	> 50	0.71	0.71	< 0.195
ND-9902	> 50	> 50	4.42	4.42	0.75
ND-9903	> 50	> 50	0.30	0.30	< 0.195
ND-9965	> 50	> 50	6.03	6.03	0.23
INH	> 500	> 500	> 500	5.82	< 1.953
EMB	> 2000	965.56	> 2000	< 7.813	< 7.813

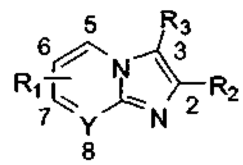
[00106] As discussed above, embodiments provide a method for treating or preventing TB. The method includes selecting a subject in need of treatment and administering to the subject a therapeutically effective amount of at least one compound disclosed herein. As used herein, the term "therapeutically effective amount" includes a quantity of a specified compound (such as one of the imidazo[1,2-a]pyridine compounds disclosed herein, for instance compound ND-8454) required to achieve a desired effect in a subject being treated. For instance, this may be the amount necessary to treat a mycobacterial infection, such as a *Mycobacterium tuberculosis, M. bovis, M. africanum* or *M. microti* infection in a subject, or a dose sufficient to prevent advancement, or to cause regression of a disease (such as TB), or that is capable of relieving symptoms caused by a disease, pulmonary or extrapulmonary symptoms. In some embodiments, a therapeutically effective amount of an imidazo[1,2-a]pyridine compound is a dose that is sufficient to inhibit the progression from latent TB to active TB, or to prevent re-activation of a TB infection.

[00107] Various dosage ranges and administration schedules may be adopted for therapeutic treatment of TB in animal and human subjects with the anti-TB agents disclosed herein. In an embodiment, such a therapeutically effective amount of active component may be in the range of about 0.1 to about 100 mg/kg, or more preferably about 0.1 to about 10 mg/kg, of body weight/day. Such dosages may vary depending upon the requirements of the patient, the severity of the disease, the duration of the disease, whether the infection is latent or active, the mycobacterial strain, whether the mycobacterium exhibits drug-resistance, or the particular symptoms (for instance, pulmonary or extrapulmonary) of the TB being treated, and the particular compound being used. In some embodiments, the anti-TB agent may be administered in conjunction with one or more other anti-TB agents, such as rifampin, isoniazid, pyrazinamide, ethambutol, streptomycin, ethionamide, kanamycin, cycloserine, thioacetazone, p-aminosalicylic acid, or ciprofloxacin.

[00108] In some embodiments, the anti-TB agent (for instance, ND-8454) may be administered systemically, whereas in other embodiments the anti-TB agent may be administered locally. An effective dose of a disclosed anti-TB agent may be administered systemically in a variety of ways. For instance, systemic administration may be by oral administration or by injection, for instance intravenous, intramuscular, or subcutaneous injection. Local (for instance pulmonary) administration may include inhalational administration. By way of example, one method of administration to the lungs of an individual may be by inhalation through the use of a nebulizer or inhaler. For example, the anti-TB agent may be formulated in an aerosol or particulate and drawn into the lungs using a standard nebulizer well known to those skilled in the art.

[00109] An effective amount of an anti-TB compound may be administered in a single dose, or in multiple doses, for example daily, or every four, eight, or twelve hours, during a course of treatment. In one embodiment, a therapeutically effective amount of an anti-TB compound may be administered as a single pulse dose, as a bolus dose, or as pulse doses administered over time. In specific, non-limiting examples, pulse doses of an anti-TB compound may be administered during the course of a day, during the course of a week, during the course of a month, or over the course of years.

[00110] In other embodiments, the imidazo[1,2-a]pyridine compounds disclosed herein are used to inhibit fungal growth on plant species. In embodiments, the imidazo[1,2-a]pyridine compound may have the formula:



or a pharmaceutically acceptable salt thereof, wherein R_1 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or heterocylic, wherein R_1 is mono or polysubstituted; R_2 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, , wherein R_2 is mono or polysubstituted; R_3 = H, alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, acyl, substituted acyl, haloacyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or heterocylic, wherein R_2 is mono or polysubstituted and wherein R_3 is not a methyl ester; and Y = CH or N anywhere on positions 5, 6, 7 or 8. Other embodiments are fungicidal compositions comprising at least one imidazo[1,2-a]pyridine compound and a phytologically acceptable carrier. Still other embodiments are antifungal formulations that further include at least one additional compound selected from the group consisting of insecticides, and herbicides.

[00111] Other embodiments are methods for controlling a fungal infestation. The methods may include, for instance, the steps of providing at least one imidazo[1,2-a]pyridine compound as described above and applying the compound to a surface having or adjacent to a fungal infection or infestation. In embodiments, the composition may include at least one additional compound selected from the group consisting of: insecticides, fungicides, and herbicides. Also disclosed are methods of controlling a fungal infestation. In embodiments, the methods may include the steps of: providing at least one

imidazo[1,2-a]pyridine compound as described herein and applying the compound to a surface having or adjacent to a fungal infection or infestation.

[00112] In embodiments, the imidazo[1,2-a]pyridine compounds described herein may have a significant fungicidal effect, particularly in agricultural applications, for instance, for use with agricultural crops and horticultural plants. In various embodiments, the imidazo[1,2-a]pyridine compounds described herein may be used to effectively control a variety of undesirable fungi that infect useful plant crops. In specific, non-limiting examples, antifungal activity has been demonstrated, for example against the following representative fungi species: brown rust of wheat (*Puccinia recondita tritici* - PUCCRT) and septoria blotch of wheat (*Septoria tritici* – SEPTTR).

[00113] Referring to Figure 3, exemplary imidazo[1,2-a]pyridine compounds were .ested in order to measure their ability to prevent fungal infections. (Figure 4 illustrates the structures of the compounds referenced in Figure 3.) In embodiments, each exemplary compound's preventative properties were determined by treating a susceptible test plant with the exemplary imidazo[1,2-a]pyridine compound and then exposing the plant to fungal spores. The antifungal activity of the imidazo[1,2-a]pyridine compounds was determined by determining the extent to which the fungal disease was controlled. The compounds were formulated at rates of 200 ppm in 10 vol.% acetone plus 90 vol.% Triton X water (deionized water 99.99 wt% + 0.01 wt% Triton X100), giving a "formulated test compound." Formulated test compounds were applied to plants using a turntable sprayer fitted with two opposing air atomization nozzles that delivered approximately 1500 L/ha of spray volume.

[00114] All test plants were inoculated with spores of the fungus (for example, PUCCRT or SEPTTR) the day after treatment with the putative fungicide. Next, the plants were incubated in an environment conducive to disease development. Disease severity was evaluated 7 to 25 days later, depending on the speed of disease development.

[00115] In a specific, non-limiting example, wheat plants (variety 'Yuma') were grown from seed in a soil-less peat-based potting mixture (Metromix) until the seedlings had a fully expanded first leaf. Each pot contained 3-8 seedlings. These plants were sprayed until wet with the formulated test compounds. On the following day, the leaves were inoculated with an aqueous spore suspension of *Puccinia recondita tritici* and the plants were kept in high humidity overnight to permit the spores to germinate and to infect the leaf. The plants were then transferred to a greenhouse until disease developed on untreated control plants. These tests were carried out at a level of 200 ppm, see, e.g., Figure 3.

[00116] In another specific, non-limiting example, wheat plants (variety 'Yuma') were grown from seed in a 50% pasteurized soil/50% soil-less mix until the seedlings had a fully expanded first leaf. Each pot contained 3-10 seedlings. These plants were sprayed until wet with the formulated test compound. On the following day, the leaves were inoculated with an aqueous spore suspension of *Septoria tritici* and the plants were kept in high humidity (one day in a dark dew chamber followed by three days in a lighted dew chamber) to permit the spores to germinate and to infect the leaf. The plants were then transferred to a greenhouse until disease developed on untreated control plants. These tests were carried out at a level of 200 ppm, see, e.g., Figure 3.

[00117] In embodiments, disease control was determined by visually estimating the percent disease severity in treated and untreated pots 7 to 24 days after inoculation, depending on speed of disease development. Evaluations were typically made 7 or 8 days after inoculation for PUCCRT and 18 to 22 days after inoculation for SEPTTR. Percent disease control (%DC) was calculated by: %DC = (1-%Disease severity treated/%disease severity untreated)*100.

[00118] In various embodiments, the imidazo[1,2-a]pyridine compounds described herein may be applied in the form of a composition comprising one or more imidazo[1,2-a]pyridine compounds with a phytologically-acceptable carrier. The compositions may include, for example, concentrated formulations that are dispersed in water or another liquid for application, or dust or granular formulations that are applied without further treatment. The compositions may be prepared according to procedures which are conventional in the agricultural chemical art.

[00119] The dispersions in which the imidazo[1,2-a]pyridine compounds are applied may be, in some examples, aqueous suspensions or emulsions prepared from concentrated formulations of the compounds. Such water-soluble, water suspendable, or emulsifiable formulations are either solids, usually known as wettable powers, or liquids, usually known as emulsifiable concentrates, or aqueous suspensions. In embodiments, any material to which the imidazo[1,2-a]pyridine compounds can be added may be used, provided it yields the desired utility without significantly interfering with the fungicidal activity of the imidazo[1,2-a]pyridine compounds.

[00120] In embodiments, wettable powders, which may be compacted to form water dispersible granules, may include an intimate mixture of the active imidazo[1,2-a]pyridine compound, an inert carrier, and one or more surfactants. The concentration of the imidazo[1,2-a]pyridine compound may be, for example, from about 10 percent

weight/weight (%w/w) to about 90% %w/w, and may be from about 25% to about 75% w/w in particular examples. In the preparation of exemplary wettable powder compositions, the active ingredients can be compounded with any finely divided solid, such as pyrophyllite, talc, chalk, gypsum, Fuller's earth, bentonite, attapulgite, starch, casein, gluten, montmorillonite clays, diatomaceous earth, purified silicate, or the like. In such examples, the finely divided carrier may be ground or mixed with the toxicant in a volatile organic solvent. Specific, non-limiting examples of effective surfactants, for instance, comprising from about 0.5% to about 10% of the wettable powder, that can be used in combination with the inventive compounds, include sulfonated lignins, naphthalenesulfonates, alkylbenzenesulfonates, alyl sulfates, and non-ionic surfactants such as ethylene oxide adducts of alkyl phenols.

[00121] In various embodiments, emulsifiable concentrates of the imidazo[1,2-a]pyridine compounds disclosed herein may comprise a convenient concentration, such as from about 10% to about 50% w/w, in a suitable liquid. Briefly, one exemplary method for creating these emulsions includes the step of dissolving the compound in an inert carrier (for instance, either a water miscible solvent or a mixture of water-immiscible organic solvents and emulsifiers). In specific embodiments, the concentrates may be diluted with water and oil to form spray mixtures in the form of oil-in-water emulsions. Specific, non-limiting examples of organic solvents that may be used include aromatics, especially the high-boiling naphthalenic and olefinic portions of petroleum such as heavy aromatic naphtha and the like. In other embodiments, other organic solvents may be used, such as terpenic solvents, for instance rosin derivatives, aliphatic ketones, such as cyclohexanone, and complex alcohols such as 1-ethoxyethanol.

[00122] In some embodiments, emulsifiers may be used, for instance various non-ionic, anionic, cationic, and amphoteric emulsifiers, or a blend of two or more emulsifiers. Specific, non-limiting examples of non-ionic emulsifiers useful in preparing the emulsifiable concentrates include the polyalkylene glycol ethers and condensation products of alkyl and aryl phenols, aliphatic alcohols, aliphatic amines, or fatty acids with ethylene oxide, propylene oxides such as the ethoxylated alkyl phenols, and carboxylic esters solubilised with polyol or polyoxyalkylene. Specific, non-limiting examples of cationic emulsifiers include quaternary ammonium compounds and fatty amine salts. Specific, non-limiting examples of nionic emulsifiers include the oil-soluble salts (e.g., calcium) of alkylaryl sulfonic acids, oil-soluble salts of sulphated polyglycol ethers, and appropriate salts of phosphated polyglycol ether.

[00123] Specific, non-limiting examples of organic liquids that may be employed in preparing the emulsifiable concentrates include aromatic liquids such as xylene, propyl benzene fractions or mixed naphtlalene fractions, mineral oils, substituted aromatic organic liquids such as dioctyl phthalate, kerosene, and dialkyl amides of various fatty acids; particularly the dimethyl amides of fatty glycols and glycol derivatives such as the n-butyl ether, ethyl ether, or methyl ether of triethylene glycol. In some embodiments, mixtures of two or more organic liquids may be employed in the preparation of the emulsifiable concentrate. Specific, non-limiting examples organic liquids that may be used include xylene and propyl benzene fractions. In specific, non-limiting examples, surface active dispersing agents may be used in liquid compositions in the amount of from about 0.1 weight % (wt. %) to about 20 (wt. %) of the combined weight of the dispersing agent and active compound. In embodiments, the imidazo[1,2-a]pyridine compositions may also contain other compatible additives, for example, plant growth regulators and other biologically active compounds used in agriculture.

[00124] According to various embodiments, aqueous suspensions may include suspensions of water-insoluble imidazo[1,2-a]pyridine compounds, dispersed in an aqueous vehicle at a concentration in the range of from about 5% to about 50% w/w. In one specific, non-limiting example, a suspension may be prepared by finely grinding the compound and vigorously mixing it into a vehicle including water and surfactants as discussed above. In embodiments, inert ingredients, such as inorganic salts and synthetic or natural gums, may also be added, for instance to increase the density and viscosity of the aqueous vehicle. In particular embodiments, it is effective to grind and mix the compound at the same time by preparing the aqueous mixture and homogenizing it in an implement such as a sand mill, ball mill, or piston-type homogenizer.

[00125] In other embodiments, the imidazo[1,2-a]pyridine compounds may be applied as granular compositions, which are particularly useful when applying the composition to the soil. Specific, non-limiting examples of granular compositions may include from about 0.5% w/w of to about 10% w/w of the compound dispersed in an inert carrier that includes entirely or in large part a coarsely divided attapulgite, bentonite, diatomite, clay, or a similar inexpensive substance. Such compositions may be prepared, for example, by dissolving the compound in a suitable solvent and applying it to a granular carrier which has been preformed to the appropriate particle size, for instance, in the range of from about 0.5 to about 3 mm. In various embodiments, such compositions may also be formulated by

making a dough or paste of the carrier and compound, and crushing, and drying to obtain the desired granular particle.

[00126] In other embodiments, dusts that include the imidazo[1,2-a]pyridine compounds may be prepared by intimately mixing the compound in powdered form with a suitable dusty agricultural carrier such as, for example, kaolin clay, ground volcanic rock, and the like. In specific, non-limiting examples, such dusts may include from about 1% w/w to about 10% w/w of the compound.

[00127] According to various embodiments, the imidazo[1,2-a]pyridine compositions may contain adjuvant surfactants to enhance properties such as deposition, wetting, and penetration of the compositions onto the target crop and organism. In embodiments, these adjuvant surfactants may be employed as a component of the formulation or as part of a ank mix. The amount of adjuvant surfactant may vary, in specific, non-limiting examples, from about 0.01 percent to about 1.0% volume/volume based on a spray-volume of water. In particular embodiments, the amount of adjuvant surfactant may be, for example, from about 0.05% to about 0.5% volume/volume. Specific, non-limiting examples of adjuvant surfactants include ethoxylated nonyl phenols, ethoxylated synthetic or natural alcohols, salts of the esters of sulphosuccinic acids, ethoxylated organosilicones, ethoxylated fatty amines, and blends of surfactants with mineral or vegetable oils.

[00128] In embodiments, the imidazo[1,2-a]pyridine compositions may include combinations that include, for instance, at least 1% of one or more imidazo[1,2-a]pyridine compounds with another agriculturally active ingredient (AI). Such additional AI may include, for example, fungicides, insecticides, nematocides, miticides, arthropodicides, bactericides, herbicidal, or combinations thereof that are compatible with the imidazo[1,2-a]pyridine compounds in the medium selected for application. Accordingly, in such embodiments, the other AI is employed as a supplemental AI for the same or for a different use with plants than the inventive compounds. In specific, non-limiting examples, the compounds in combination may generally be present in a ratio of from about 1:10 to about 100:1.

[00129] Other embodiments are methods for the control or prevention of fungal infection. These methods may include applying the active imidazo[1,2-a]pyridine compounds to the locus of the fungus, or to a locus in which the infestation is to be prevented (for example applying it to a cereal or grape plant). In embodiments, the imidazo[1,2-a]pyridine compounds may be used for treatment of various plants at fungicidal levels while exhibiting low phytotoxicity. In addition, in embodiments, the compounds may be used as a protectant or eradicant. In embodiments, such compounds may be applied by any of a variety of known techniques, either as the compounds or as compositions including the compounds. For example, the compounds may be applied to the roots, seeds, or foliage of plants for the control of various fungi without damaging the commercial value of the plants. In embodiments, the materials are applied in the form of any of the generally used formulation types, for example, as solutions, dusts, wettable powders, flowable concentrates, or emulsifiable concentrates.

[00130] As described above, in embodiments, the imidazo[1,2-a]pyridine compounds may have significant fungicidal effects, particularly for agricultural use. In particular embodiments, the imidazo[1,2-a]pyridine compounds are effective for use with agricultural crops and horticultural plants, or for the prevention or treatment of fungal growth in other materials, such as wood, paint, leather, or carpet backing.

[00131] In particular embodiments, the imidazo[1,2-a]pyridine compounds may effectively control a variety of undesirable fungi which infect useful plant crops. In specific embodiments, the imidazo[1,2-a]pyridine compounds may have activity against a variety of fungi, including, for example, the following representative fungi species: downy mildew of grape (*Plasmopara viticola* – PLASVI), late blight of tomato (*Phytophthora infestants* – PHYTIN), apple scab (*Venturia inaequalis* – VENTIN), brown rust of wheat (*Puccinia recondita tritici* – PUCCRT), stripe rust of wheat (*Puccinia striiformis* – PUCCST), rice blast (*Pyricularia oryzae* – PYRIOR), Cercospora leaf spot of beet (*Cercospora beticola* – CERCBE), powdery mildew of wheat (*Erysiphe graminis* – ERYSGT), leaf blotch of wheat (*Septoria tritici* – SEPTTR), sheath blight of rice (*Rhizoctonia solani* – RHIZSO), eyespot of wheat (*Pseudocercosporella herpotrichoides* – PSDCHE), brown rot of peach (*Monilinia fructicola* – MONIFC), and glume blotch of wheat (*Leptosphaeria nodorum* – LEPTNO).

[00132] In embodiments, the amount of imidazo[1,2-a]pyridine compound applied for a particular use may depend not only on the specific active material being applied, but also on the particular action desired, the fungal species to be controlled, and the stage of growth thereof, as well as the part of the plant or other product to be contacted with the active ingredient.

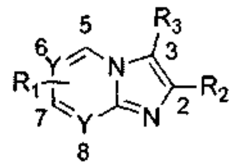
[00133] Although certain embodiments have been illustrated and described herein, it will be appreciated by those of ordinary skill in the art that a wide variety of alternate and/or equivalent embodiments or implementations calculated to achieve the same purposes may be substituted for the embodiments shown and described without departing from the scope. Those with skill in the art will readily appreciate that embodiments may be implemented in a very wide variety of ways. This application is intended to cover any adaptations or variations of the embodiments discussed herein. Therefore, it is manifestly intended that embodiments be limited only by the claims and the equivalents thereof.

Claims

We Claim:

What is claimed is:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

R_1 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, halogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or heterocylic, wherein R_1 is mono or polysubstituted;

R_2 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, wherein R_2 is mono or polysubstituted;

R_3 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, acyl, substituted acyl, haloacyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or heterocylic, wherein R_3 is mono or polysubstituted, and wherein R_3 is not a methyl ester, ethyl ester, t-butyl ester, pyrazoline, pyrrole or a thiazole; and

Y = CH or N.

2. The compound of claim 1, wherein R_1 comprises a functionalized alkyl, and wherein the functionalized alkyl comprises an alkene, an alkyne, an alcohol, an epoxide, a ketone, an ester, an ether, an aldehyde, a nitrile, a nitro, a thiol, a sulfide, a disulfide, a sulfone, a sulfoxide, a sulfonamide, an amine, an amide, a urea, a carbamate, SF_3, SOF_3, or SO_2F_3.

3. The compound of claim 1, wherein R_1 comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a morpholine, a thiomorpholine, a piperazine, a piperidine, 2-methyl-1,4-dioxa-8-azaspiro[4.5]decane, 2,3-dimethyl-1,4-dioxa-8-azaspiro[4.5]decane, 3-methyl-1,5-dioxa-9-azaspiro[5.5]undecane, or 2,4-dimethyl-1,5-dioxa-9-azaspiro[5.5]undecane.

4. The compound of claim 1, wherein R_1 comprises a heterocylic, and wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone.

5. The compound of claim 1, wherein R_2 comprises a functionalized alkyl, and wherein the functionalized alkyl comprises an alkene, an alkyne, an alcohol, an epoxide, an ester, an ether, an aldehyde, a nitrile, a nitro, a thiol, a sulfide, a disulfide, a sulfone, a sulfoxide, a sulfonamide or an amine.

6. The compound of claim 1, wherein R_2 comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a morpholine, a thiomorpholine, a piperazine, or a piperidine.

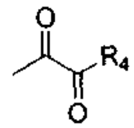
7. The compound of claim 1, wherein R_2 is alkyl, alkoxy, or aryloxy.

8. The compound of claim 1, wherein R_2 is CH_3 or CF_3.

9. The compound of claim 1, wherein R_3 comprises a functionalized alkyl, and wherein the functionalized alkyl comprises an alkene, an alkyne, an alcohol, an epoxide, a ketone, an ester, an ether, an aldehyde, a nitrile, a nitro, a thiol, a sulfide, a disulfide, a sulfone, a sulfoxide, a sulfonamide, an amine, an amide, a urea, or a carbamate.

10. The compound of claim 1, wherein R_3 comprises a heterocylic, and wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone.

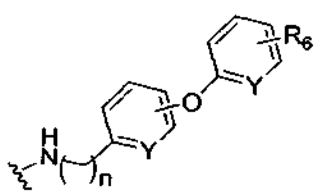
11. The compound of claim 1, wherein R_3 has the formula:



wherein R_4 is:

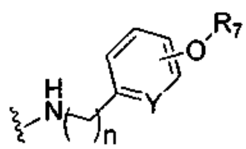
(a) OR_1 or NHR_1, wherein R_4 is not NR_1R_2;

(b)



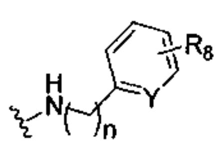
wherein R_6 is CF_3, OCF_3, a halogen, a alkyl-sulfone, a sulfonamide, an alkoxy, an amine or a nitrile; wherein R_6 is mono or polysubstituted; wherein Y is CH or N at any position, and wherein n=0 or 1-4;

(c)



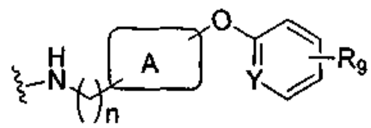
wherein R_7 comprises a heterocylic, wherein the heterocylic comprises a furan, a thiophene, an imidazole, , an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone, and wherein n=0 or 1-4;

(d)



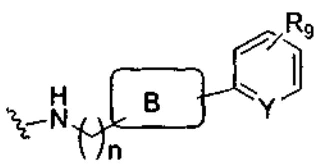
wherein R_8 comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a morpholine, a thiomorpholine, a piperazine, or a piperidine; CF_3, OCF_3, a halogen, a alkyl-sulfone, a sulfaminde, an amine, an alkoxy, or a nitrile; wherein R_8 is mono or polysubstituted; wherein Y is CH or N at any position, and wherein n=0 or 1-4;

(e)



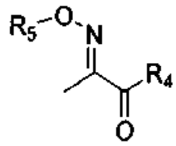
wherein A comprises a heterocylic, and wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone; and wherein R_9 comprises CF_3, OCF_3, a halogen, a alkyl-sulfone, a sulfonamide, an amine, an alkoxy, or a nitrile; wherein R_9 is mono or polysubstituted ; wherein Y is CH or N at any position; and wherein n=0 or 1-4; or

(f)



wherein B comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a piperazine, or a piperidine; wherein R_9 comprises CF_3, OCF3, a halogen, a alkyl-sulfone, a sulfonamide, an amine, an alkoxy, or a nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4.

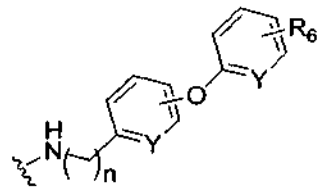
12. The compound of claim 1, wherein R_3 has the formula:



wherein R_4 is:

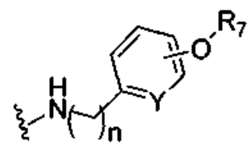
(a) OR_1, NHR_1, or NR_1R_2;

(b)



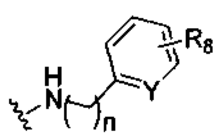
wherein R_6 is CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_6 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

(c)



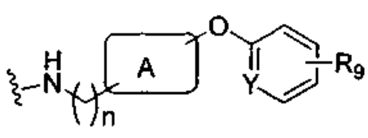
wherein R_7 comprises a heterocylic, wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone, and wherein n=0 or 1-4;

(d)



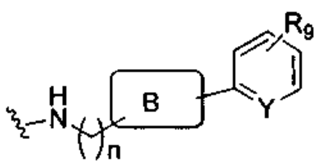
wherein R_8 comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a morpholine, a thiomorpholine, a piperazine, or a piperidine; CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_8 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

(e)



wherein A comprises a heterocylic, and wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone; and wherein R_9 comprises CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4; or

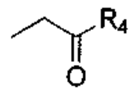
(f)



wherein B comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a piperazine, or a piperidine; wherein R_9 comprises CF_3, OCF3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4; and

wherein R_5 is an alkyl, a substituted alkyl, a cycloalkyl, a functionalized alkyl, a cycloheteroalkyl, an aryl, a substituted aryl, a heteroaryl, a substituted heteroaryl, or a heterocylic, wherein R_1 is mono or polysubstituted; and wherein oximine comprises an E or Z stereoisomer.

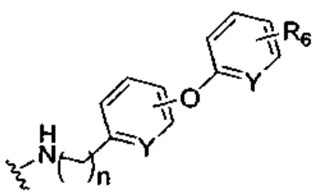
13. The compound of claim 1, wherein R_3 has the formula:



wherein R_4 is:

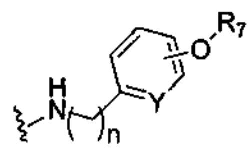
(a) OR_1 or NHR_1, wherein R_4 is not NR_1R_2;

(b)



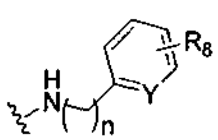
wherein R_6 is CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_6 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

(c)



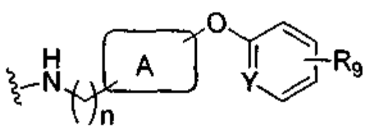
wherein R_7 comprises a heterocylic, wherein the heterocylic comprises a furan, a thiophene, an imidazole, , an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone, and wherein n=0 or 1-4;

(d)



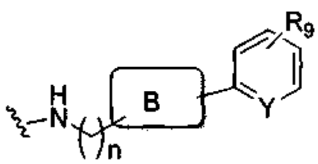
wherein R_8 comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a morpholine, a thiomorpholine, a piperazine, or a piperidine; CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_8 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

(e)



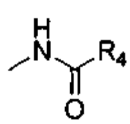
wherein A comprises a heterocylic, and wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone; and wherein R_9 comprises CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4; or

(f)



wherein B comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a piperazine, or a piperidine; wherein R_9 comprises CF_3, OCF3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4.

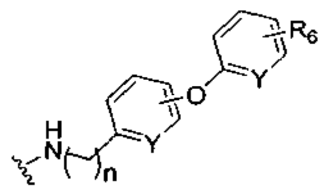
14. The compound of claim 1, wherein R_3 comprises has the formula:



wherein R_4 is:

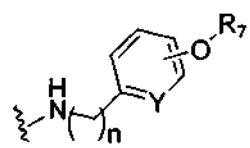
(a) OR_1 or NHR_1, wherein R_4 is not NR_1R_2;

(b)



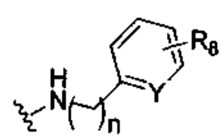
wherein R_6 is CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_6 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

(c)



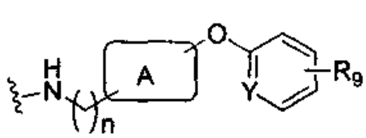
wherein R_7 comprises a heterocylic, wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, oxadiazole, thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, a isoquinoline, imidazopyridine, or oxazolindinone; and wherein n=0 or 1-4;

(d)



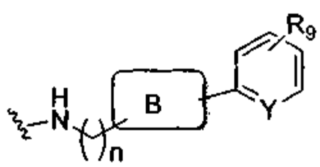
wherein R_8 comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a morpholine, a thiomorpholine, a piperazine, or a piperidine; CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_8 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

(e)



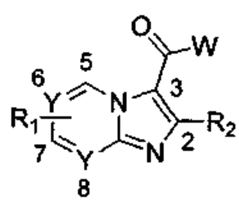
wherein A comprises a heterocylic, and wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone; and wherein R_9 comprises CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4; or

(f)



wherein B comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a piperazine, or a piperidine; wherein R_9 comprises CF_3, OCF3, a halogen, a alkyl-sulfone, an alkoxy,a sulfonamide, an amine, or a nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4.

15. The compound of claim 1, wherein the compound has the formula:



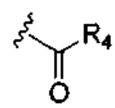
or a pharmaceutically acceptable salt thereof, wherein

R_1 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, halogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or heterocylic, wherein R_1 is mono or polysubstituted;

R_2 = alkyl, substituted alkyl, cycloalkyl, functionalized alkyl, cycloheteroalkyl, alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, wherein R_2 is mono or polysubstituted; wherein Y = CH or N, and wherein W is selected from the group consisting of:

(a) OR_1, NHR_1, or NR_1R_2;

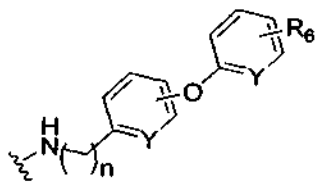
(b)



wherein R_4 is:

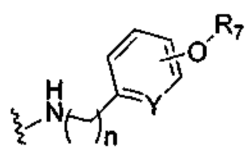
i. OR_1 or NHR_1, wherein R_4 is not NR_1R_2;

ii.



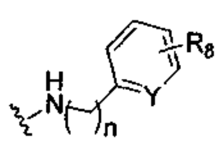
wherein R_6 is CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_6 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

iii.



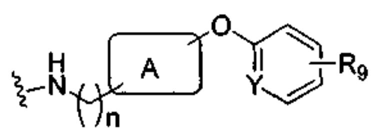
wherein R_7 comprises a heterocylic, wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, oxadiazole, thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, a isoquinoline, imidazopyridine, or oxazolindinone; and wherein n=0 or 1-4;

iv.



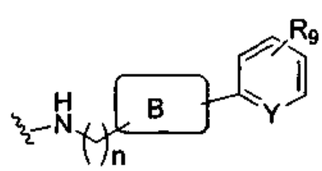
wherein R_8 comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a morpholine, a thiomorpholine, a piperazine, or a piperidine; CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_8 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

v.



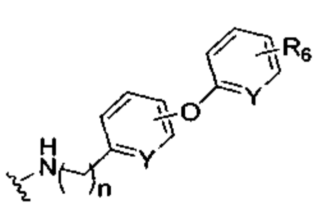
wherein A comprises a heterocylic, and wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone; and wherein R_9 comprises CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, or a nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4; or

vi.



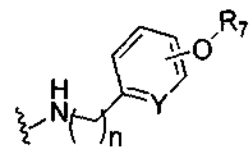
wherein B comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a piperazine, or a piperidine; wherein R_9 comprises CF_3, OCF3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

(c)



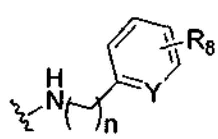
wherein R_6 is CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_6 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

(d)



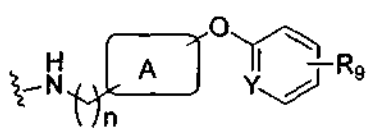
wherein R_7 comprises a heterocylic, wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, oxadiazole, thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, a isoquinoline, imidazopyridine, or oxazolindinone; and wherein n=0 or 1-4;

(e)



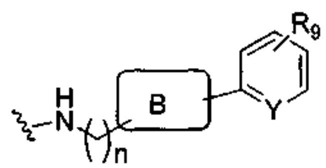
wherein R_8 comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a morpholine, a thiomorpholine, a piperazine, a piperidine, CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_8 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4;

(f)



wherein A comprises a heterocylic, and wherein the heterocylic comprises a furan, a thiophene, an imidazole, an oxazole, an oxazoline, an oxadiazole, a thiadiazole, a thiazole, a thiazoline, a triazole, a pyridine, a pyrazine, a naphthalene, a diketopiperazine, a quinoline, an isoquinoline, an imidazopyridine, an oxazolindinone, or a substituted furan, thiophene, imidazole, oxazole, oxazoline, an oxadiazole, a thiadiazole, thiazole, thiazoline, triazole, pyridine, pyrazine, naphthalene, diketopiperazine, quinoline, isoquinoline, imidazopyridine, or oxazolindinone; wherein R_9 comprises CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or a nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4; or

(g)



wherein B comprises a cycloheteroalkyl, and wherein the cycloheteroalkyl comprises a piperazine or a piperidine; wherein R_9 comprises CF_3, OCF_3, a halogen, a alkyl-sulfone, an alkoxy, a sulfonamide, an amine, or nitrile; wherein R_9 is mono or polysubstituted; wherein Y is CH or N at any position; and wherein n=0 or 1-4.

16. The compound of claim 15, wherein R_2 is alkyl or alkoxy.

17. The compound of claim 15, wherein R_2 is CH_3 or CF_3.

18. The compound of claim 1, wherein the compound is an imidazo[1,2-a]pyridine benzyl amide analog.

19. The compound of claim 18, wherein the compound is *N*-benzyl-2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamide (ND-8454).

20. The compound of claim 1, wherein the compound is a benzyl ester derivative.

21. The compound of claim 1, wherein R_1 = 7-CH_3, R_2 = CH_3, R_3 = (2,4-methyl)benzyloxy (ND-8448).

22. The compound of claim 1, wherein R_1 = 7-CH_3, R_2 = CH_3, R_3 = (3-trifluoromethyl) benzyloxy (ND-8451).

23. The compound of claim 1, wherein R_1 = 8-CH_3; R_2 = CH_3, and R_3 = (4-methoxy)benzoxy (ND-9432).

24. The compound of claim 1, wherein R_1 = 8-CH_3; R_2 = CH_3, and R_3 = (2-ethyl)benzyloxy (ND-9433).

25. The compound of claim 1, wherein the compound is a benzyl imidazo[1,2-a]pyridine-3-carboxylate (ester) derivative.

26. The compound of claim 1, wherein the compound is a substituted alkoxy benzyl analog.

27. The compound of claim 26, wherein R_1 = 7-CH_3, R_2 = CH_3, R_3 = (4-methoxy)benzylamino (ND-8668).

28. The compound of claim 26, wherein R_1 = 7-CH_3, R_2 = CH_3, R_3 = (3-ethoxy)benzylamino (ND-9906).

29. The compound of claim 26, wherein R_1 = 7-CH_3, R_2 = CH_3, R_3 = (3-isopropoxy)benzylamino (ND-9872).

30. The compound of claim 1, wherein the compound is a substituted 2-pyridyl analog.

31. The compound of claim 30, wherein R_1 = 7-CH_3, R_2 = CH_3, R_3 = (3-chloro-5-(trifluoromethyl)pyridin-2-yl)methanamine (ND-9902).

32. The compound of claim 1, wherein the compound is a substituted benzyl sulfone analog.

33. The compound of claim 32, wherein R_1 = 6-CH_3, R_2 = CH_3, R_3 = (4-(methylsulfonyl)benzylamino (ND-9965).

34. The compound of claim 1, wherein the compound is a substituted bi-aryl ether aniline analog.

35. The compound of claim 34, wherein R_1 = 7-CH_3, R_2 = CH_3, R_3 = 4-(4-(trifluoromethyl)phenoxy)aniline (ND-9903).

36. The compound of claim 1, wherein the compound is a substituted bi-aryl ether benzyl analog.

37. The compound of claim 36, wherein R_1 = 7-CH_3, R_2 = CH_3, R_3 = 4-(4-fluorophenoxy)benzylamino (ND-9758).

38. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

39. The compound of claim 1, wherein the compound has antifungal activity.

40. A fungicidal composition, comprising at least one compound according to claim 1, and a phytologically acceptable carrier.

41. The composition according to claim 40, further including at least one additional compound selected from the group consisting of: insecticides, fungicides, and herbicides.

42. A method of preventing or controlling a fungal infection, comprising the steps of:

providing at least one compound according to claim 1; and

applying the compound to an object or surface having or adjacent to a fungal infection.

Dated this 04th day of June, 2012

B. Naveen Kumar Varma
IN/PA- 873
Agent for the Applicant

ORIGINAL

Abstract of the Disclosure

IMIDAZO[1,2-a]PYRIDINE COMPOUNDS, SYNTHESIS THEREOF, AND METHODS OF USING SAME

[00134] Embodiments relate to the field of chemistry and biochemistry, and, more specifically, to imidazopyridine compounds, synthesis thereof, and methods of using same. Disclosed herein are various imidazo[1,2-a]pyridine compounds and methods of using the novel compounds to treat or prevent tuberculosis in a subject or to inhibit fungal growth on plant species. Other embodiments include methods of synthesizing imidazo[1,2-a]pyridine compounds, such as the disclosed imidazo[1,2-a]pyridine compounds.

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Functionalized 3-amino-imidazo[1,2-*a*]pyridines: A novel class of drug-like *Mycobacterium tuberculosis* glutamine synthetase inhibitors

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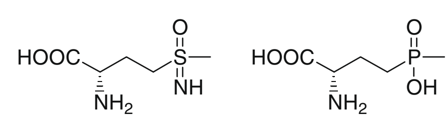
ABSTRACT

3-Amino-imidazo[1,2-*a*]pyridines have been identified as a novel class of *Mycobacterium tuberculosis* glutamine synthetase inhibitors. Moreover, these compounds represent the first drug-like inhibitors of this enzyme. A series of compounds exploring structural diversity in the pyridine and phenyl rings have been synthesized and biologically evaluated. Compound **4n** was found to be the most potent inhibitor (IC_{50} = 0.38 ± 0.02 μM). This compound was significantly more potent than the known inhibitors, L-methionine-*SR*-sulfoximine and phosphinothricin.

Tuberculosis (TB) is one of the world's major public health problems and has been declared a global health emergency by the World Health Organization.[1] In 2006, there were approximately 9 million new cases of TB, resulting in an estimated 1.7 million deaths.[2] In addition, the emergence of multi-drug resistant *Mycobacterium tuberculosis* strains (causing MDR-TB), the growing rate of TB incidence, the lethal combination represented by HIV co-infection and the lack of any new antituberculosis agent in the last 40 years, all indicate an urgent need for the development of novel TB therapies. In particular, new lead structures are required with novel modes of action.[3,4] In the last decade *M. tuberculosis* glutamine synthetase (*Mt*GS), a key enzyme required for nitrogen metabolism and mycobacterial cell-wall biosynthesis, has emerged as a potential target for antibiotics against TB.[1,4–6] Exposure of *M. tuberculosis* to the known GS inhibitor L-methionine-*SR*-sulfoximine **1** (MSO) (Fig. 1) has been shown to inhibit both cell wall formation and mycobacterial growth.[1,6] Thus, the development of new *Mt*GS inhibitors could be useful in developing an effective treatment for MDR-TB. The majority of known GS inhibitors are simple glutamate analogues and of these, MSO and phosphinothricin **2** (PPT) are the most widely investigated.[7] These inhibitors have been used as lead compounds in several studies,[5,7–12] albeit they are polar, flexible, non-selective[13] and not particularly drug-like. Accordingly, we were interested in the identification and development of more drug-like non-amino acid derived *Mt*GS inhibitors.



1 **2**

Figure 1. Structure of MSO (**1**) and PPT (**2**).

During the course of a high-throughput compound screen and a subsequent lead validation process, 3-amino-imidazo[1,2-*a*]pyridines were identified as a novel class of *Mt*GS inhibitors (Fig. 2). It was quickly recognized that this would provide a scaffold amenable to the rapid exploration of structure–activity relationships. Indeed, a diverse range of analogues can be readily obtained, in one step, via an Ugi-type cyclization.[14–19] Herein, we describe the high-speed synthesis and *Mt*GS inhibitory activity of two libraries of differentially substituted 3-amino-imidazo[1,2-*a*]pyridines, **3** and **4**.

We decided to focus our initial investigations on evaluating the effect of altering the pyridine ring substituent. Accordingly, 3-amino-imidazo[1,2-*a*]pyridines (**3a**–**m**) were prepared by a microwave-assisted multicomponent reaction (MCR) between cyclopentylisonitrile, 3-hydroxy-4-methoxy benzaldehyde and an appropriately substituted 2-aminopyridine.[19] All 2-aminopyridines were commercially available with the exception of 5-methoxy-2-aminopyridine, which was prepared by the treatment of 5-iodo-2-aminopyridine with MeOH and CuI under Buchwald's

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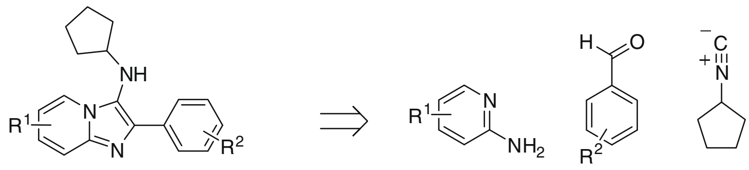
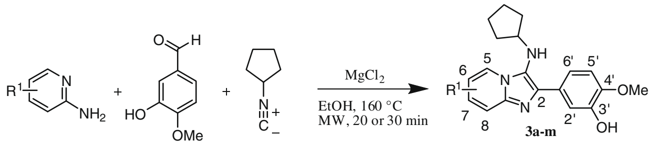


3 and **4**

Figure 2. 3-Amino-imidazo[1,2-*a*]pyridines and retrosynthetic analysis showing assembly via a one-pot three-component condensation reaction.

Table 1
Synthesis and biological evaluation of 3-amino-imidazo[1,2-*a*]pyridines (**3a**–**m**)



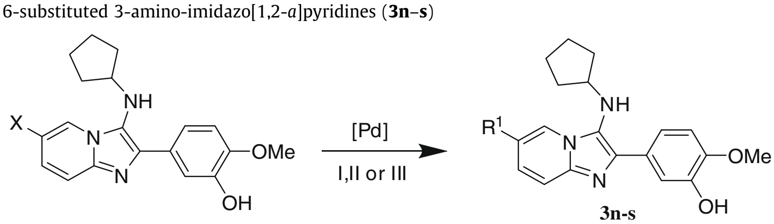
Entry	Product[a]	R[1]	IC_{50}[b] (μM)
1	**3a**	H	>50
2	**3b**	6-Me	>50
3	**3c**	6-OMe	31.3 ± 0.7
4	**3d**	6-F	>50
5	**3e**	6-Cl	11.2 ± 1.5
6	**3f**	6-Br	8.8 ± 0.4
7	**3g**	6-I	4.8 ± 0.5
8	**3h**	6-CF_3	>50
9	**3i**	6-CN	>50
10	**3j**	5-Br	>50
11	**3k**	8-Br	21.3 ± 1.6
12	**3l**	6-Br, 8-Br	>50
13	**3m**	6-Br, 8-Me	12.7 ± 0.7
MSO	–	–	51 ± 6[c]
PPT	–	–	1.9 ± 0.4[c]

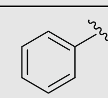
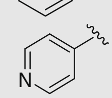
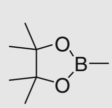
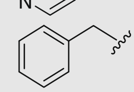
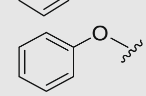
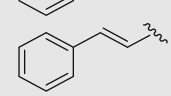
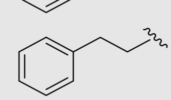
[a] Purity >95% by HPLC or ^{1}H NMR.
[b] Values are means of three experiments ± standard error.
[c] See Ref. 10.

modified Ullman reaction conditions (1,10-phenanthroline, Cs_2CO_3, 110 °C)[20] providing **3c**. The MCR reactions were typically irradiated, in a sealed vessel, for 20–30 min at 160 °C in the presence of $MgCl_2$ and the products were isolated either by simple filtration, recrystallization or flash chromatography.[21] The potency of the compounds **3a**–**m** from this first series against *Mt*GS was evaluated[22] and these results are reported in Table 1.

From Table 1 it is clear that a pyridine ring substituent is beneficial for *Mt*GS inhibition and that a number of synthesized analogues were significantly more active than MSO (i.e., **3c**, **3e**–**g**, **3k**, **3m**). The most active compounds contained large halogen atoms (Cl, Br or I) in the 6-position (i.e., **3f**, IC_{50} = 8.8 ± 0.4 μM and **3g** IC_{50} = 4.8 ± 0.5 μM). Interestingly, the 6-fluorine, 6-trifluoromethyl and 6-nitrile containing compounds were essentially inactive (**3d**, **3h** and **3i** IC_{50} >50 μM), suggesting that the potency of **3e**, **3f** and **3g** is not related purely to their electron withdrawing nature. The corresponding 5- and 8-bromine substituted analogues displayed considerably weaker inhibitory activity (**3j**, IC_{50} >50 μM and **3k**, IC_{50} = 21.3 ± 1.6 μM) compared to **3f**, indicating that there may be some specific hydrophobic or van der Waals interactions accessible only by a substituent in the 6-position. The introduction of an additional 8-bromine or 8-methyl substituent did not improve compound potency (**3l**, IC_{50} >50 μM and **3m**, IC_{50} = 12.7 ± 0.7 μM, respectively).

Table 2
Synthesis and biological evaluation of 6-substituted 3-amino-imidazo[1,2-*a*]pyridines (**3n**–**s**)



Entry	Starting material (X)	Method	Product[a]	R_1	IC_{50}[b] (μM)
1	Br–	I	**3n**		>50
2	Br–	I	**3o**		>50
3		II	**3p**		>50
4	–	As per **3c**	**3q**		>50
5	Br–	I	**3r**		>50
6	**3r**	III	**3s**		>50

[a] Purity >95% by HPLC or ^{1}H NMR.
[b] Values are means of three experiments. I; Boronic acid (3 equiv), $Pd(PPh_3)_4$ (7%), Cs_2CO_3 (3.5 equiv), DMF, MW, 120 °C, 20 min. II; benzyl bromide (0.8 equiv), $Pd(dppf)Cl_2$ (10%), K_2CO_3 (3 equiv), EtOH, H_2O, MW, 130 °C, 30 min. III; **3r** 10% Pd/C (10%), H_2 (1 atm.), DMF, 25 °C, 18 h.

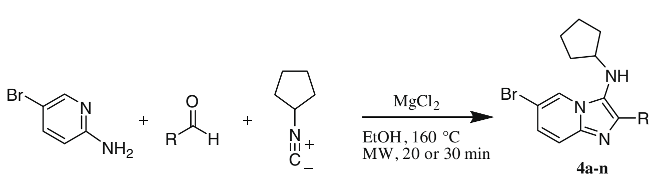
To further explore the effect of large hydrophobic groups in the 6-position, we decided to prepare a series of compounds where the halogen was exchanged for various aryl moieties. The target compounds were designed to explore the available chemical space and, in the case of **3o** increase solubility and H-bond potential. These molecules were smoothly prepared via microwave-assisted Suzuki cross-coupling reactions[23–25] utilizing either aryl bromide **3f** or the corresponding 6-boronic acid pinacol ester derivative, which was prepared from 2-aminopyridine-5-boronic acid pinacol ester according to Table 1. Compound **3q** was synthesized as per **3c**, however MeOH was replaced by phenol in the Ullman reaction. In addition, treatment of **3r** under catalytic hydrogenation conditions (Pd/C, H_2) afforded the saturated phenylethylene derivative **3s**. These compounds were then assessed for their ability to inhibit *Mt*GS and the results are reported in Table 2.

Unfortunately, the compounds in this series (**3n**–**s**) failed to show any significant *Mt*GS inhibitory activity, highlighting a lack of tolerance towards the introduction of large aryl substituents in the 6-position of the 3-amino-imidazo[1,2-*a*]pyridines.

Finally, utilizing compound **3f** as the lead structure, we decided to investigate the effect of altering the C-2 aryl substituent (R) on *Mt*GS inhibition. Thus, a series of compounds were synthesized from cyclopentylisonitrile, 5-bromo-2-aminopyridine and an appropriately substituted aldehyde as per Table 1. Compounds **4a**–**n** were evaluated for their *Mt*GS inhibitory activity and the results are presented in Table 3.

Table 3 shows that a C-2 phenyl ring with a hydrogen bond donor in the 3′-position (i.e., **4e**, OH or **4l**, NH_2) is a clear requisite for enzyme inhibition. Placement of the –OH in the 2′- or 4′-positions (**4f** and **4b**, respectively) results in complete loss in activity. Removal of the hydrogen bond donor capacity through the introduction of a methoxy group rendered the inactive compound **4g**. Interestingly, **4e** displays a twofold increase in activity compared to **3f** suggesting that the 4′-methoxy group is not required for inhibition. The introduction of electron withdrawing substituents (**4i** and **4j**) was also detrimental to activity. However, these substituents may also disrupt the orientation of the phenyl ring (**4i**) or intramolecularly bind the 3′-OH (**4j**) giving rise to the loss in potency. The corresponding 3′-aniline (**4l**) and 3-methylalcohol (**4m**) compounds were twofold less potent than **4e** (IC_{50} = 10.1 ± 1.1 μM and 13.2 ± 1.5 μM vs 3.3 ± 0.6 μM, respectively) demonstrating a preference for a phenol group in the 3′-position. Rewardingly, the introduction of a carboxylic acid rendered the nanomolar potent inhibitor, **4n** (IC_{50} = 0.38 ± 0.02 μM).

Table 3
Synthesis and biological evaluation of 3-amino-imidazo[1,2-*a*]pyridines (**4a**–**n**)



Entry	Product[a]	R	IC_{50}[b] (μM)
1	**4a**	H	>50
2	**4b**	3′-OMe,4′-OHC_6H_3	>50
3	**4c**	C_6H_5	>50
4	**4d**	4′-OHC_6H_4	nd[c]
5	**4e**	3′-OHC_6H_4	3.3 ± 0.6
6	**4f**	2′-OHC_6H_4	>50
7	**4g**	3′-$OMeC_6H_4$	>50
8	**4h**	2′,3′-$DiOMeC_6H_3$	>50
9	**4i**	2′-Cl,3′-OHC_6H_3	>50
10	**4j**	3′-OH,4′-$NO_2C_6H_3$	>50
11	**4k**	3′-$NO_2C_6H_4$	>50
12	**4l**	3′-$NH_2C_6H_4$	10.1 ± 1.1
13	**4m**	3′-$(CH_2OH)C_6H_4$	13.2 ± 1.5
14	**4n**	3′-$(COOH)C_6H_4$	0.38 ± 0.02

[a] Purity >95% by HPLC or ^{1}H NMR.
[b] Values are means of three experiments ± standard error.
[c] IC_{50} could not be determined due to poor solubility.

In summary, three small series of trisubstituted 3-amino-imidazo[1,2-*a*]pyridines have been investigated as *Mt*GS inhibitors. The compounds represent the first non-amino acid derived inhibitors of this enzyme. The most effective compounds possessed low micromolar (**3f**, IC_{50} = 8.8 ± 0.4 μM, **3g**, IC_{50} = 4.8 ± 0.5 μM, **4e**, IC_{50} = 3.3 ± 0.6 μM) or nanomolar potency (**4n** IC_{50} = 0.38 ± 0.02 μM). Compound **4n** was significantly more active than both MSO (IC_{50} = 51 ± 6 μM) and PPT (IC_{50} = 1.9 ± 0.4 μM) the most potent known *Mt*GS inhibitors. Given their drug-like nature, we anticipate they will serve as important lead compounds in the search for new anti-tuberculosis agents. The chemistry established can easily be used to smoothly produce additional inhibitors. Work is currently underway within our laboratory utilizing these structures to expand the SAR developed herein.

Acknowledgments

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21. *Example synthesis: Compound* **3f**. To a microwave transparent vial (2–5 mL) with a teflon coated stirring bar was added cyclopentylisonitrile (0.192 g, 2 mmol), 3-hydroxy-4-methoxybenzaldehyde (0.304 g, 2 mmol), 2-amino-5-bromopyridine (0.346 g, 2 mmol), $MgCl_2$ (0.019 g, 0.1 mmol) and EtOH (2 mL). The vial was then sealed under air and heated at 160 °C by microwave irradiation for 20 min using a fixed hold time. After cooling, the mixture was diluted with ethyl acetate and brine (20 mL each) and the two layers separated. The aqueous layer was washed twice with ethyl acetate (20 mL) and the combined organic phases were concentrated in vacuo. The crude product was thereafter purified by recrystallization from ethyl acetate. Yield: 0.530 g, 66%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39–1.48 (m, 2H), 1.53–1.58 (m, 2H), 1.67–1.77 (m, 4H), 3.05 (d, *J* = 4.4 Hz, 1H), 3.61–3.66 (m, 1H), 3.92 (s, 3H), 6.02 (br s, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.15 (dd, *J* = 2.0, 9.2 Hz, 1H), 7.40 (d, *J* = 9.2 Hz, 1H), 7.50 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 8.22 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 33.7, 56.2, 59.3, 106.6, 111.0, 113.8, 118.2, 119.6,

122.9, 125.5, 127.3, 127.7, 137.9, 140.0, 146.0, 146.6. LC–ESI-MS: *m/z* 402 (M+1). Calcd for $C_{19}H_{20}BrN_3O_2$: C, 56.73; H, 5.01; N, 10.45. Found: C, 56.44; H, 5.01; N, 10.27.

22. The assay was performed essentially as previously described.[10] However, 25 mM of $MgCl_2$, 1 mM of ATP and 30 mM of monosodium L-glutamate were used and stock solutions of the compounds (10 mM) were prepared in DMSO. A concentration of 50 μM was chosen as the upper limit for IC_{50} determinations due to solubility problems encountered with some compounds at higher concentrations.
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25. *Example synthesis: Compound* **3r**. To a microwave transparent vial (2–5 mL) with a teflon coated stirring bar was added **3f** (0.080 g, 0.2 mmol), *trans*-2-phenylvinylboronic acid (0.088 g, 0.6 mmol), Cs_2CO_3 (0.234 g, 0.7 mmol), $Pd(PPh_3)_4$ (0.016 g, 0.013 mmol) and DMF (2 mL). The vial was then sealed under air and heated at 120 °C by microwave irradiation for 30 min using a fixed hold time. After cooling, the mixture was diluted with ethyl acetate and brine (20 mL each) and the two layers separated. The aqueous layer was washed twice with ethyl acetate (20 mL) and the combined organic phases were concentrated in vacuo. The crude product was thereafter purified by flash chromatography eluting with ethyl acetate/hexane (3:2). Yield: 0.064 g, 65%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45–1.50 (m, 4H), 1.58–1.62 (m, 2H), 1.70–1.74 (m, 2H), 3.55–3.58 (m, 1H), 3.80 (s, 3H), 4.26 (d, *J* = 4.6 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 16.4 Hz, 1H), 7.18 (d, *J* = 16.4 Hz, 1H), 7.19–7.22 (m, 1H), 7.28–7.37 (m, 3H), 7.45 (dd, *J* = 1.7, 9.5 Hz, 1H) 7.51 (d, *J* = 7.5, 2H) 7.55 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.65 (d, *J* = 2.4 Hz, 1H), 8.25 (br s, 1H), 8.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 33.5, 56.2, 59.0, 112.7, 114.9, 117.0, 118.6, 121.5, 122.3, 122.3, 125.7, 126.3, 126.8, 128.0, 128.2, 128.4, 129.1, 136.5, 137.5, 140.5, 146.7, 147.4. LC–ESI-MS: *m/z* 426 (M+1) Calcd for $C_{27}H_{27}N_3O_2$: C, 76.21; H, 6.40; N, 9.87. Found: C, 76.02; H, 6.39; N, 9.79.

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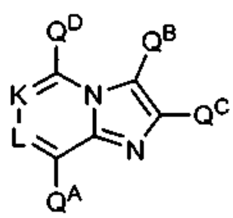

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(57) Abstract: Disclosed are substituted imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrazines, imidazo[1,2-c]pyrimidines and imidazo[1,2-d]triazines compounds of the formula: (1.0) Also disclosed are methods for treating JNK1 and ERK mediated diseases using the compounds of formula 1.0.

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NOVEL JNK INHIBITORS

REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/875989 filed December 20, 2007, the disclosure of which is incorporated herein by reference thereto.

FIELD OF THE INVENTION

The present invention relates to novel substituted imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrazines, imidazo[1,2-c]pyrimidines and imidazo[1,2-d]triazines, pharmaceutical compositions comprising said compounds, and methods for treating diseases or conditions, such as, for example, inflammation, autoimmune diseases, rheumatoid arthritis (RA), psoriasis, metabolic diseases, cardiovascular disease, and neurodegenerative diseases, by administering at least one of said compounds. The novel compounds of this invention are inhibitors of Kinases, and are therefore inhibitors of MAP kinases, and in turn are therefore inhibitors of JNK, ERK1 and ERK2. Thus, for example, the novel compounds of this invention inhibit c-Jun-N-terminal kinase, and therefore the novel compounds of this invention are used to treat or inhibit diseases mediated by c-Jun-N-terminal kinase.

BACKGROUND OF THE INVENTION

Protein Kinases are divided into two families (1) tyrosine kinase family and (2) serine and threonine kinase family depending on their phosphorylation site (tyrosine, or serine and threonine. Protein kinse activity controls a wide variety of cell life such as growth, differentiation and proliferation. Some of the examples for tyrosine kinase are ALK4, Azl, Brk, EphB4, Fer, Fgr, JAK family (JAK1 and JAK2), Ret, TrkA, Tec family BTK, IKK, ITK and examples for serine and threonine kinase are Ark5, Msk1, Nek2, Pim (Pim1 and Pim2), PLK, RockI and II, SGK1,2 3, MEK, Erk, Chk, Aurrora and C-met kinases.

C-Jun-N-terminal kinases (i.e., JNKs), which belong to the mitogen activated protein kinase family, are triggered in response to cytokines, mitogens, osmotic stress and ultraviolet readiation. JNKs are divided into three (JNK1, JNK2 and JNK3) major isoforms depending on their gene sequence. Further, these JNKs are divided into 10 splicing isoforms in cells (Gupta, S., T. Barret, A. J., Whitmarsh, J. Cavanagh, H.K. Sluss, B. Derijard, and R. J. Davis 1996, EMBO J. 15, 2760-2770). JNK1 and JNK2 are ubiquitously expressed (Mohit, A.A., Martin, J.H., Miller, C.A Neuron 14, 67-70, 1995), where as JNK3 is expressed in brain and to a lesser extent in the heart and testes.

JNKs are activated by dual phosphorylation of Thr 183 and Tyr 185 by MKK4 and MKK7 kinases (Lin A., Minden A., Martinetto H., Claret F.-Z., Lange-Carter C., Mercurio F., Johnson G.L., and Karin M. Science 268: 286-289, 1995). MKK4 preferentially phosphorylates JNK on tyrosine whereas MKK7 phosphorylates JNK on threonine. Activated c-Jun-N-terminal kinase in turn activates by phosphorylating various transcription factors such as c-Jun, AP1, ATF2, IRS1, NFAT4 and Bcl-2, etc. (Karin M and Hunter T. Curr. Biol. 5,747-757, 1995 and Shaulian, E., and Karin, M., Nat. Cell Biol. 4, E131-136, 2002). Either JNK1 or JNK2 knockout studies in mice revealed a deficiency in T-helper cells (Dong, C.; Yang, D. D.; Wysk, M.; Whitmarsh, A. J.; Davis, R. J.; Flavell, R. A., *Science* **1998**, *282*, 2092-2095; Yang, D. D.; Conze, D.; Whitmarsh, A. J.; Barrett, T.; Davis, R. J.; Rincon, M.; Flavell, R. A. *Immunity* **1998**, *9*, 575-585.; Sabapathy, K.; Hu, Y.; Kallunki, T.; Schreiber, M.; David, J. P.; Jochum, W.; Wagner, E. F.; Karin, M., *Curr. Biol.* **1999**, *9*, 116-125), whereas double knockouts are embryonic lethal (Tournier, C.; Hess, P.; Yang, D. D.; Xu, J.; Turner, T. K.; Nimnual, A.; Bar-Sagi, D.; Jones, S. N.; Flavell, R. A.; Davis, R. J., *Science* **2000**, *288*, 870-874). The JNK3 knockout mouse exhibit resistance to kainic acid induced apoptosis in the hippocampus and to subsequent seizures (Yang, D. D.; Kuan, C. Y.; Whitmarsh, A. J.; Rincon, M.; Zheng, T. S.; Davis, R. J.; Rakic, P.; Flavell, R. A., *Nature* 1997, *389*, 865-870).

Those skilled in the art know that the JNK pathway is activated in several diseases, such as, for example, inflammatory, neurodegenerative and metabolic diseases. Those skilled in the art also know that JNK activation is required for the transformation induced by RAS, an oncogene activated in many human cancers.

In view of the interest in treating diseases mediated by c-Jun-N-terminal kinase, compounds that inhibit c-Jun-N-terminal kinase would be a welcome contribution to the art. This invention provides that contribution.

The processes involved in tumor growth, progression, and metastasis are mediated by signaling pathways that are activated in cancer cells. The ERK pathway plays a central role in regulating mammalian cell growth by relaying extracellular signals from ligand-bound cell surface tyrosine kinase receptors such as erbB family, PDGF, FGF, and VEGF receptor tyrosine kinase. Activation of the ERK pathway is via a cascade of phosphorylation events that begins with activation of Ras. Activation of Ras leads to the recruitment and activation of Raf, a serine-threonine kinase. Activated Raf then phosphorylates and activates MEK1/2, which then phosphorylates and activates ERK1/2. When activated, ERK1/2 phosphorylates several downstream targets involved in a multitude of cellular events including cytoskeletal changes and transcriptional activation. The ERK/MAPK pathway is one of the most important for cell proliferation, and it is believed that the ERK/MAPK pathway is frequently activated in many tumors. Ras genes, which are upstream of ERK1/2, are mutated in several cancers including colorectal, melanoma, breast and pancreatic tumors. The high Ras activity is accompanied by elevated ERK activity in many human tumors. In addition, mutations of BRAF, a serine-threonine kinase of the Raf family, are associated with increased kinase activity. Mutations in BRAF have been identified in melanomas (60%), thyroid cancers (greater than 40%) and colorectal cancers. These observations indicate that the ERK1/2 signalling pathway is an attractive pathway for anticancer therapies in a broad spectrum of human tumours.

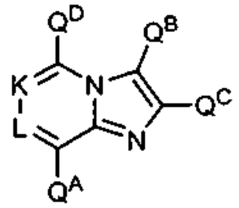
Therefore, a welcome contribution to the art would be small-molecules (i.e., compounds) that inhibit ERK activity (i.e., ERK1 and ERK2 activity), which small-molecules would be useful for treating a broad spectrum of cancers, such as, for example, melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer. Such a contribution is provided by this invention.

SUMMARY OF THE INVENTION

The present invention provides novel compounds useful for treating or preventing diseases (or conditions) associated with the Kinase pathway. Thus, the present invention provides novel compounds useful for treating or preventing diseases (or conditions) associated with MAP Kinases, such as, for example, JNK1, ERK1 and ERK2.

Thus, for example, the present invention provides a method of treating or preventing conditions associated with JNK activation or JNK pathway using novel compounds of formula 1.0.

This invention provides novel compounds that are inhibitors of Kinase, and therefore MAP Kinases, such as, for example, inhibitors of JNK (e.g., JNK1). The novel compounds of this invention have the formula:



(1.0)

or the pharmaceutically acceptable salts, esters and solvates thereof.

This invention also provides Compound Numbers: 13-94, 97-101, 111-125, 130, 131, 139, 140, 150, 154-158, 162, 167, 170-246, 271-289, 291-303, 305-307, 321-324, 326-328, 350-354, 404-410, 444-506, 542-546, 573-576, 578, 584, 588, 590, 593, 597, 598-600, 605-629, 635, 647, 650-652, 659, 664-665, 673-680, 686, 691, 692, 699, 703, 720-727, 734, 736, 740-743, 755, 756, 762-776, 780, 784, and 791-794.

This invention also provides compounds of formula 1.0 (e.g., Compound Numbers: 13-94, 97-101, 111-125, 130, 131, 139, 140, 150, 154-158, 162, 167, 170-246, 271-289, 291-303, 305-307, 321-324, 326-328, 350-354, 404-410, 444-506, 542-546, 573-576, 578, 584, 588, 590, 593, 597, 598-600, 605-629, 635, 647, 650-652, 659, 664-665, 673-680, 686, 691, 692, 699, 703, 720-727, 734, 736, 740-743, 755, 756, 762-776, 780, 784, and 791-794.) in purified and isolated form.

This invention also provides compounds of formula 1.0 (e.g., Compound Numbers: 13-94, 97-101, 111-125, 130, 131, 139, 140, 150, 154-158, 162, 167, 170-246, 271-289, 291-303, 305-307, 321-324, 326-328, 350-354, 404-410, 444-506, 542-546, 573-576, 578, 584, 588, 590, 593, 597, 598-600, 605-629, 635, 647, 650-652, 659, 664-665, 673-680, 686, 691, 692, 699, 703, 720-727, 734, 736, 740-743, 755, 756, 762-776, 780, 784, and 791-794) in purified form.

This invention also provides compounds of formula 1.0 (e.g., Compound Numbers: 13-94, 97-101, 111-125, 130, 131, 139, 140, 150, 154-158, 162, 167, 170-246, 271-289, 291-303, 305-307, 321-324, 326-328, 350-354, 404-410, 444-506, 542-546, 573-576, 578, 584, 588, 590, 593, 597, 598-600, 605-629, 635, 647, 650-652, 659, 664-665, 673-680, 686, 691, 692, 699, 703, 720-727, 734, 736, 740-743, 755, 756, 762-776, 780, 784, and 791-794) in isolated form.

This invention also provides pharmaceutically acceptable salts of the compounds of formula 1.0 (e.g., Compound Numbers: 13-94, 97-101, 111-125, 130, 131, 139, 140, 150, 154-158, 162, 167, 170-246, 271-289, 291-303, 305-307, 321-324, 326-328, 350-354, 404-410, 444-506, 542-546, 573-576, 578, 584, 588, 590, 593, 597, 598-600, 605-629, 635, 647, 650-652, 659, 664-665, 673-680, 686, 691, 692, 699, 703, 720-727, 734, 736, 740-743, 755, 756, 762-776, 780, 784, and 791-794).

This invention also provides pharmaceutically acceptable esters of the compounds of formula 1.0 (e.g., Compound Numbers: 13-94, 97-101, 111-125, 130, 131, 139, 140, 150, 154-158, 162, 167, 170-246, 271-289, 291-303, 305-307, 321-324, 326-328, 350-354, 404-410, 444-506, 542-546, 573-576, 578, 584, 588, 590, 593, 597, 598-600, 605-629, 635, 647, 650-652, 659, 664-665, 673-680, 686, 691, 692, 699, 703, 720-727, 734, 736, 740-743, 755, 756, 762-776, 780, 784, and 791-794).

This invention also provides solvates of the compounds of formula 1.0 (e.g., Compound Numbers: 13-94, 97-101, 111-125, 130, 131, 139, 140, 150, 154-158, 162, 167, 170-246, 271-289, 291-303, 305-307, 321-324, 326-328, 350-354, 404-410, 444-506, 542-546, 573-576, 578, 584, 588, 590, 593, 597, 598-600, 605-629, 635, 647, 650-652, 659, 664-665, 673-680, 686, 691, 692, 699, 703, 720-727, 734, 736, 740-743, 755, 756, 762-776, 780, 784, and 791-794).

This invention also provides a pharmaceutical composition comprising at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and a pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising a compound of formula 1.0, and a pharmaceutically acceptable carrier.

This invention also provides a method of inhibiting JNK (e.g., JNK1) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0.

This invention also provides a method of inhibiting JNK (e.g., JNK1) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a compound of formula 1.0.

This invention also provides a method of treating a JNK (e.g., JNK1) mediated disease in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0.

This invention also provides a method of treating a JNK (e.g., JNK1) mediated disease in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of a compound of formula 1.0.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein said JNK mediated disease is selected from the group consisting of: inflammation, autoimmune disorders (such as, for example, rheumatoid arthritis, multiple sclerosis, asthma, inflammatory bowel disease, psoriasis, pancreatitis, septic shock, transplant rejection and bronchitis), metabolic diseases (such as, for example, diabetes, insulin resistance, and obesity), neurological diseases (such as, for example, Alzeimer's, epilepsy, parkinson's disease, spinal card injury, memory and attention disorders), pain and related syndromes, cancer (such as, for example, breast, colorectal, pancreatic, ovarian, prostate and small cell lung cancer), cardiovascular diseases (such as, for example, hypertrophy and other types of left ventricular remodeling, ischemia/reperfusion injury, angiogenesis and atherogenesis), hepatic ischemia, reperfusion injury, lung fibrosism and liver fibrosis.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein inflammation is treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein rheumatoid arthritis is treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein asthma is treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein multiple sclerosis is treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein inflammatory bowel disease is treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein psorisis is treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein diabetes is treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein autoimmune disorders are treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein metabolic diseases are treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein neurological diseases are treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein pain is treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein cancer is treated.

This invention also provides any one of the above methods for treating a JNK mediated disease wherein cardiovascular diseases are treated.

This invention is provides any one of the above methods for treating a JNK mediated disease wherein the compound of formula 1 is administered in combination with at least one other active ingredient know in the art for the treatment of said disease. For example, in the treatment of cancer, the compound of formula 1 is administered in combination with at least one (e.g., 1, 2 or 3, or 1 or 2, or 1) chemotherapeutic agent. Administration "in combination with" means the drugs are administered during the same treatment protocol, for example, administration sequentially or consecutively during the treatment protocol. Examples of a chemotherapeutic agents include, for example, antimetabolites, such as, for example, taxol.

This invention also provides any one of the above methods wherein said treatment comprises administering to said patient an effective amount of a pharmaceutical composition comprising at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 and a pharmaceutically acceptable carrier.

This invention also provides any one of the above methods wherein said treatment comprises administering to said patient an effective amount of a pharmaceutical composition comprising a compound of formula 1.0 and a pharmaceutically acceptable carrier.

This invention also provides a method of inhibiting ERK (i.e., inhibiting the activity of ERK) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method of inhibiting ERK1 (i.e., inhibiting the activity of ERK1) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method of inhibiting ERK2 (i.e., inhibiting the activity of ERK2) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method of inhibiting ERK1 and ERK2 (i.e., inhibiting the activity of ERK1 and ERK2) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 in combination with at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) signal transduction inhibitor.

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 in combination with at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) signal transduction inhibitor.

This invention also provides a method for treating lung cancer, pancreatic cancer, colon cancer (e.g., colorectal cancer), myeloid leukemias (e.g., AML, CML, and CMML), thyroid cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers (e.g., squamous cell cancer of the head and neck), ovarian cancer, brain cancers (e.g., gliomas, such as glioma blastoma multiforme), cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas), sarcomas, tetracarcinomas, nuroblastomas, kidney carcinomas, hepatomas, non-Hodgkin's lymphoma, multiple myeloma, or anaplastic thyroid carcinoma, in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating lung cancer, pancreatic cancer, colon cancer (e.g., colorectal cancer), myeloid leukemias (e.g., AML, CML, and CMML), thyroid cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers (e.g., squamous cell cancer of the head and neck), ovarian cancer, brain cancers (e.g., gliomas, such as glioma blastoma multiforme), cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas), sarcomas, tetracarcinomas, nuroblastomas, kidney carcinomas, hepatomas, non-Hodgkin's lymphoma, multiple myeloma, or anaplastic thyroid carcinoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating lung cancer, pancreatic cancer, colon cancer (e.g., colorectal cancer), myeloid leukemias (e.g., AML, CML, and CMML), thyroid cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers (e.g., squamous cell cancer of the head and neck), ovarian cancer, brain cancers (e.g., gliomas, such as glioma blastoma multiforme), cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas), sarcomas, tetracarcinomas, nuroblastomas, kidney carcinomas, hepatomas, non-Hodgkin's lymphoma, multiple myeloma, or anaplastic thyroid carcinoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating lung cancer, pancreatic cancer, colon cancer (e.g., colorectal cancer), myeloid leukemias (e.g., AML, CML, and CMML), thyroid cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers (e.g., squamous cell cancer of the head and neck), ovarian cancer, brain cancers (e.g., gliomas, such as glioma blastoma multiforme), cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas), sarcomas, tetracarcinomas, nuroblastomas, kidney carcinomas, hepatomas, non-Hodgkin's lymphoma, multiple myeloma, or anaplastic thyroid carcinoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent wherein said cancer is selected from the group consisting of: melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

This invention also provides a method for treating melanoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating melanoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating melanoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating melanoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating pancreatic cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating pancreatic cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating pancreatic cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating pancreatic cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating thyroid cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating thyroid cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating thyroid cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating thyroid cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating colorectal cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating colorectal cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating colorectal cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating colorectal cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating lung cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating lung cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating lung cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating lung cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating breast cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating breast cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating breast cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating breast cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating ovarian cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating ovarian cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating ovarian cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating ovarian cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides methods of treating breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 in combination with hormonal therapies (i.e., antihormonal agents).

This invention also provides methods of treating breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 in combination with hormonal therapies (i.e., antihormonal agents).

This invention also provides methods of treating breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 in combination with hormonal therapies (i.e., antihormonal agents), and in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides methods of treating breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 in combination with hormonal therapies (i.e., antihormonal agents), and in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

The methods of treating breast cancer described herein include the treatment of hormone-dependent metastatic and advanced breast cancer, adjuvant therapy for hormone-dependent primary and early breast cancer, the treatment of ductal carcinoma in situ, and the treatment of inflammatory breast cancer in situ.

The methods of treating hormone-dependent breast cancer can also be used to prevent breast cancer in patients having a high risk of developing breast cancer.

Thus, this invention also provides methods of preventing breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 in combination with hormonal therapies (i.e., antihormonal agents).

This invention also provides methods of preventing breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 in combination with hormonal therapies (i.e., antihormonal agents).

This invention also provides methods of preventing breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 in combination with hormonal therapies (i.e., antihormonal agents), and in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides methods of preventing breast cancer (i.e., post-menopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment, said treatment comprising the administration of an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0 in combination with hormonal therapies (i.e., antihormonal agents), and in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) a in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of a chemotherapeutic agent wherein said chemotherapeutic agent is temozolomide.

This invention also provides a method for treating brain cancer (e.g., glioma, such as glioma blastoma multiforme) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of a chemotherapeutic agent, wherein said chemotherapeutic agent is temozolomide.

This invention also provides a method for treating prostate cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating prostate cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating prostate cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating prostate cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myelodysplastic syndrome in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating myelodysplastic syndrome in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myelodysplastic syndrome in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating myelodysplastic syndrome in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating acute myelogenous leukemia (AML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating acute myelogenous leukemia (AML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating acute myelogenous leukemia (AML)in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating acute myelogenous leukemia (AML)in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating chronic myelomonocytic leukemia (CMML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating chronic myelomonocytic leukemia (CMML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating chronic myelomonocytic leukemia (CMML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating chronic myelomonocytic leukemia (CMML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating chronic myelogenous leukemia (chronic myeloid leukemia, CML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating chronic myelogenous leukemia (chronic myeloid leukemia, CML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating chronic myelogenous leukemia (chronic myeloid leukemia, CML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating chronic myelogenous leukemia (chronic myeloid leukemia, CML) in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating myeloid leukemias in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating bladder cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating bladder cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating bladder cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating bladder cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

This invention also provides a method for treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0.

This invention also provides a method for treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, and usually 1) compound of formula 1.0, in combination with an effective amount of at least one (e.g., 1, 2 or 3, 1 or 2, or 1) chemotherapeutic agent.

In the methods of this invention the compounds of this invention can be administered concurrently or sequentially (i.e., consecutively) with the chemotherapeutic agents or the signal transduction inhibitor.

The methods of treating cancers described herein can optionally include the administration of an effective amount of radiation (i.e., the methods of treating cancers described herein optionally include the administration of radiation therapy).

DETAILED DESCRIPTION OF THE INVENTION

As used herein, unless indicated otherwise, the abbreviations below have the meanings indicated.

ACN	Acetonitrile
AcOH	Acetic acid
DCC	Dicyclohexylcarbodiimide
DCU	Dicyclohexylurea
DCM	Dichloromethane
DIAD	Diisopropylazodicarboxylate
DIEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMFDMA	N,N-Dimethylformamide dimethylacetal
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
EtOH	Ethanol
HATU	N,N,N',N'-Tetramethyl-O-(7-Azabenzotriazol-1-yl)Uronium hexafluorophosphate
Hex	hexanes
HPLC	High pressure liquid chromatography
LCMS	Liquid chromatography mass spectrometry
mCPBA	*meta*-Chloroperoxybenzoic acid
MeOH	Methanol
NaH	Sodium hydride
NMR	Nuclear magnetic resonance
PFP	Pentafluorophenol

PMB	p-methoxybenzyl
Pyr	Pyridine
RT	Room temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl

As herein, the following terms, unless indicated otherwise, have thefollowing meanings indicated:

"Patient" includes both human and animals (and preferably a human being).

"Mammal" means humans and other mammalian animals.

"One or more" includes, for example, 1, 2 or 3, or 1 or 2, or 1.

"At least one" includes, for example, 1, 2 or 3, or 1 or 2, or 1.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl. aryl, cycloalkyl, cyano, alkoxy and –S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. "Alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

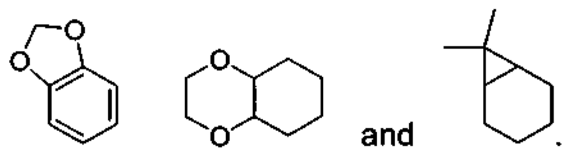
"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl and the like.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

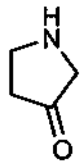
"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(alkyl)$, Z_1Z_2N-, Z_1Z_2N-alkyl-, $Z_1Z_2NC(O)-$, $Z_1Z_2NSO_2-$ and $-SO_2NZ_1Z_2$, wherein Z_1 and Z_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:



"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

"Heterocyclyl" (e.g., "heterocycloalkyl") means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. "Heterocyclyl" may also mean a ring system (as described above) that is substituted with a single moiety (e.g., =O) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. An example of such a heterocyclyl is pyrrolidone:



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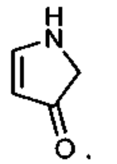
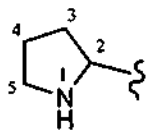
"Heterocyclylalkyl" (e.g., "heterocycloalkylalkyl") means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4-tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. "Heterocyclenyl" may also mean a ring systemt (as described above) that is substituted with a single moiety (e.g., =O) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. An example of such a heterocyclenyl is pyrrolidinone:



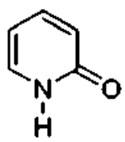
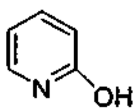
"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:

 and 

are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-$S(O_2)$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^3, etc.) occurs more than one time in any constituent or in Formula 1.0, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

"Prodrug" represents compounds that are rapidly transformed, for example, by hydrolysis in blood, in vivo to the parent compound, i.e., to the compounds of formula 1.0 or to a salt and/or to a solvate thereof; A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference. The scope of this invention includes Prodrugs of the novel compounds of this invention.

For example, if a compound of Formula 1.0 or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, $(C_1–C_8)$alkyl, $(C_2$-$C_{12})$alkanoyl-oxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxy-carbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-

crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkyl-carbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of Formula 1.0 contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)-ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, -$P(O)(O(C_1$-$C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula 1.0 incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —C(OY^2)Y^3 wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

This invention is also provides compounds of formula 1.0 in pure or isolated form.

This invention also includes pharmaceutically esters of the compounds of formula 1.0.

This invention also includes pharmaceutically acceptable solvates of the compounds of formula 1.0.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of formula 1.0 can form salts which are also within the scope of this invention. Reference to a compound of formula 1.0 herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of formula 1.0 contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the formula 1.0 may be formed, for example, by reacting a compound of formula 1.0 with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) <u>66(1)</u> 1-19; P. Gould, *International J. of Pharmaceutics* (1986) <u>33</u> 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Compounds of formula 1.0, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

The compounds of formula 1.0 may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of formula 1.0 as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of formula 1.0 incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of formula 1.0 may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of formula 1.0 may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.) Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of Formula (I) (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula 1.0 can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

Polymorphic forms of the compounds of formula 1.0, and of the salts, solvates, esters and prodrugs of the compounds of formula 1.0, are intended to be included in the present invention.

The compounds according to the invention have pharmacological properties; in particular, the compounds of formula 1.0 are inhibitors of JNK (e.g., JNK1, 2 or 3).

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

"Anti-cancer agent", "chemotherapeutic agent", and "antineoplastic agent" have the same meaning, and these terms represent the drugs (medicaments) used to treat cancer.

"Antineoplastic agent" represents a chemotherapeutic agent effective against cancer.

"Compound", with reference to the antineoplastic agents, includes the agents that are antibodies.

"Concurrently" represents (1) simultaneously in time (e.g., at the same time); or (2) at different times during the course of a common treatment schedule;

"Consecutively" means one following the other;

"Different", as used in the phrase "different antineoplastic agents", means that the agents are not the same compound or structure. Preferably, "different" as used in the phrase "different antineoplastic agents" means not from the same class of antineoplastic agents. For example, one antineoplastic agent is a taxane, and another antineoplastic agent is a platinum coordinator compound.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting or treating the diseases described herein, e.g., cancer, or effective in inhibiting JNK (e.g., JNK1). That is, an effective amount is that amount that produces the desired therapeutic, ameliorative, inhibitory or preventative effect. For example, the amount of the compound or composition that results in: (a) the reduction, alleviation or disappearance of one or more symptoms caused by the disease (e.g., the cancer), (b) the reduction of tumor size, (c) the elimination of the tumor, and/or (d) long-term disease stabilization (growth arrest) of the tumor.

"Sequentially" means (1) administration of one component of the method ((a) compound of the invention, or (b) chemotherapeutic agent and/or radiation therapy) followed by administration of the other component or components. After adminsitration of one component, the next component can be administered substantially immediately after the first component, or the next component can be administered after an effective time period after the first component. The effective time period is the amount of time given for realization of maximum benefit from the administration of the first component; and

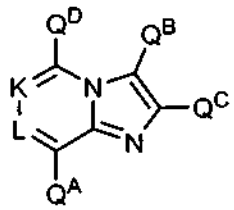
"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms of any ring when more than one ring is present.

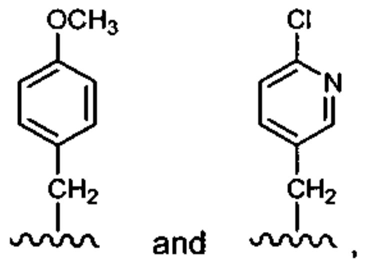
It should also be noted that any carbon or heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

This invention provides novel compounds that are JNK (e.g., JNK1) inhibitors. The novel compounds of this invention have the formula:


(1.0)

or the pharmaceutically acceptable salts, esters, and solvates thereof, wherein:

K is selected from the group consisting of:CH, N, -C(alkyl)- (e.g., $-C(CH_3)-$), -C(aryl)- (e.g., -C(phenyl)-), -C(halo)- (e.g., -C(F)-, or –C(Cl)- or –C(Br)-), and $-C(R^C)-$ wherein R^C is selected from the group consisting of:



(and preferably K is CH);

L is CH or N (and preferably CH);

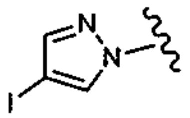
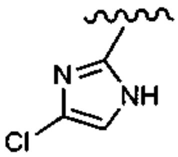
Q^A is selected from the group consisting of:

(A) $-C(O)NR^1R^2$;

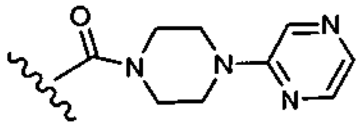
(B) $-N(R^{14})_2$ (e.g., $-NH_2$);

(C) unsubstituted heteroaryl (such as, for example, imidazolyl, pyrazolyl, oxadiazolyl, pyrimidinyl, pyridazinyl, and benzo fused heteroaryls (i.e., a heteroaryl fused to a benzene ring such that the heteroaryl ring and the benzene ring have two adjacent carbons in common, such as, for example, benzoimidazolyl and quinolinyl);

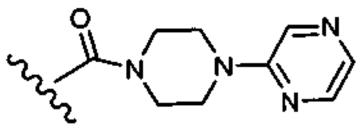
(D) substituted heteroaryl (such as, for example, substituted imidazolyl, substituted pyrazolyl, substituted oxadiazolyl, substituted pyrimidinyl, substituted pyridazinyl, and substituted benzo fused heteroaryls (i.e., a heteroaryl fused to a benzene ring such that the heteroaryl ring and the benzene ring have two adjacent carbons in common, such as, for example, substituted benzoimidazolyl and substituted quinolinyl), and wherein said substituted heteroaryl is substituted with one or more (e.g., 1 to 3) substituents selected from the group consisting of: (1) halo (e.g., Cl, F, Br, and I), (2) heteroaryl (e.g., pyridyl and pyrazinyl), benzo fused heteroaryl (e.g., benzoimidazolyl), (3) heterocycloalkyl (e.g., morpholinyl and pyrrolidinyl), (4) benzodioxolyl, (5) aryl (e.g., phenyl), (6) substituted aryl (e.g., substituted phenyl) wherein the substituent is $-S(O)_2$alkyl (e.g., $-S(O)_2CH_3$), (7) alkyl (e.g., methyl), (8) $-CF_3$, and wherein examples of said substituted heteroaryl moiety (D) include, but are not limited to:

 and  ;

(E)

 ;

(F)



substituted with one or more (e.g., 1 to 3) substituents selected from the group consisting of:

(1) $-(\text{alkylene})_{1\text{-}6}$-heterocycloalkyl (e.g., $-(\text{alkylene})_{1\text{-}2}$-heterocycloalkyl), such as, for example, $-(CH_2)_2$morpholinyl and $-CH_2$piperidinyl,

(2) aryl (e.g., phenyl),

(3) substituted aryl (e.g., substituted phenyl, such as, for example, chlorophenyl, fluorophenyl and cyanophenyl),

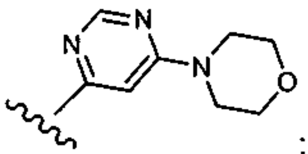
(4) $-C(O)R^{11}$,

(5) $-C(O)$-aryl (e.g. $-C(O)$phenyl), and

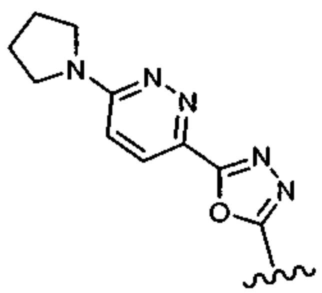
(6) –(alkylene)$_{1-6}$-N(R^{12})$_2$ (e.g., –(alkylene)$_{1-3}$- N(R^{12})$_2$), such as, for example, -(CH$_2$)$_3$N(R^{12})$_2$, and

wherein said substituted aryl moiety (3) (e.g., substituted phenyl) is substituted with one or more (e.g., 1 to 3) substitutents independently selected from the group consisting of: halo (e.g., Cl and F), and –CN;

(G)


;

(H)


;

(I)

—NH—pyrimidinyl——morpholinyl;

(J) H;

(K) –C(O)-heterocycloalkyl-heteroaryl (e.g., -C(O)-piperazinyl-piperidyl);

(L) –C(O)-piperazinyl-(alkylene)$_{1-6}$-substituted aryl wherein the substituents are independently selected from halo (e.g., Cl, F, Br);

(M) –C(O)-heterocycloalkyl-(alkylene)$_{1-6}$-heterocycloalkyl (e.g., –C(O)-piperazinyl-(alkylene)$_{1-6}$-heterocycloalkyl);

(N) –C(O)-piperazinyl-(alkylene)$_{1-6}$-heteroaryl;

(O) alkyl (e.g., C$_{1-6}$alkyl);

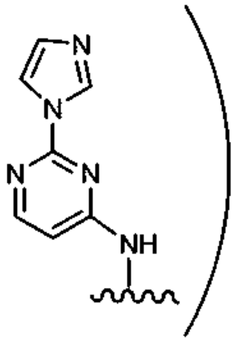
(P) –C(O)-heterocycloalkyl wherein said heterocycloalkyl is substituted with -(alkylene)$_{1-6}$-N(R^{12})$_2$ wherein each R^{12} is independently selected;

(Q) –C(O)-heterocycloalkyl-(alkylene)$_{1-6}$-(alkyl (e.g., C$_{1-6}$alkyl) substituted heterocycloalkyl) (e.g.,–C(O)-piperazinyl-CH$_2$-N-methylpiperidinyl);

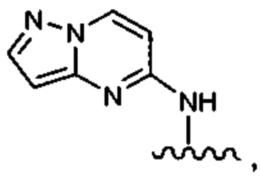
(R) -(alkylene)$_{1-6}$-benzo[1,3]dioxolyl;

(S) -(alkylene)$_{1-6}$-N(R^1)(R^2) wherein R^1 and R^2 are as defined above,

(T) –NH-heteroaryl-heteroaryl (e.g.,

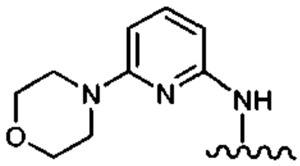
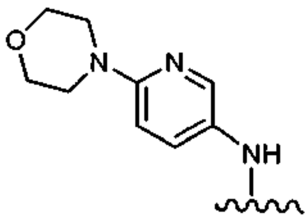
,

(U) –NH-(fused heteroarylheteroaryl), such as, for example,

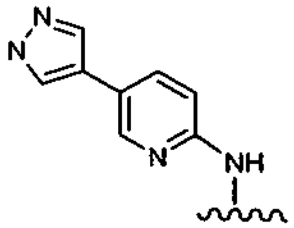
,

(V) –NH-(substituted heteroaryl), such as, for example:

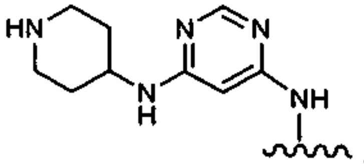
-NH-heteroaryl-heterocycloalkyl, such as, for example,

 and , and

-NH-heteroaryl-heteroaryl, such as, for example,

,

(W) –NH-heteroaryl-NH-heterocycloalkyl, such as, for example,

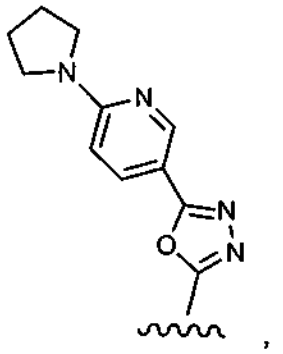
,

(X) biaryl (i.e., -aryl-aryl),

(Y) biheteroaryl (-heteroaryl-heteroaryl),

(Z) substituted biaryl (i.e., substituted aryl-aryl), and

(AA) substituted biheteroaryl (i.e., -substitued heteroaryl-heteroaryl), such as, for example, -heteroaryl-heteroaryl-heterocycloalkyl, such as,

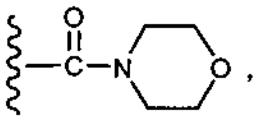
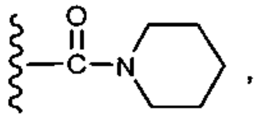
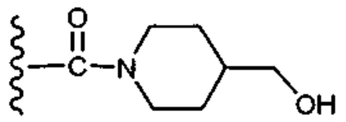


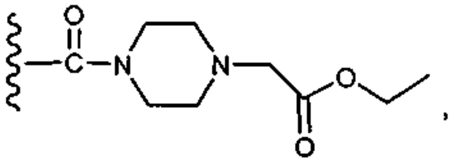
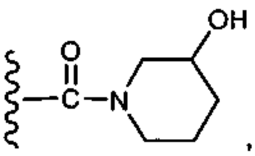
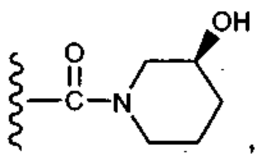
Q^B is selected from the group consisting of:

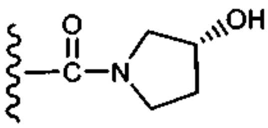
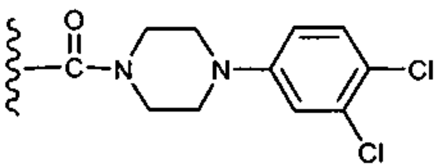
(A) $-C(O)NR^{15}R^{16}$;

(B) $-C(O)-R^{21}$, and

wherein examples of said $-C(O)-R^{21}$ moiety include, but are not limited to:

, , ,

, , ,

 and ;

(C) H;

(D) $-N(R^{12})_2$, wherein each R^{12} isindependently selected, and wherein one example of said (D) moiety is $-NH_2$;

(E) $-CH_2OH$;

(F) $-CH_2OCH_3$;

(G) $-CH_2SCH_3$,

(H) $-CH_2N(R^B)$ wherein each R^B is independently selected from the group consisting of: H, alkyl, cycloalkyl, heterocycloalkyl, heteroaryl (e.g., pyrazolyl, thiazolyl, and imidazolyl), and aryl (e.g., phenyl);

(I) $-N(R^{12})_2$ wherein each R^{12} is independently selected, examples or said $-N(R^{12})_2$ moiety include, for example, $-NH_2$, and –NHalkyl;

(J) –NH-C(O)-alkyl (e.g., $-NH-C(O)-CH_3$ and $-NH-C(O)-(CH_2)_2CH(CH_3)_2$);

(K) –NH-C(O)-(hydroxyl substituted alkyl);

(L) $-NH-S(O)_2$-alkyl (e.g., $-NH-S(O)_2-CH_3$);

(M) $-NH-C(O)-C(=CH_2)CH_2(CH_3)_2$;

(N) $-NH-C(O)-C(O)-CH_2(CH_3)_2$;

(O) alkyl (e.g., ethyl); and

(P) aryl (e.g., phenyl);

Q^C is selected from the group consisting of:

(A) heteroaryl (e.g., thienyl and pyridyl);

(B) heterocycloalkyl (e.g., pyrrolidinyl);

(C) H;

(D) alkyl (e.g., C_1 to C_6 alkyl, such as, for example, C_1 to C_4 alkyl) such as, for example, methyl, ethyl, and t-butyl;

(E) $-C(O)N(R^{12})_2$, such as, for example, $-C(O)NHCH_3$;

(F) cycloalkyl (e.g., C_{3-7} cycloalkyl);

(G) halo (e.g., Cl, Br, and I);

(H) –CN;

(I) $-CF_3$;

(J) $-CH_2CF_3$;

(K) $-SR^A$ wherein R^A is selected from the group consisting of: alkyl, cycloalkyl, heterocycloalkyl, heteroaryl (e.g., pyrazolyl, thiazolyl, and imidazolyl), and aryl (e.g., phenyl);

(L) $-N(R^B)_2$ wherein each R^B is independently selected from the group consisting of: H, alkyl, cycloalkyl, heterocycloalkyl, heteroaryl (e.g., pyrazolyl, thiazolyl, and imidazolyl), and aryl (e.g., phenyl);

(M) $-OR^A$ wherein R^A is as defined above;

(N) $-C(O)R^A$ wherein R^A is as defined above;

(O) aryl (e.g., phenyl);

(P) arylalkyl-;

(Q) heteroarylalkyl-;

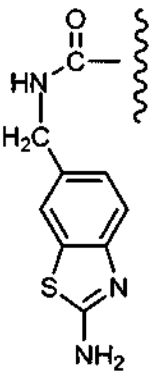
(R) substituted aryl (e.g., substituted phenyl), such as for example, halo substituted aryl (such has halo substituted phenyl) wherein each halo is independently selected (examples of said halo are Cl, Br, F) and wherein there are 1 to 3 substituents on said substituted aryl;

(S) substituted heteroaryl;

(T) substituted heteroarylalkyl;

(U) substituted aralkyl;

(V)



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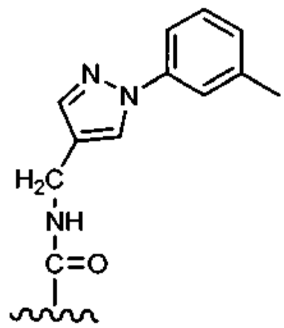
(W)



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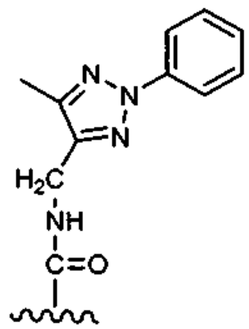
(X)



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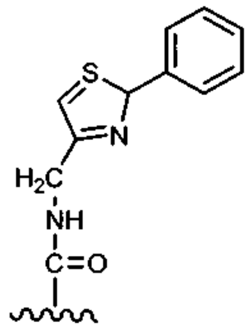
(Y)



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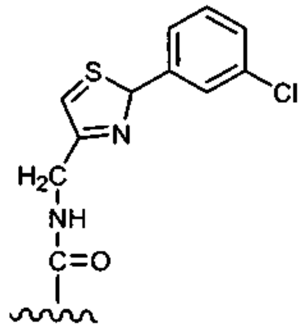
(Z)



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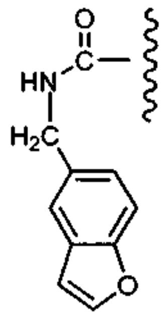
(AA)



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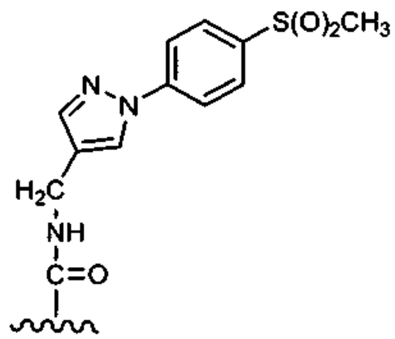
(AB)



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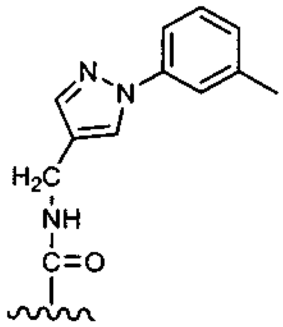
(AC)



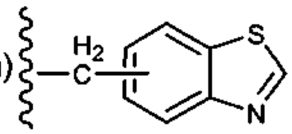
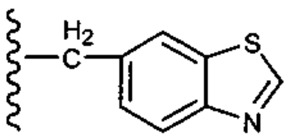
;

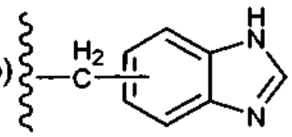
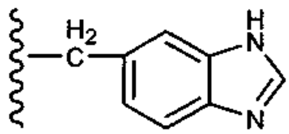
Q^D is selected from the group consisting of: H and alkyl (e.g., methyl);

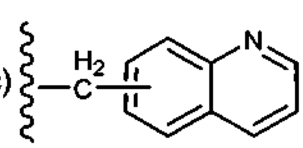
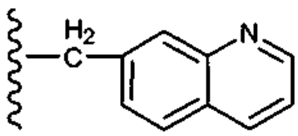
R^1 and R^2 are each independently selected from the group consisting of:

(1) H;

(2) unsubstituted –(alkylene)$_{1-6}$-benzoheteroaryl (e.g., unsubstituted -CH_2-benzoheteroaryl), wherein examples of said benzoheteroaryl moiety include, but are not limited to, benzothiazolyl, indazolyl, benzothienyl, quinolinyl and benzoimidazolyl, and wherein examples also include, but are not limited to:

(a)  , for example,  ,

(b)  , for example,  , and

(c)  , for example,  ;

(3) substituted –(alkylene)$_{1-6}$-benzoheteroaryl, wherein examples of said benzoheteroaryl moiety include, but are not limited to, benzothiazolyl, indazolyl, benzothienyl, quinolinyl and benzoimidazolyl, and wherein:

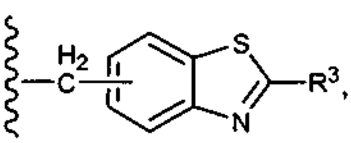
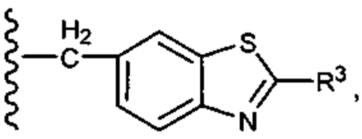
(a) either the alkylene or benzoheteroaryl moieties are substituted, or both the alkylene and benzoheteroaryl moieties are substituted,

(b) when the alkylene moiety is substitued the substitutents (e.g., 1 to 3 substituents) are independently selected from the group consisting of: alkyl (e.g., C_1

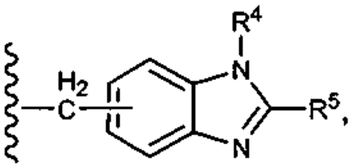
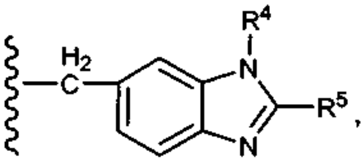
to C_6 alkyl), cycloalkyl (e.g., C_3 to C_6 cycloalkyl), -C(O)OH, -C(O)Oalkyl (e.g., -C(O)O(C_1 to C_6 alkyl)), and wherein the substituted alkylene moieties comprise R or S stereochemical centers,

(c) when the benzoheteroaryl moiety is substituted the substituents (one or more, e.g., 1 or 2 substituents) are independently selected from the group consisting of: (1) $-NH_2$, (2) -NH(alkyl) (e.g., -NH(C_1-C_6alkyl), such as, for example, $-NHCH_3$), (3) -NHC(O)(alkyl) (e.g., -NHC(O)(C_1-C_6alkyl), such as, for example, $-NHC(O)CH_3$), (4) alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl and isopropyl), (5) –S(alkyl) (e.g., -S(C_1-C_6 alkyl), such as, for example, $-SCH_3$), and (6) heteroaryl (e.g., pyridyl, such as, for example, m-pyridyl),

(d) wherein examples of said substituted $-(alkylene)_{1-6}$-benzoheteroaryl include, but are not limited to:

, for example, ,

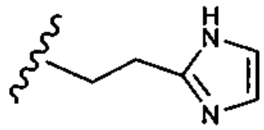
wherein R^3 is selected from the group consisting of: (1) $-NH_2$, (2) -NH(alkyl) (e.g., -NH(C_1-C_6alkyl), such as, for example, $-NHCH_3$), (3) -NHC(O)(alkyl) (e.g., -NHC(O)(C_1-C_6alkyl), such as, for example, $-NHC(O)CH_3$), (4) alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl and isopropyl (5) –S(alkyl) (e.g., -S(C_1-C_6 alkyl), such as, for example, $-SCH_3$), and (6) heteroaryl (e.g., pyridyl, such as, for example, m-pyridyl); and wherein R^3 is preferably $-NH_2$; and

, for example, ,

wherein R^4 and R^5 are each independently selected from the group consisting of: H and alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl and isopropyl) provided that at least one of R^4 or R^5 is other than H; and in one example R^4 is H and R^5 is alkyl; in another example R^4 is H and R^5 is methyl; in another example R^4 is H and R^5 is isopropyl; in another example R^4 is alkyl and R^5 is H; in another example R^4 is methyl and R^5 is H; in another example R^4 is alkyl and R^5 is alkyl; and in another example R^4 is methyl and R^5 is methyl;

(4) unsubstituted $-(alkylene)_{1-6}$-heteroaryl (e.g., unsubstituted $-(alkylene)_{1-2}$-heteroaryl), wherein examples of said heteroaryl moiety include, but are

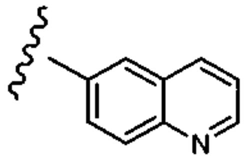
not limited to: imidazolyl, pyridyl (e.g., o-pyridyl, m-pyridyl, and p-pyridyl), thiophenyl (i.e., thienyl), pyrimidinyl, and pyrazinyl, one example of said unsubstituted –(alkylene)$_{1-6}$-heteroaryl is:



;

(5) substituted –(alkylene)$_{1-6}$-heteroaryl (e.g., substituted –(alkylene)$_{1-2}$-heteroaryl) substituted with one or more (e.g. 1 to 3) substitutents independently selected from the group consisting of: halo (e.g., Cl, F, and Br), -C(O)N(R^6)$_2$, and –NHS(O)$_2R^7$, wherein each R^6 is independently selected from the group consisting of H and alkyl (e.g., C_1 to C_6 alkyl), and wherein R^7 is alkyl (e.g., C_1 to C_6 alkyl), and wherein examples of the substituted heteroaryl moiety include, but are not limited to: substituted imidazolyl, substituted pyridyl (e.g., substituted o-pyridyl, m-pyridyl, and p-pyridyl), substituted thiophenyl (i.e., substituted thienyl), substituted pyrimidinyl, and substituted pyrazinyl;

(6) unsubstituted –benzoheteroaryl, wherein examples of said benzoheteroaryl moiety include, but are not limited to, benzothiazolyl, indazolyl, benzothienyl, quinolinyl and benzoimidazolyl, and wherein in one example said unsubstituted –benzoheteroaryl moiety is:



(quinolinyl)

(7) substituted –benzoheteroaryl, wherein examples of said substituted benzoheteroaryl moiety include, but are not limited to, substituted benzothiazolyl, substituted indazolyl, substituted benzothienyl, substituted quinolinyl and substitued benzoimidazolyl, and wherein said substituted benzoheteroaryl is substituted with one or more (e.g., 1 to 3) substitutents independently selected from the group consisting of: heteroaryl (e.g., pyridyl, imidazolyl, and pyrazolyl), heterocycloalkyl (e.g., morpholinyl and piperidyl), and –S(alkyl) (e.g., -S(C_1 to C_6 alkyl) such as, for example, -SCH_3);

(8) heteroaryl (e.g., pyrimidinyl, pyridyl, and pyrazolo[1.5-a]pyrimidinyl);

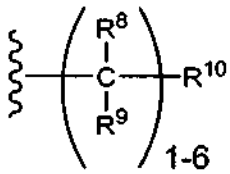
(9) substituted heteroaryl substituted with one or more substitutents (e.g., 1 to 3 substituents) independently selected from the group consisting of: heteroaryl

(e.g., pyridyl, imidazolyl, and pyrazolyl), heterocycloalkyl (e.g., morpholinyl and piperidyl), and–S(alkyl) (e.g., -S(C_1 to C_6 alkyl) such as, for example, -SCH_3), and wherein examples of the heteroaryl moiety of said substituted heteroaryl include but are not limited to pyrimidinyl, pyridyl, and pyrazolo[1.5-a]pyrimidinyl;

(10) aryl (e.g., phenyl);

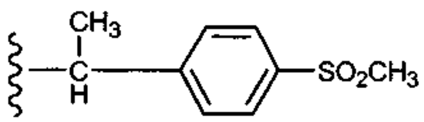
(11) substituted aryl (e.g., substituted phenyl) substituted with one or more (e.g., 1 to 3) substitutents independently selected from the group consisting of: heteroaryl (e.g., pyridyl, imidazolyl, and pyrazolyl), heterocycloalkyl (e.g., morpholinyl and piperidyl), and –S(alkyl) (e.g., -S(C_1 to C_6 alkyl) such as, for example, -SCH_3);

(12)



, and

wherein an example of said moiety (12) is:



;

(13) unsubstituted –(alkylene)$_{1-6}$-heterocycloalkyl (e.g., unsubstituted –(alkylene)$_{1-2}$-heterocycloalkyl), wherein examples of said heterocycloalkyl include, but are not limited to: piperidinyl (e.g. p-piperidinyl, i.e., the N of the piperidinyl is para to the carbon bonded to the rest of the molecule) and pyrrolidinyl, and in one example said heterocycloalkyl moiety is piperidinyl;

(14) substituted –(alkylene)$_{1-6}$-heterocycloalkyl (e.g., substituted –(alkylene)$_{1-2}$-heterocycloalkyl), wherein examples of said heterocycloalkyl include, but are not limited to: piperidinyl (e.g. p-piperidinyl, i.e., the N of the piperidinyl is para to the carbon bonded to the rest of the molecule) and pyrrolidinyl, and in one example said heterocycloalkyl moiety is piperidinyl, wherein said substituted moiety (14) is substituted with one or more substituents (e.g., 1 to 3) selected from the group consisting of –SO_2R^{13}, and wherein R^{13} is selected from the group consisting of:

(a) alkyl (e.g., C_1 to C_8 alkyl, and in one example, methyl),

(b) aryl (e.g., phenyl),

(c) substituted aryl (e.g., substitued phenyl, such as, for example, chlorophenyl, fluorophenyl, and cyanophenyl),

(d) heteroaryl (e.g., pyrazinyl and pyridyl),

(e) substituted heteroaryl (e.g., substituted pyrazinyl and substituted pyridyl),

(f) –(alkylene)$_{1-6}$heterocylcoalkyl (e.g., -(alkylene)$_{1-2}$heterocycloalkyl), such as, for example, -$(CH_2)_2$-morpholinyl and –CH_2-piperidinyl,

(g) –(alkylene)$_{1-6}$-heteroaryl (e.g., -(alkylene)$_{1-2}$heteroaryl), such as, for example, –CH_2-pyridyl,

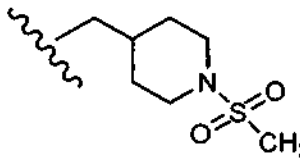
(h) –C(O)R^{11} (wherein R^{11} is as previously defined),

(i) –C(O)aryl (e.g., -C(O)phenyl), and

(j) –(alkylene)$_{1-6}$N$(R^{12})_2$ (e.g., -(alkylene)$_{1-3}$N$(R^{12})_2$), such as, for example, -$(CH_2)_3$N$(R^{12})_2$, and

(k) wherein said substituted groups (c) and (e) of said moiety (14) are independently substituted with one or more (e.g., 1 to 3) substitutents independently selected from the group consisting of: (i) halo (e.g., Cl, F, Br, and I), (ii) –OH, (iii) –OR^{11}, (iv) –CF_3, (v) –$S(O)_2R^{11}$ (e.g., -$S(O)_2CH_3$), and (vi) –$S(O)_2N(R^{12})_2$, and

(l) wherein an example of said moiety (14) is:



;

(15) –(alkylene)$_{1-6}$-bicyclic bridged cycloalkyl (e.g., –(alkylene)$_{1-6}$-adamantyl);

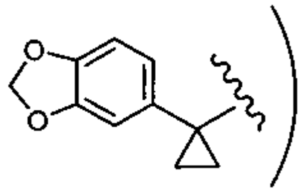
(16) –(alkylene)$_{1-6}$-bicyclic bridged heterocycloalkyl;

(17) –(alkylene)$_{1-6}$-bicyclic bridged spirocycloalkyl;

(18) –(alkylene)$_{1-6}$-bicyclic bridged spiroheterocycloalkyl;

(19) –(alkylene)$_{1-6}$-(substituted heteroaryl) wherein the substituents on said heteroaryl are independently selected from the group consisting of: -C(O)N$(R^{12})_2$ wherein each R^{12} is independently selected, -NHS$(O)_2$-alkyl (e.g., -NHS$(O)_2$-(C_{1-6}alkyl), such as, for example, -NHS$(O)_2$-CH_3), and –(alkylene)$_{1-6}$-NHS$(O)_2$-alkyl (e.g., –(alkylene)$_{1-6}$-NHS$(O)_2$-(C_{1-6}alkyl), such as, for example, –(alkylene)$_{1-6}$-NHS$(O)_2$-CH_3);

(20) –cycloalkyl-benzodioxolyl (e.g.,



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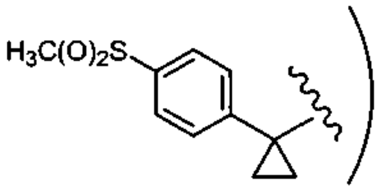
(21) –cycloalkyl-(substituted aryl) wherein the substituents are independently selected from the group consisting of methylene dioxy and $-S(O)_2CH_3$ (examples of said –cycloalkyl-(substituted aryl) include but are not limited to:



;

(22) alkyl (e.g., (C_{1-6} alkyl, such as for example, methyl)

(23) cycloalkyl;

(24) alkyl;

(25) hydroxyl substituted alkyl;

R^8 and R^9 are each independently selected from the group consisting of: H, alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl), cycloalkyl (e.g., C_3 to C_6 cycloalkyl), C(O)OH, $-C(O)OR^{11}$, substituted alkyl (e.g., substituted C_1 to C_6 alkyl) and substituted cycloalkyl (e.g., C_3 to C_6 cycloalkyl);

R^{10} is selected from the group consisting of:

(a) aryl (e.g., phenyl),

(b) substituted aryl (e.g., substituted phenyl),

(c) heteroaryl (e.g., pyrazinyl, pyridyl (such as, for example, o-pyridyl, m-pyridyl and p-pyridyl), thiophenyl (i.e., thienyl), pyrazolyl (e.g., 3-pyrazolyl and 4-pyrazolyl), thiazolyl, oxazolyl, and pyrimidinyl),

(d) substituted heteroaryl (e.g., substitued pyrazinyl, substituted pyridyl (such as, for example, substituted o-pyridyl, substituted m-pyridyl and substituted p-pyridyl), substituted thiophenyl (i.e., substituted thienyl), substituted pyrazolyl (e.g., substituted 3-pyrazolyl and substituted 4-pyrazolyl), substituted thiazolyl, substituted oxazolyl, and substituted pyrimidinyl),

(e) benzoheteroaryl,

(f) heterocycloalkyl,

(g) substituted heterocycloalkyl,

(h) –piperidinyl-$S(O)_2$-(alkyl substituted heteroaryl),

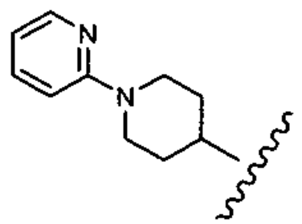
(i) –piperidinyl-$S(O)_2$-aryl-heteroaryl),

(j) –piperidinyl-C(O)-pyridyl,

(k) –piperidinyl-C(O)-alkyl,

(l) –piperidinyl-(substituted aryl) wherein said substituents are independently selected from the groups consisting of: halo (e.g., F) and CN,

(m) –piperidinyl-pyridyl (such as, for example,



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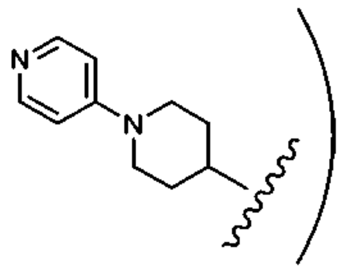
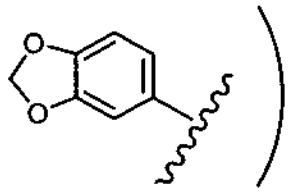


,

(n) benzodioxolyl (i.e.,

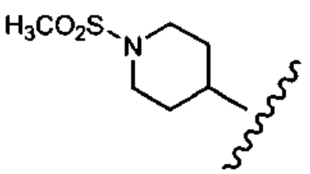


,

(o) –heteroaryl-NH-cycloalkylalkyl (e.g., -pyridyl-NH-cycloalkylalkyl), and

(p) –heteroaryl-NH-cycloalkyl (e.g., e.g., -pyridyl-NH-cycloalkyl), and

(wherein examples of said R^{10} groups (g) – (j) include but are not limited to:



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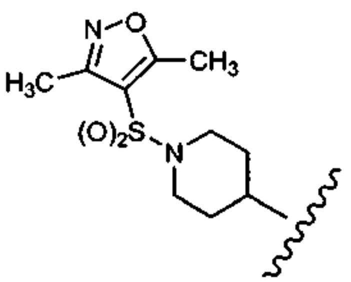

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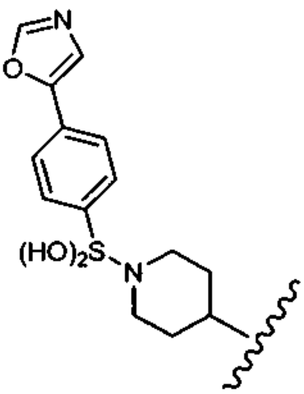

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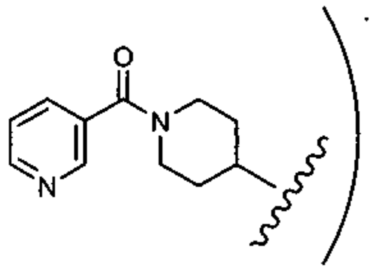


;

wherein said substituted R^8, R^9 and R^{10} groups are substituted with one or more (e.g., 1 to 3) substitutents independently selected from the group consisting of:

(a) halo (e.g., Cl, F, Br, and I),

(b) –OH,

(c) -OR^{11},

(d) -CF_3,

(e) heterocycloalkyl (e.g., pyrrolidinyl, piperazinyl, morpholinyl, and piperidinyl),

(f) substituted heterocycloalkyl (e.g., substituted pyrrolidinyl (e.g., pyrrolidinonyl, i.e., pyrrolidinyl substituted with =O), substituted piperazinyl, substituted morpholinyl, and substituted piperidinyl),

(g) heteroaryl (e.g., pyrazolyl and thiazolyl),

(h) substituted heteroaryl (e.g., substituted pyrazolyl and substituted thiazolyl),

(i) aryl (e.g., phenyl),

(j) substituted aryl (e.g., substituted phenyl),

(k) –$C(O)OR^{11}$,

(l) –$N(R^{12})_2$ (e.g.,–NHR^{12}),

(m) alkyl (e.g., C_1 to C_6 alkyl),

(n) cycloalkyl (e.g., C_3 to C_6 alkyl),

(o) –SO_2R^{11},

(p) –N(alkyl)-cycloalkyl,

(q) –C(O)OH,

(r) benzoheteroaryl (e.g., benzoimidazolyl), and

(s) substituted benzoheteroaryl (e.g., substituted benzoimidazolyl), such as for example substituted benzoheteroaryl substituted with 1 to 2 alkyl groups (e.g., methyl), such as for example, alkyl (e.g., methyl) substituted benzoimidazolyl, and wherein said substituted groups (f), (h), and (j) are independently substituted with one or more substitutents (e.g., 1 to 3 substituents) independently selected from the group consisting of:

(i) halo (e.g., Cl, F, Br, and I),

(ii) –OH,

(iii) $-OR^{11}$,

(iv) $-CF_3$,

(v) $-S(O)_2R^{11}$ (e.g., $-S(O)_2CH_3$),

(vi) $-S(O)_2N(R^{12})_2$,

(vii) =O,

(viii) substituted benzoheteroaryl (e.g., substituted benzoimidazolyl) substituted with 1 to 3 groups independently selected from the group consisting of: C_1 to C_6 alkyl, cycloalkyl, $-NH_2$, $-NH(C_1$ to C_6 alkyl), and $-N(C_1$ to C_6 alkyl$)_2$ wherein each alkyl is independently selected,

(ix) alkyl (e.g., C_{1-6}alkyl, such as, for example, methyl),

(x) CN,

(xi) cycloalkyl, and

(xii) –C(O)-morpholinyl,

(xiii) amino,

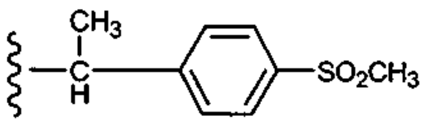
(xiv) alkylamino (e.g., $-NHCH_3$), and

(xv) and dialkylamino;

R^{11} is alkyl (e.g., C_1 to C_6 alkyl);

each R^{12} is independently selected from the group consisting of H, alkyl (e.g., C_1 to C_6 alkyl), and hydroxyl substituted alkyl,

wherein an example of said moiety (12) is:



;

each R^{14} is independently selected from the group consisting of: H, $-C(O)-(CH_2)_{1-2}$-aryl (e.g., $-C(O)-(CH_2)_{1-2}$-phenyl, such as, for example, $-C(O)-CH_2$-phenyl), substituted aryl (e.g., substituted phenyl), and benzodioxyl, and wherein said substituted aryl (e.g., substituted phenyl) is substituted with one or more (e.g., 1 to 3) substituents independently selected from the group consisting of: halo (e.g., Cl. F, and Br), -OH, -OR^{11} (wherein R^{11} is as previously described), -CN, -CF_3, alkyl (e.g., C_1 to C_6 alkyl), -NH_2 and –NO_2;

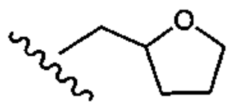
R^{15} and R^{16} are each independently selected from the group consisting of:

(1) hydroxyl substituted alkyl, such as hydroxyl substituted C_1 to C_8 (preferably C_1 to C_6) alkyl, such as, for example, -$CH(CH_2OH)CH_2CH(CH_3)_2$, –CH_2OH, -$(CH_2)_2OH$, -$CH(CH_2OH)CH_2CH_3$, -$CH(CH_2OH)C(CH_3)_3$, -$CH(CH_3)CH_2OH$, and –$CH(CH_2OH)_2$, and when the carbon atom bound to the N has a chiral center then the S-isomer of said chiral center is preferred,

(2) alkyl (e.g., C_1 to C_6 alkyl) such as, for example, i-propyl, methyl, ethyl, -$CH_2CH(CH_3)_2$, and -$(CH_2)_2CH(CH_3)_2$,

(3) –SO_2R^{11}, e.g., -SO_2CH_3,

(4) unsubstituted –(alkylene)$_{1-6}$-R^{17} (e.g., unsubstituted –(alkylene)$_{1-2}$-R^{17}) wherein R^{17} is selected from the group consisting of: (a) heterocycloalkyl (e.g., tetrahydrofuran, piperidinyl, pyrrolidinyl, piperazinyl, and morpholinyl), (b) heteroaryl (e.g., pyridyl), and (c) cycloalkyl (e.g., C_3 to C_6 cycloalkyl), and wherein in one example said alkylene-R^{17} moiety is: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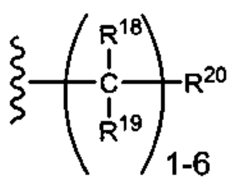
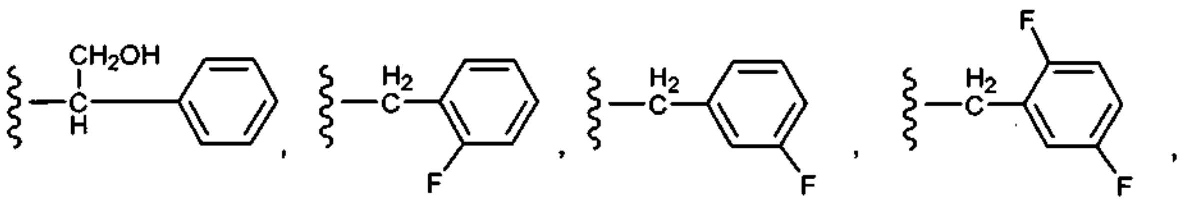
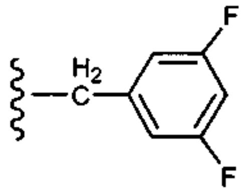
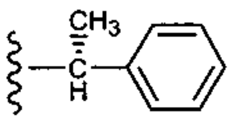
(5)


, and

wherein examples of said moiety (5) include, but are not limited to:

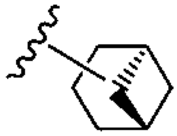


 and  ;

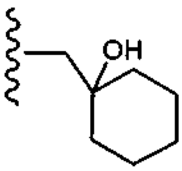
(6) –C(O)-alkyl (e.g., -C(O)(C_1 to C_6)alkyl) such as –C(O)CH_3,

(7) substituted alkyl wherein said substituents are selected from the group consisting of –OR^{11}, such as, for example, -$(CHR^{12})_{1-6}$-OR^{11} (wherein R^{12} is as previously defined), and also, for example, -$(CHR^{12})_{1-3}$-OR^{11}, wherein examples of said substituted alkyl moiety (7) include, but are not limited to: -$CH(CH_3)CH_2OCH_3$, and -$(CH_2)_3OCH_3$,

(8) saturated bicyclic rings, such as, for example,

 ,

(9) hydroxyl substituted –(alkylene)$_{1-6}$-cycloalkyl, such as, for example, (e.g., substituted –(alkylene)$_{1-6}$- C_3-C_6 cycloalkyl, such as, for example, substituted –(alkylene)$_{1-2}$- C_3-C_6 cycloalkyl), such as for example,

 ,

(10) H,

(11) heterocycloalkyl substituted with heterocycloalkyl,

(12) cycloalkyl (e.g., C_{3-8} cycloalkyl, such as, for example, cyclohexyl), and

(13) cycloalkyl (e.g., C_{3-8} cycloalkyl, such as, for example, cyclohexyl) substituted with 1 to 2 –OH groups,

(14) –(alkylene)$_{1-6}$-aryl (e.g., –(alkylene)$_{1-6}$-phenyl),

(15) –(alkylene)$_{1-6}$-aryl (e.g., –(alkylene)$_{1-6}$-phenyl) substituted with 1 to 2 substituents independently selected from the group consisting –OH and alkylamino (e.g., -$NHCH_3$),

(16) –(alkylene)$_{1-6}$-heteroaryl substituted with 1 to 2 substituents independently selected from the group consisting –OH and alkylamino (e.g., -$NHCH_3$);

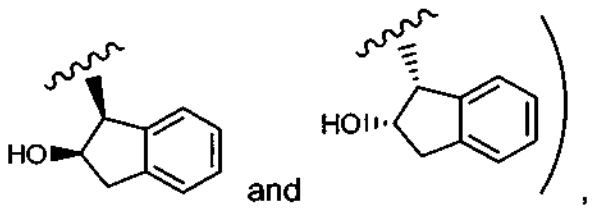
(17) heterocycloalkyl,

(18) substituted heterocycloalkyl, such as heterocycloalkyl substituted with alkyl, such as heterocycloalkyl substituted with methyl,

(19) –(alkylene)$_{1-6}$-heterocycloalkyl wherein said alkylene moiety is substituted with hydroxyl,

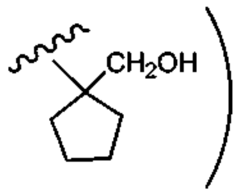
(20) –(alkylene)$_{1-6}$-C(O)OH,

(21) fused hydroxyl substituted benzocycloalkyl (e.g.,

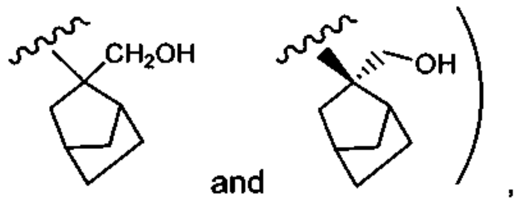


(22) fused hydroxyl substituted arylheteroaryl (e.g., fused hydroxyl substituted benzoheteroaryl),

(23) hydroxyl-(alkylene)$_{1-6}$-cycloalkyl (e.g.,



(24) hydroxyl-(alkylene)$_{1-6}$-bridged cycloalkyl (e.g.,



(25) hydroxyl-(alkylene)$_{1-6}$-spirocycloalkyl,

(26) hydroxyl-(alkylene)$_{1-6}$-bridged heterocycloalkyl,

(27) hydroxyl-(alkylene)$_{1-6}$-spiroheterocycloalkyl, and

(28) heterocycloalkyl;

each R^{18} and each R^{19} is independently selected from the group consisting of: H, alkyl (e.g., C_1 to C_6 alkyl, such as, for example, methyl), and hydroxyalkyl- (e.g., $-CH_2OH$), and when the carbon atom to which R^{18}, R^{19}, and R^{20} are bound is a chiral center then the S-isomer of said chiral center is preferred;

R^{20} is selected from the group consisting of:

(a) aryl (e.g., phenyl),

(b) substituted aryl (e.g., substituted phenyl),

(c) heteroaryl (e.g., pyridyl),

(d) benzo fused heteroaryl (e.g., indolyl),

(e) –(alkylene)$_{1-6}$-heteroaryl (e.g., –(alkylene)$_{1-2}$-heteroaryl), such as, for example, -CH_2imidazolyl,

(f) –(alkylene)$_{1-6}$aryl,

(g) –(alkylene)$_{1-6}$aryl substituted with –OH,

(h) benzoheteroaryl-(alkylene)$_{1-6}$-,

(i) cycloalkylalkyl,

(j) cycloalkyl (e.g., hexyl),

(k) heterocycloalkyl,

(l) –(alkylene)$_{1-6}$aryl substituted with halo (e.g., Cl, F, and Br) such as p-chlorobenzyl,

(m) -(alkylene)$_{1-6}$-S-alkyl (e.g., -$(CH_2)_2$-S-CH_3),

(n) -(alkylene)$_{1-6}$-O-alkyl,

(o) -(alkylene)$_{1-6}$-N-alkyl,

(p) -(alkylene)$_{1-6}$-cycloalkyl,

and wherein said substituted aryl (e.g., substituted phenyl) is substituted with one or more substituents (e.g., 1 to 3) independently selected from the group consisting of: halo (e.g., Cl. F, and Br), -OH, -OR^{11}, -CN, -CF_3, alkyl (e.g., C_1 to C_6 alkyl), -NH_2 and –NO_2;

R^{21} is selected from the group consisting of:

(1) heterocycloalkyl (e.g., morpholinyl, piperidinyl, piperazinyl, and pyrrolidinyl),

(2) benzo fused cycloalkyl (i.e., a benzene ring fused to a cycloalkyl ring wherein there are two adjacent carbon atoms common to the benzene ring and the cycloalkyl ring), such as, for example, indanyl,

(3) cycloalkyl (e.g., C_3 to C_6 cycloalkyl), such as, for example, cyclopentyl,

(4) multicyclic cycloalkyl ring, such as, for example, adamantly, and

(5) substituted heterocycloalkyl (e.g., substituted morpholinyl, substituted piperidinyl, substituted piperazinyl, and substituted pyrrolidinyl) substituted with one or more (e.g., 1 to 3) substituents independently selected from the group consisting of: (a) hydroxyl substituted alkyl (e.g., -CH_2OH), (b) -OH, (c) -(alkylene)$_{1-6}$C(O)O-(alkyl)$_{1-6}$ (such as, for example, -$CH_2C(O)OCH_2CH_3$), (d) aryl (e.g., phenyl), and (e) substituted aryl (e.g., substituted phenyl) wherein said

substituted aryl (e.g., said substituted phenyl) is substituted with one or more (e.g., 1-3) substitutents independently selected from the group consisting of: halo (e.g., F, Cl, and Br), and

(6) heterocycloalkyl substituted with 1 to 3 substituents selected from the group consisting of: amino, alkylamino, dialkylamino, and –C(O)alkyl,

(7) heterocycloalkyl (e.g., a 4 to 7 membered heterocycloalkyl ring, examples include but are not limited to piperazinyl, piperidinyl, and pyrrolidinyl),

(8) hydroxy substituted heterocycloalkyl (e.g., a 4 to 7 membered hydroxyl substituted heterocycloalkyl ring, examples include but are not limited to hydroxyl substituted piperazinyl, hydroxyl substituted piperidinyl, and hydroxyl substituted pyrrolidinyl), and

(9) –OH.

In one embodiment of the invention K is CH.

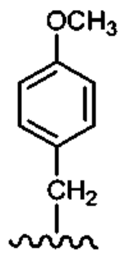
In one embodiment of the invention K is N.

In one embodiment of the invention K is -C(alkyl)- (e.g., -C(CH_3)-).

In one embodiment of the invention K is -C(aryl)- (e.g., -C(phenyl)-).

In one embodiment of the invention K is -C(halo)- (e.g., -C(F)-, or –C(Cl)- or –C(Br)-).

In one embodiment of the invention K is -C(R^C)- wherein R^C is selected from the group consisting of:



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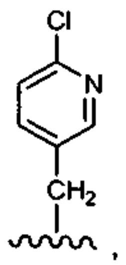

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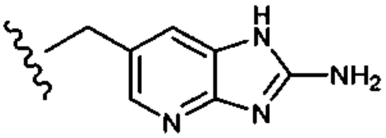
Examples of R^1 and R^2 groups include, but are not limited to:



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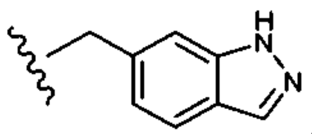

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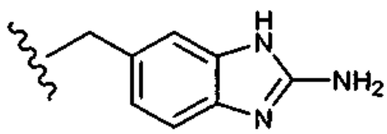

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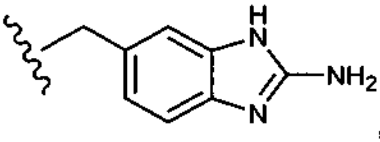
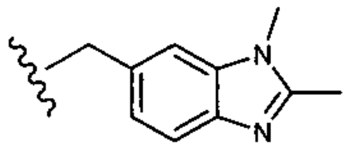
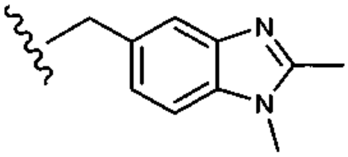
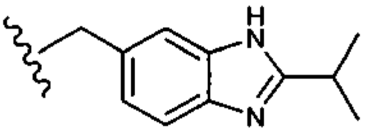
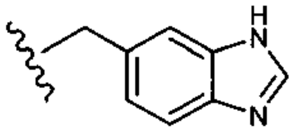
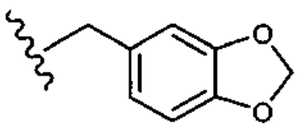
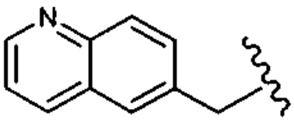
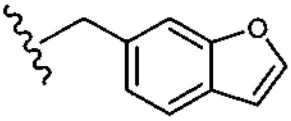
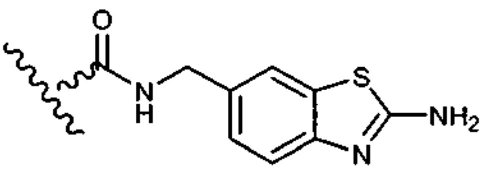
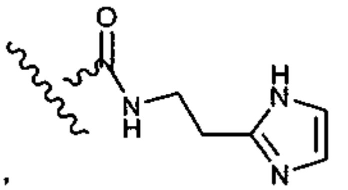
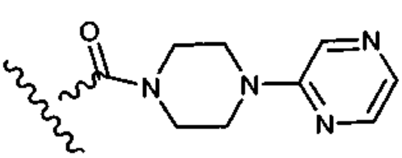
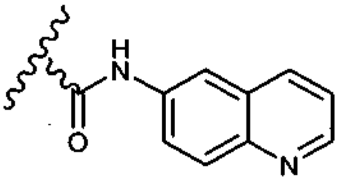
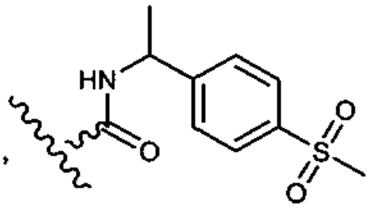
, , ,

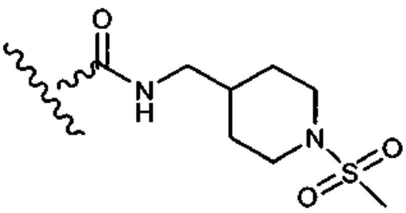
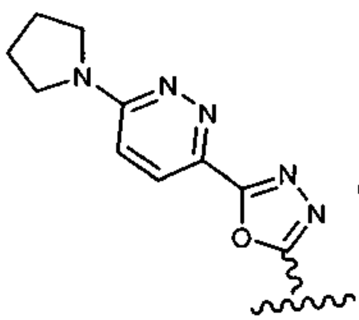
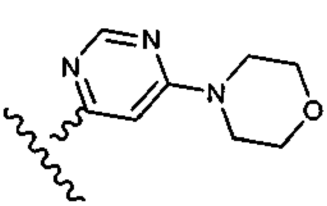
, , ,

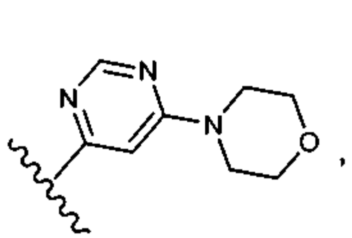
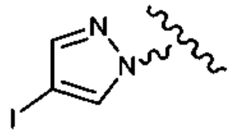
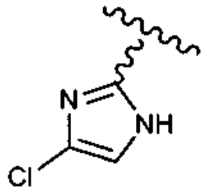
 and .

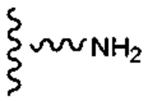
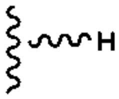
Examples of Q^A groups include, but are not limited to:

, ,

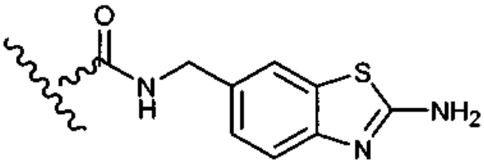
, , ,

, , ,

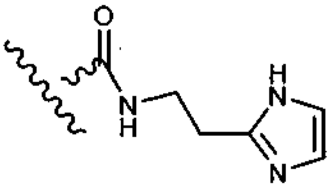
, , ,

 and .

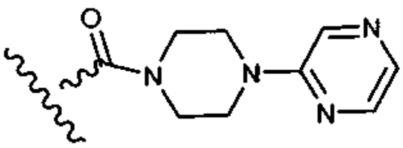
In one embodiment of this invention Q^A is:

.

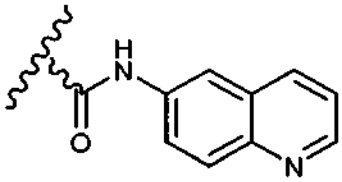
In another embodiment of this invention Q^A is:

.

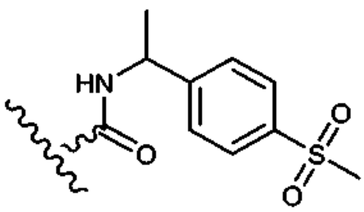
In another embodiment of this invention Q^A is:

.

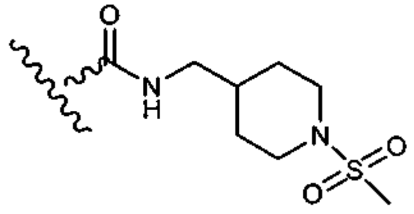
In another embodiment of this invention Q^A is:

, .

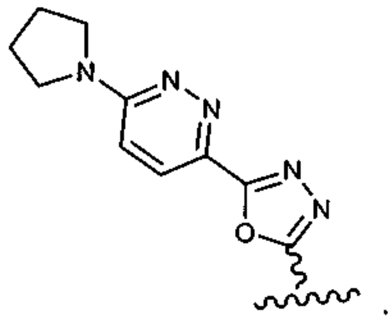
In another embodiment of this invention Q^A is:

.

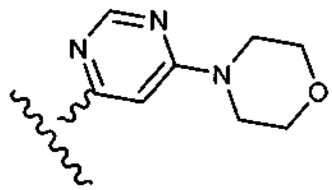
In another embodiment of this invention Q^A is:



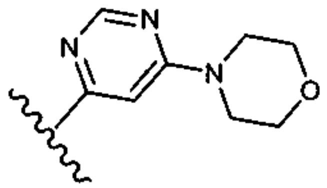
In another embodiment of this invention Q^A is:



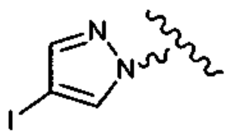
In another embodiment of this invention Q^A is:



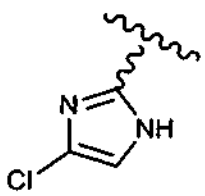
In another embodiment of this invention Q^A is:



In another embodiment of this invention Q^A is:



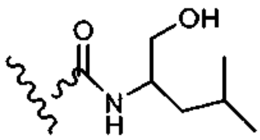
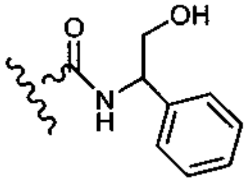
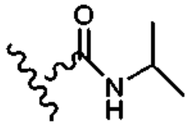
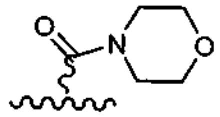
In another embodiment of this invention Q^A is:

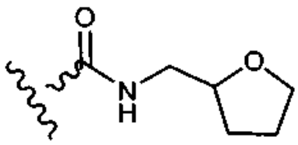
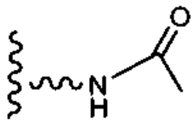
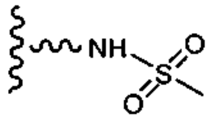


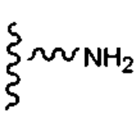
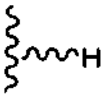
In another embodiment of this invention Q^A is $-NH_2$.

In another embodiment of this invention Q^A is H.

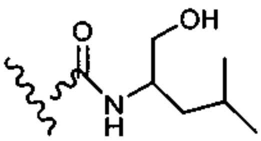
Examples of Q^B include, but are not limited to:

 ,  ,  ,  ,

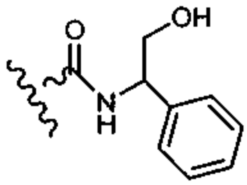
 ,  ,  ,  ,

 and  .

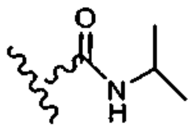
In one embodiment of this invention Q^B is:

 .

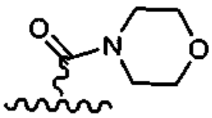
In another embodiment of this invention Q^B is:

 .

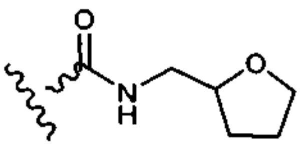
In another embodiment of this invention Q^B is:

 .

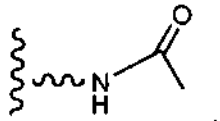
In another embodiment of this invention Q^B is

 .

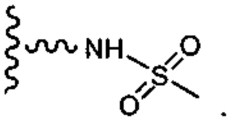
In another embodiment of this invention Q^B is:

 .

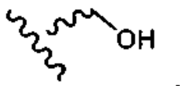
In another embodiment of this invention Q^B is:



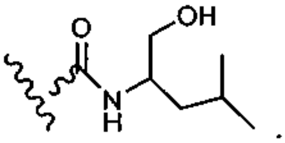
In another embodiment of this invention Q^B is:



In another embodiment of this invention Q^B is:

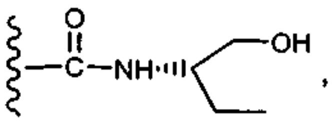
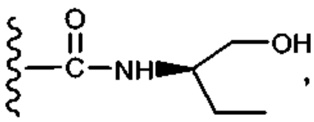
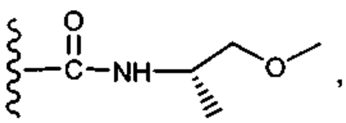


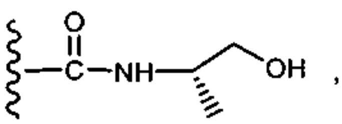
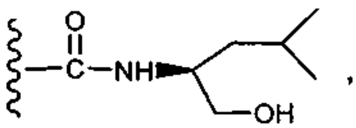
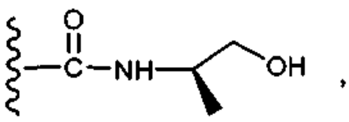
In another embodiment of this invention Q^B is $-NH_2$.

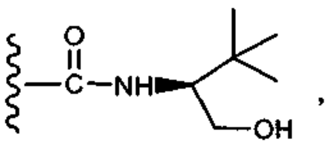
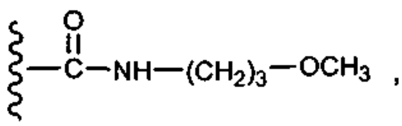
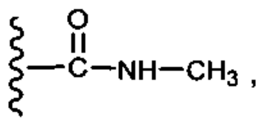


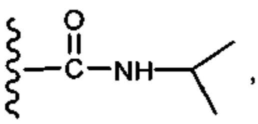
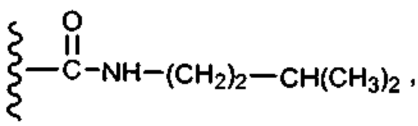
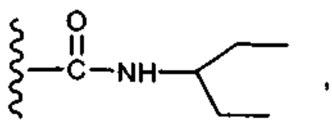
In another embodiment of this invention Q^B is H.

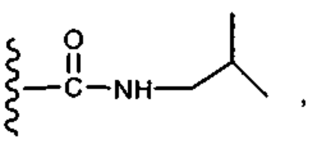
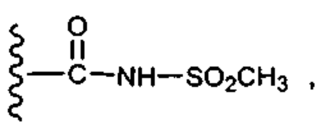
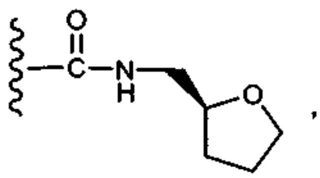
Examples of Q^B also include, but are not limited to:

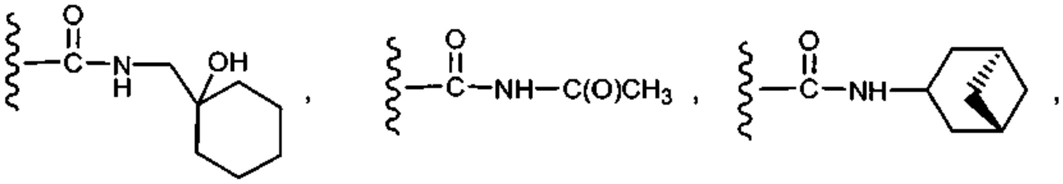




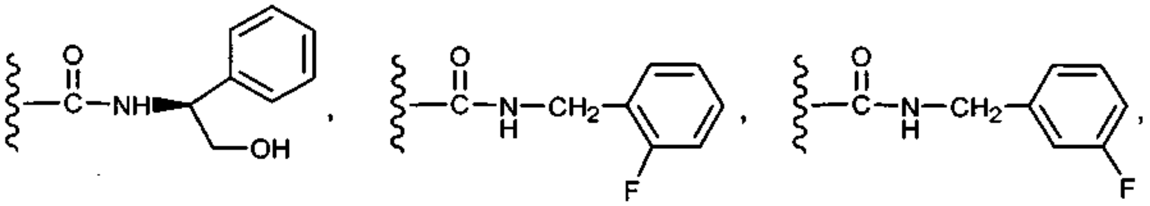




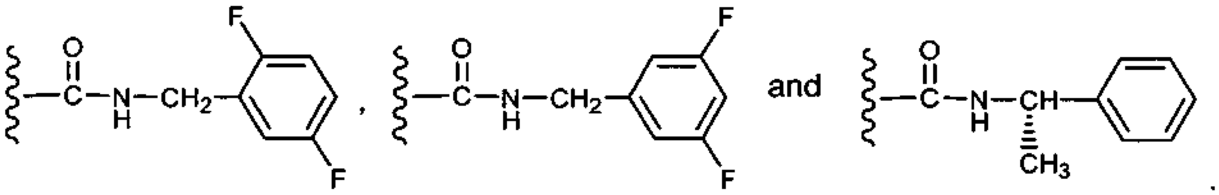




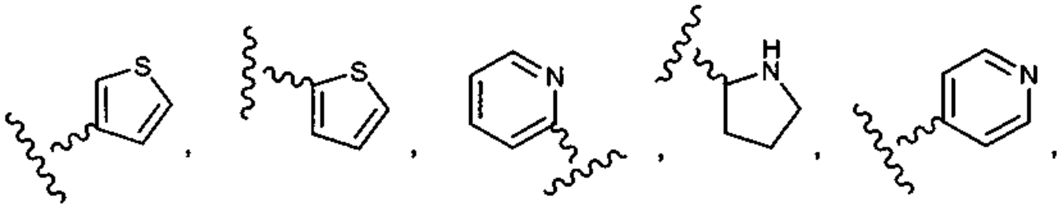




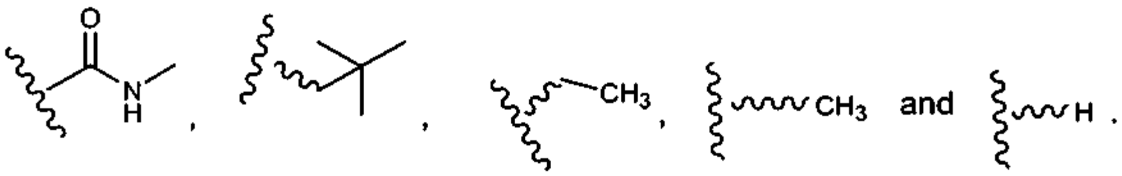




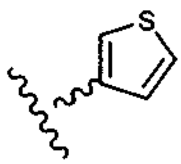


Examples of Q^C include, but are not limited to:

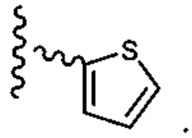




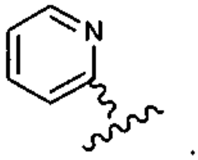
In one embodiment of this invention Q^C is:



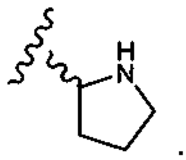
In another embodiment of this invention Q^C is:



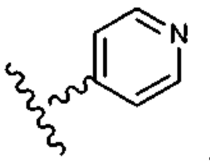
In another embodiment of this invention Q^C is:



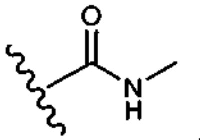
In another embodiment of this invention Q^C is:



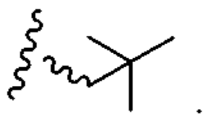
In another embodiment of this invention Q^C is:



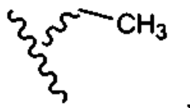
In another embodiment of this invention Q^C is:



In another embodiment of this invention Q^C is:



In another embodiment of this invention Q^C is:



In another embodiment of this invention Q^C is $-CH_3$.

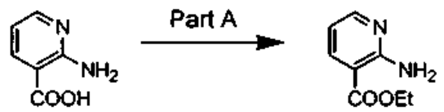
In another embodiment of this invention Q^C is H.

The compounds of the invention can be made according to the processes described below. The compounds of this invention are also exemplified in the examples below, which examples should not be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

In the tables below EMW stands for Exact Molecular Weght. The LC-MS data for the EMW was obtained using an Agilent 1100 Series LC/MSD (quadrupole, API-ES (Atmospheric Pressure Interface Electrospray)) with a capillary voltage set to 3500 V and running in positive mode.

In the tables below, the retention time is for the purification via reverse phase chromatography which was accomplished using a C18 reverse phase column with a gradient of 0.1 % trifluoroacetic acid in water to 95:5 acetonitrile:water at a flow rate of 20 mL/min. Samples were collected using a UV (Gilson, 254 nm) or mass spectra (Agilent 1100 Series LC/MSD model SL) signal.

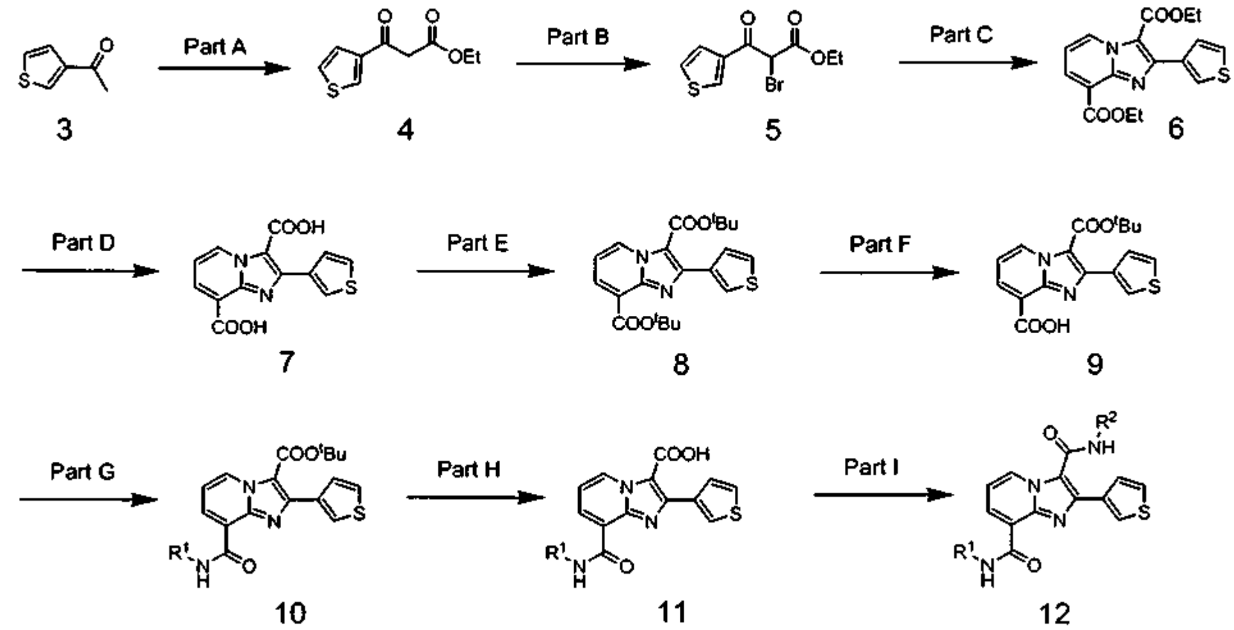
Example 1A



1 2

To a solution of 2-aminonicotinic acid (1) (5g, 36 mmol) in ethanol (100 mL) was added concentrated sulfuric acid (10 mL). The reaction mixture was heated at reflux for 16 hours, and then cooled to room temperature. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, water was added and the crude basified to p*H* 8.0 with 1*N* NaOH. The product was extracted into ethyl acetate (x2), dried over magnesium sulfate and concentrated to afford compound 2 (6.0 g, 100 % yield) as a white crystalline solid. HPLC-MS t_R = 0.41 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_{10}N_2O_2$ 166.1, observed LCMS m/z 167.1 (M+H).

Example 1B



(wherein R^1 is remaining moiety of the Q^A group, and R^2 is the remaining moiety of the Q^B group in formula 1.0)

Part A:

To a mixture containing sodium hydride (18.6 g, 465 mmol) (60% dispersion in mineral oil, washed with hexane to remove mineral oil) and diethyl carbonate (36 mL, 296 mmol) in toluene (200 mL) at reflux, was added 3-acetylthiophene (3) (18.7 g, 148 mmol) in toluene (60 mL) *via* dropwise addition using an addition funnel. After the addition was complete, the mixture was refluxed for an additional 30 minutes. The reaction mixture was then cooled to room temperature and placed in an ice bath, quenched with acetic acid (42 mL), water, and extracted with toluene. The combined toluene extracts were washed with water (x4), and brine, dried over magnesium sulfate and concentrated to give a brown oil which was subjected to vacuum distillation. The fraction boiling at approximately 140^{0}C afforded compound 4 (13.8 g, 47 % yield).

Part B:

Bromine (2.7 mL, 53 mmol) in chloroform (40 mL) was added dropwise *via* an addition funnel to a stirred solution of compound 4 (10.5 g, 53 mmol) in chloroform (60 mL) at 0 ^{0}C (ice-bath). After the addition was complete the solution was stirred at room temperature for 20 minutes, during which time the course of the reaction was monitored by Thin Layer Chromatography (dichloromethane as solvent). Bromine (0.3 mL) was added to ensure complete conversion of starting material. The reaction mixture was then washed with saturated $NaHCO_3$ solution, water, and brine, dried over magnesium sulfate and concentrated to afford compound 5 (14.4 g , 97 % yield) as a yellow oil.

Part C:

A mixture of compound 5 (31.6 g, 114 mmol) and compound 2 (18.9 g, 114 mmol) in ethanol (400 mL) was heated at reflux for 60 hours. After cooling to room temperature, some of the ethanol was removed under reduced pressure, and upon addition of ether a solid formed which was collected by filtration, and confirmed by 1H NMR to be the hydrobromide salt of compound 2 (12 g). The ether filtrate was concentrated to afford a residue which when dissolved in 10 % HCl solution, separated out unreacted compound 5 as an oil. The oil was removed, and the acidic aqueous solution was neutralized with saturated $NaHCO_3$ to p*H* 7.0, and then extracted with dichloromethane (x2). The organics were concentrated to afford compound 6 (20 g, 51 %) as a white solid.

Part D:

A mixture of compound 6 (20 g, 58 mmol) and LiOH (1*M*, 180 mL, 180 mmol) in THF (250 mL) was stirred at room temperature for 16 hours. The volatiles were removed *in vacuo*, water was added and the aqueous acidified to p*H* 2.0 with 1*N* HCl. The resulting precipitate was collected by filtration, washed with water, and dried to afford compound 7 (9.7 g, 58 % yield).

Part E:

A mixture of compound 7 (1.05 g, 3.6 mmol) and 2-*tert*-butyl-1,3-diisopropylisourea (6 g, 29.2 mmol) in dichloromethane (60 mL) was heated at reflux for 6 hours and then cooled to room temperature. LC-MS analysis of the reaction indicated that the reaction was complete. The resulting precipitate was removed by filtration and washed through with dichloromethane. The filtrate was concentrated, and purified by flash column chromatography (SiO_2, dichloromethane / ethyl acetate – 100:1) to afford compound 8 as a white foam (1.22 g, 88 % yield). HPLC-MS t_R =

2.42 min ($UV_{254\ nm}$); mass calculated for formula C21H24N2O4S 400.1, observed LCMS m/z 401.2 (M+H).

Part F:

A mixture of compound 8 (1.22 g, 3.05 mmol) and LiOH (1*M*, 3.05 mL, 3.05 mmol) in THF (20 mL) and water (10 mL) was stirred at room temperature for 16 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, water was added and the aqueous acidified to p*H* 2.0 with 1*N* HCl. The product was extracted with ethyl acetate (x2), dried over magnesium sulfate and concentrated to afford compound 9 (0.85 g, 81 % yield). HPLC-MS t_R = 1.47 min ($UV_{254\ nm}$); mass calculated for formula C17H16N2O4S 344.1, observed LCMS m/z 345.1 (M+H).

Part G:

To a mixture of compound 9 (50 mg, 0.145 mmol) and *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (66 mg, 0.174 mmol) in DMF (2 mL) was added amine building block (1.2 equivalents) and diisopropylamine (3 equivalents). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, ethyl acetate was added, and washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded compound 10 as a white solid (50 – 90 % yield).

Part H:

To a solution of compound 10 (0.1 mmol) in dioxane (1 mL) was added 4 *N* HCl in dioxane (2 mL) and water (0.2 mL). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, acetonitrile was added, concentrated and dried to afford compound 11 (100 % yield).

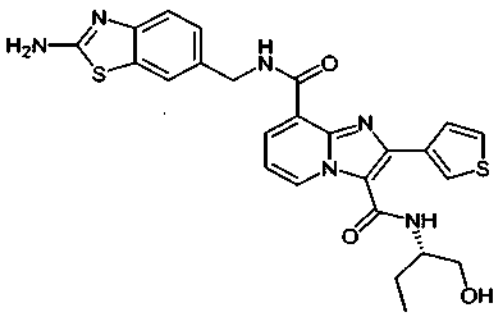
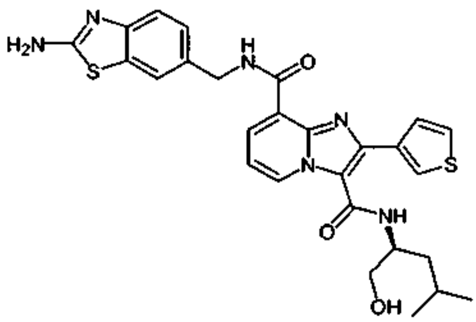
Part I:

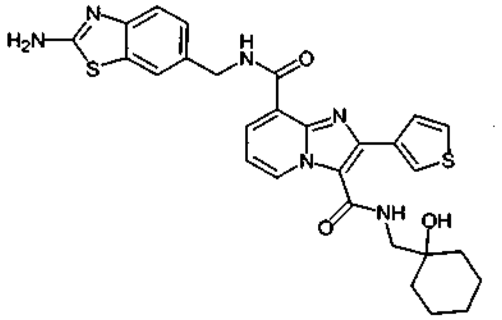
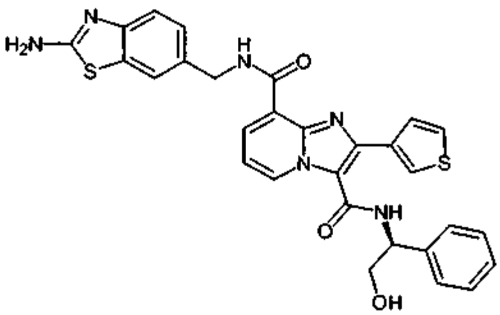
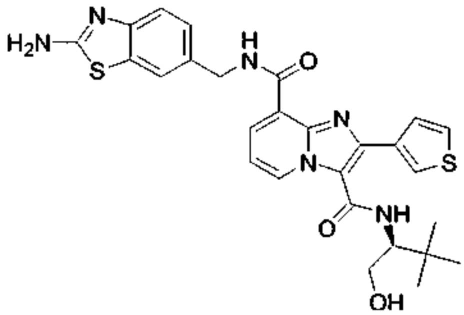
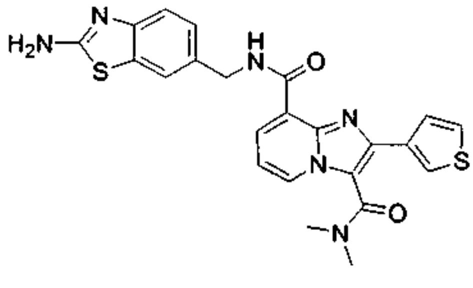
To a mixture of compound 11 (0.1 mmol) and HATU (46 mg, 0.12 mmol) in DMF (2 mL) was added amine building block (1.2 equivalents) and diisopropylamine

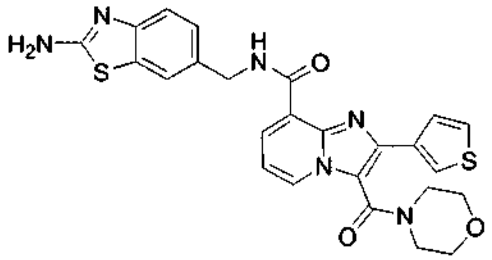
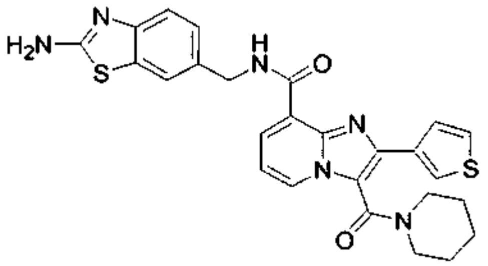
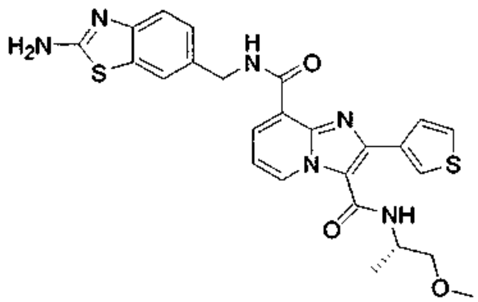
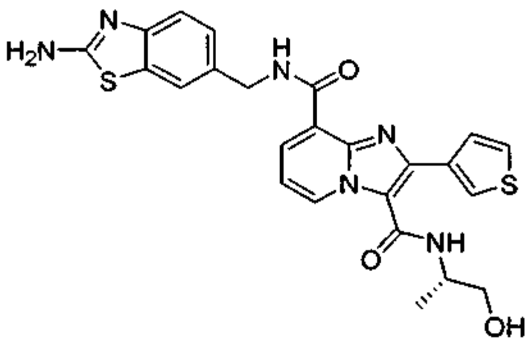
(3 equivalents). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, ethyl acetate was added, and washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. Purification by Prep-LC and conversion to a hydrochlorde salt afforded compounds as white solids.

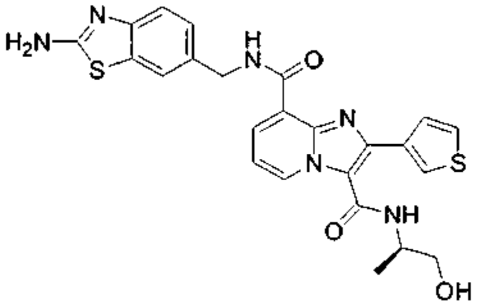
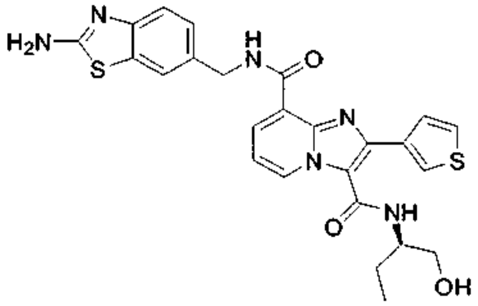
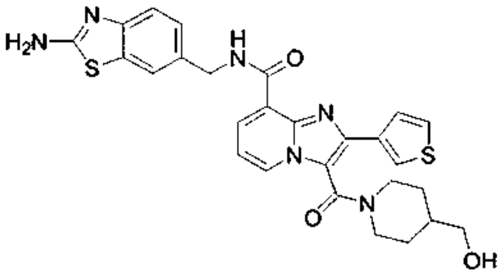
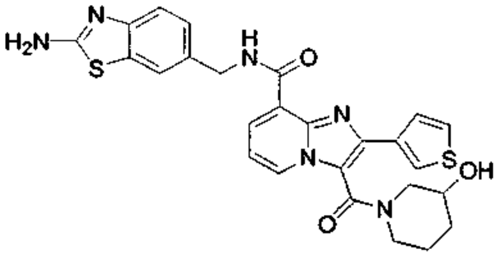
Using procedures similar to those in Example 1B, the compounds in Table 1 were synthesized.

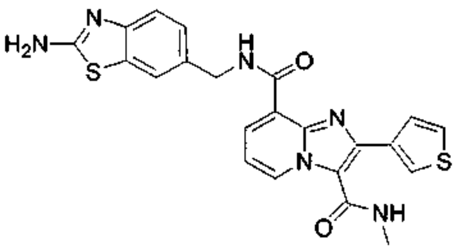
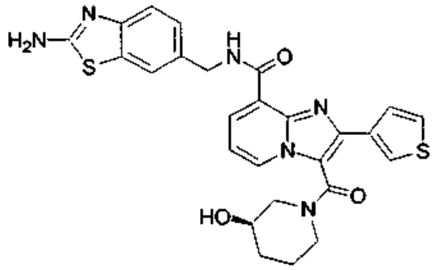
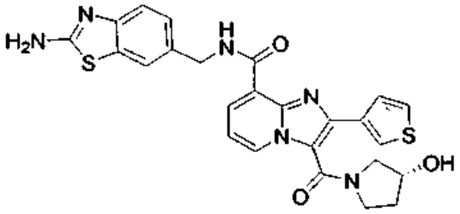
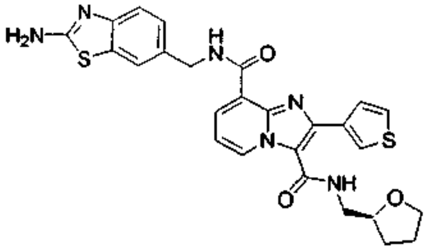
Table 1

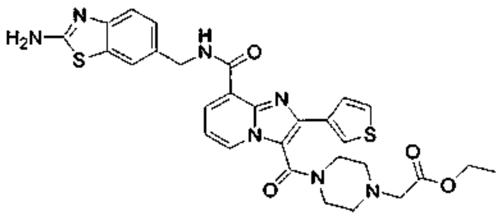
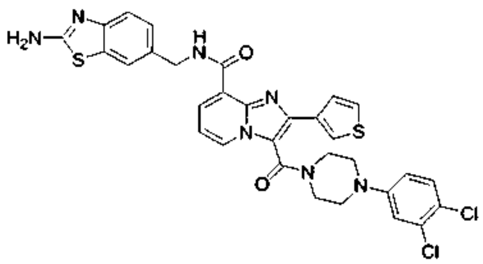
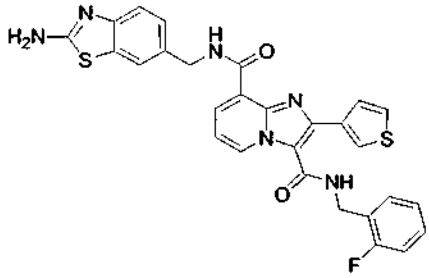
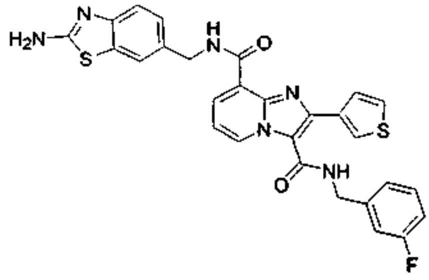
Compd No.	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
13		520.1	521.1	3.28
14		548.2	549.2	3.70

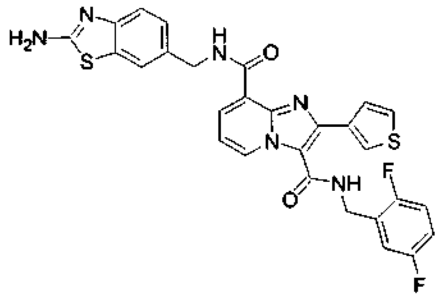
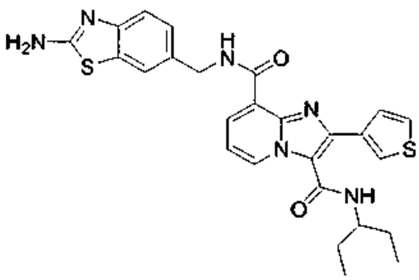
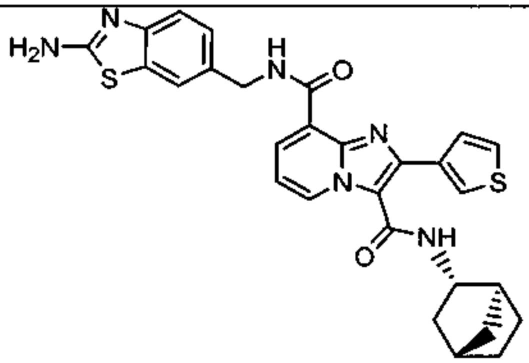
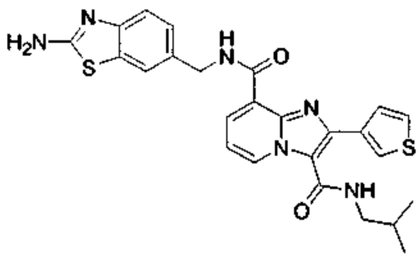
15		560.2	561.2	3.76
16		568.1	569.1	3.60
17		548.2	549.1	3.78
18		476.11	477.1	3.137

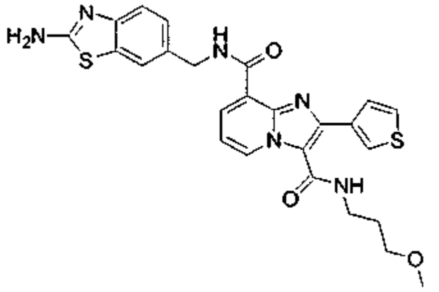
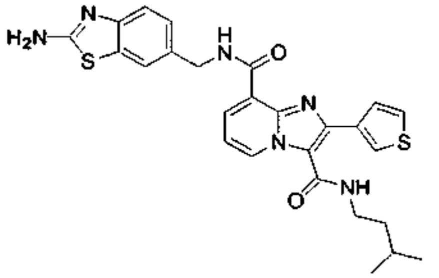
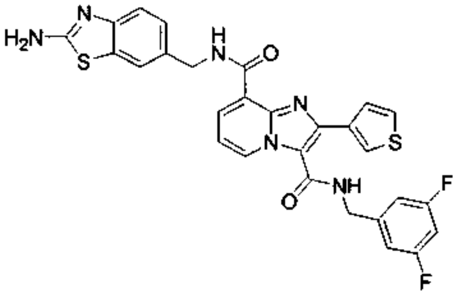
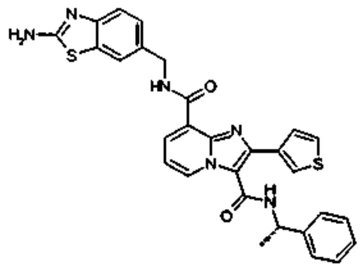
19		518.12	519.1	3.150
20		516.14	517.2	3.748
21		520.14	521.0	3.555
22		506.12	507.1	2.939

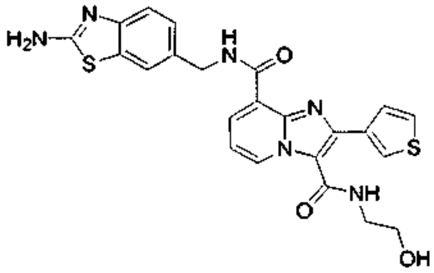
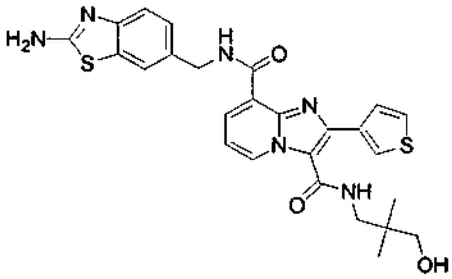
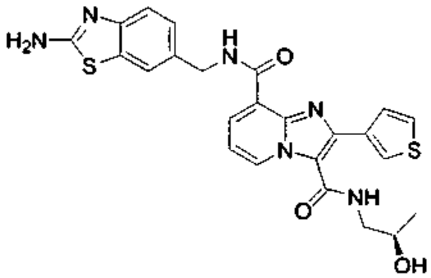
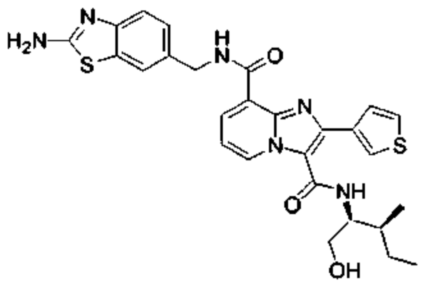
23		506.12	507.1	2.933
24		520.14	521.1	3.166
25		546.15	547.2	2.994
26		532.14	533.0	3.031

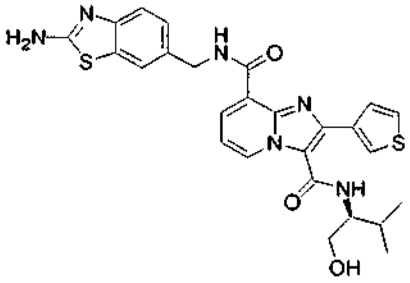
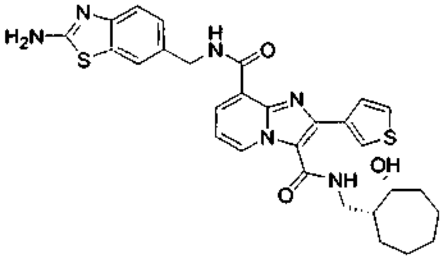
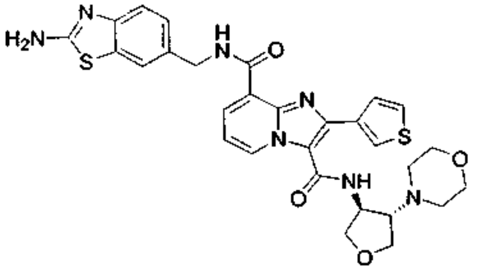
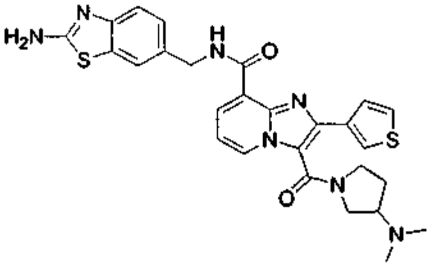
27		462.09	463.0	3.008
28		532.14	533.1	3.020
29		518.12	519.1	2.800
30		532.14	533.0	3.497

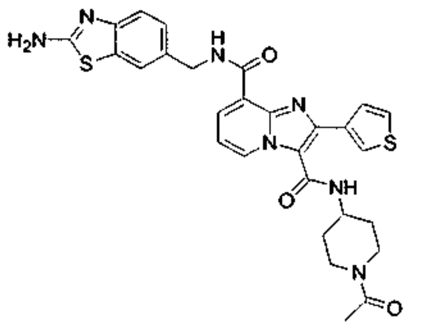
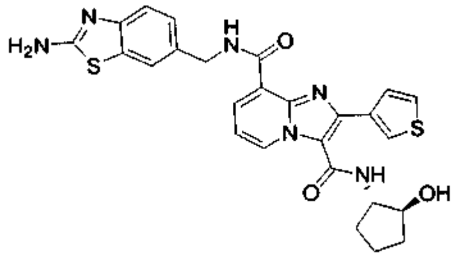
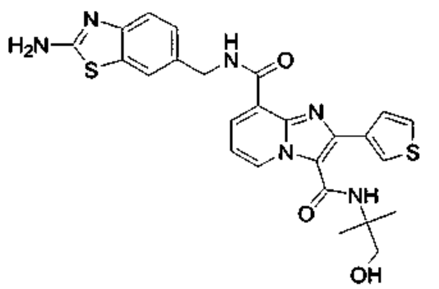
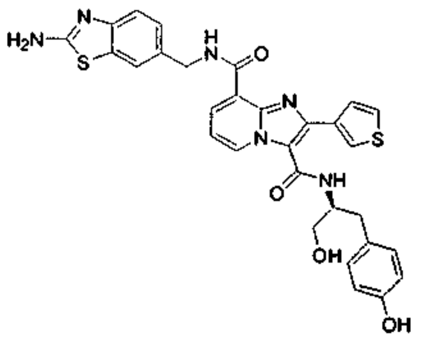
31		603.17	604.2	2.776
32		661.09	662.0	4.867
33		556.12	557.0	4.050
34		556.12	557.0	4.071

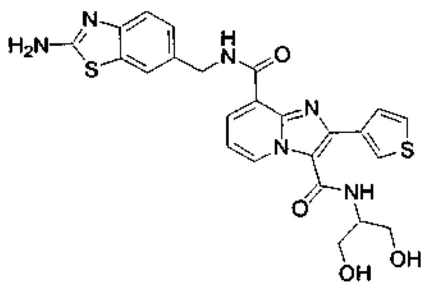
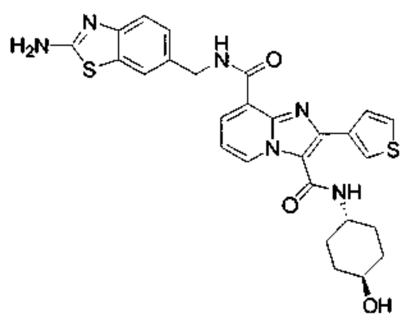
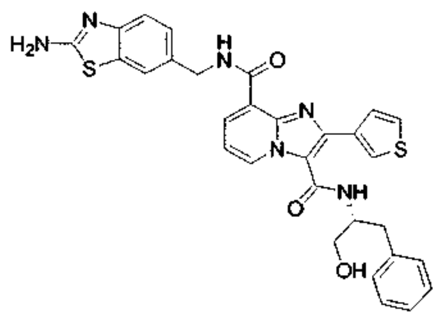
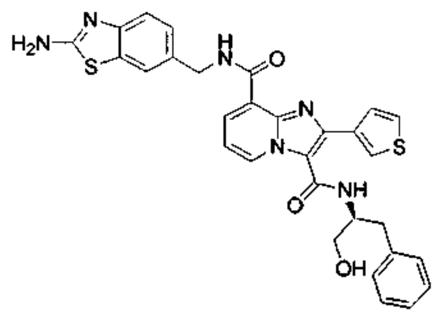
35		574.11	575.0	4.101
36		518.16	519.1	4.141
37		542.16	543.1	4.350
38		504.14	505.1	3.931

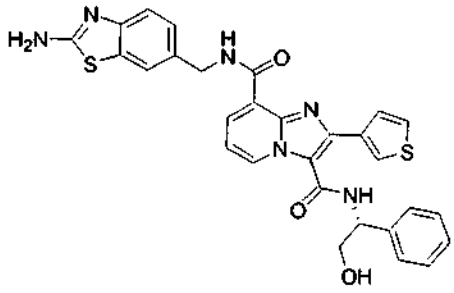
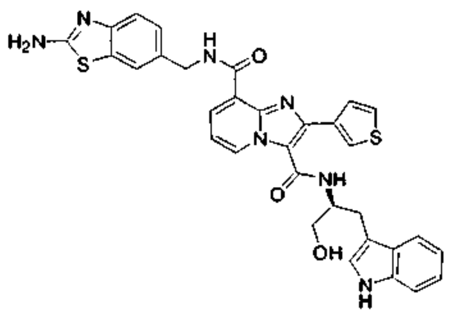
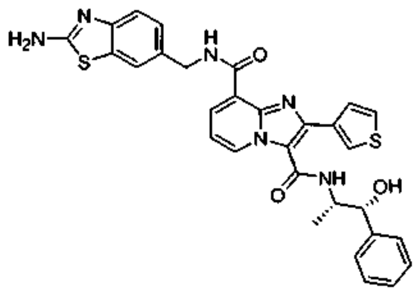
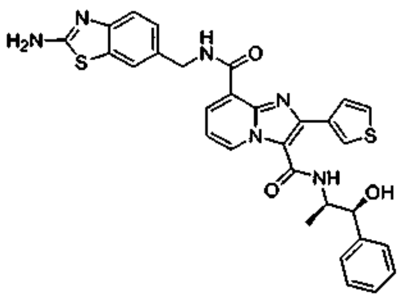
39		520.14	521.0	3.377
40		518.16	519.1	4.232
41		574.11	575.0	4.191
42		552.14	553.1	4.156

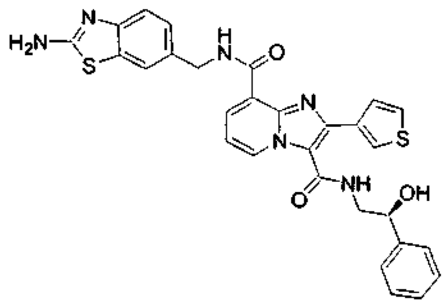
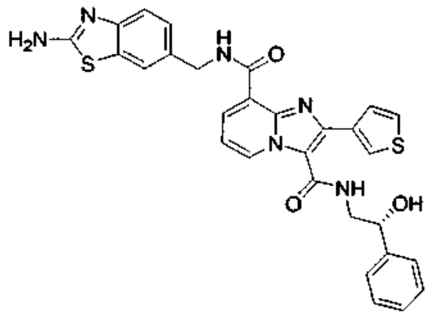
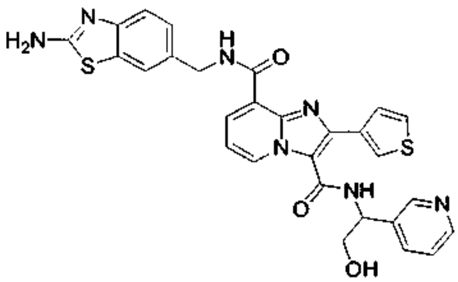
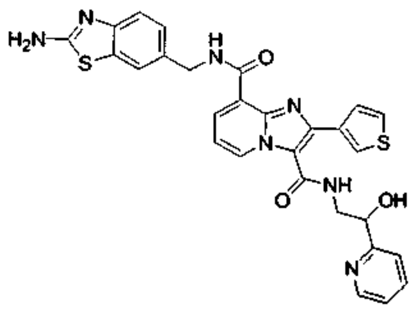
43		492.10	493.0	2.735
44		534.15	535.1	3.333
45		506.12	507.1	2.926
46		548.17	549.1	3.713

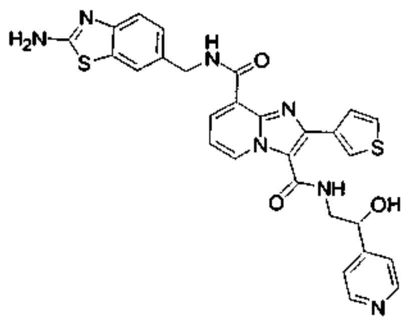
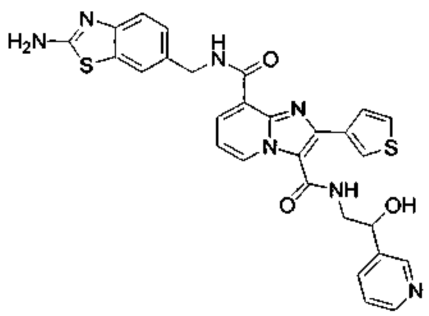
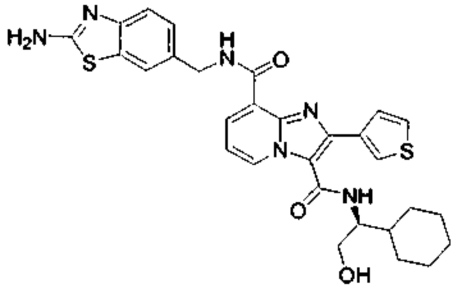
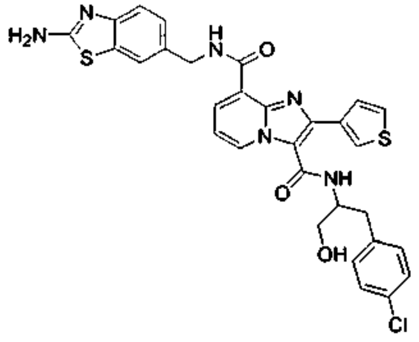
47		534.15	535.2	3.436
48		574.18	575.0	3.902
49		603.17	604.2	2.453
50		545.17	546.1	2.371

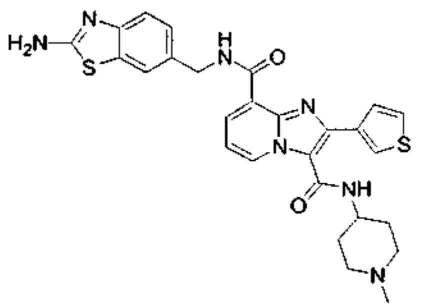
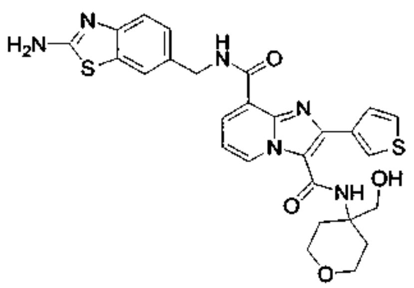
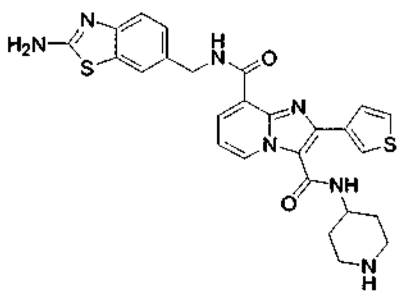
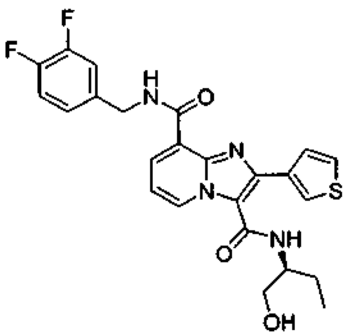
51		573.16	574.1	3.092
52		532.14	533.0	3.211
53		520.14	521.0	3.306
54		598.15	599.0	3.045

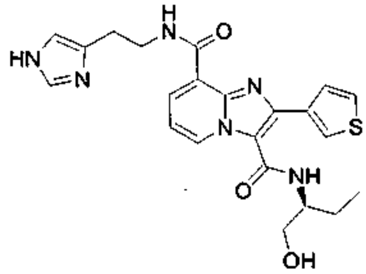
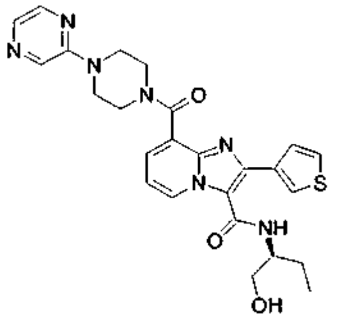
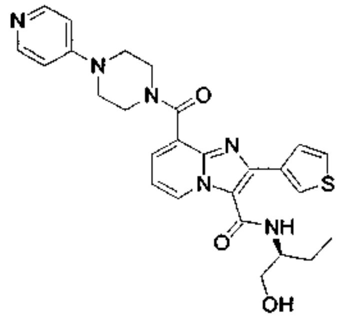
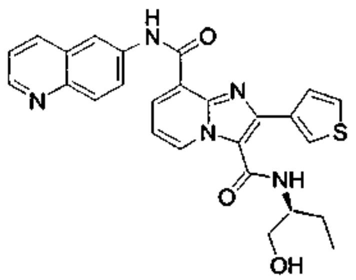
55		522.11	523.0	2.586
56		546.15	547.0	3.105
57		582.15	583.0	3.714
58		582.15	583.0	3.609

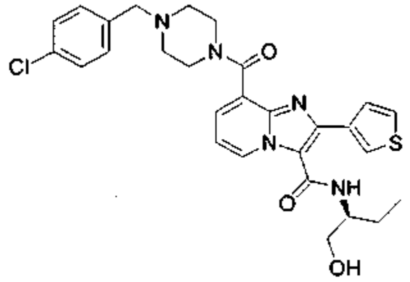
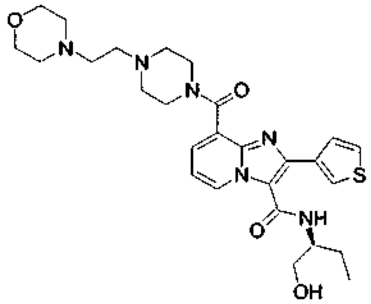
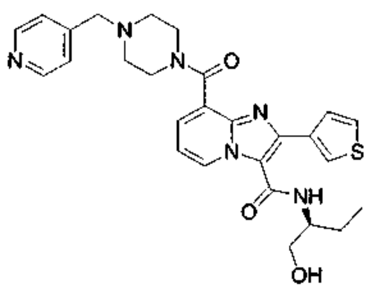
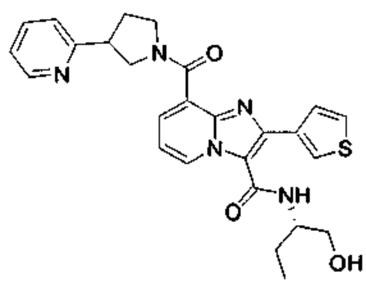
59		568.14	569.0	3.568
60		621.16	622.0	3.548
61		582.15	583.0	3.767
62		582.15	583.1	3.775

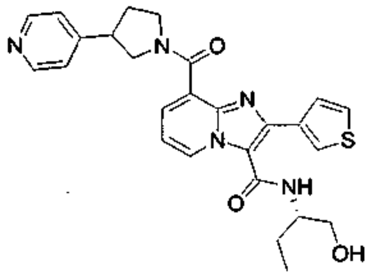
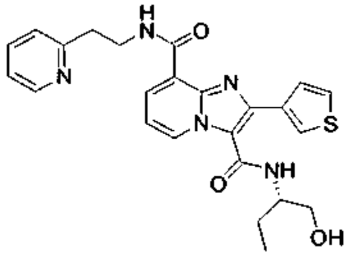
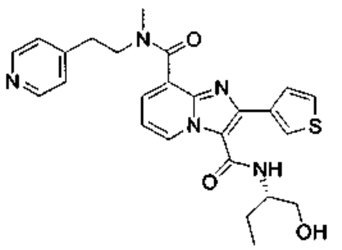
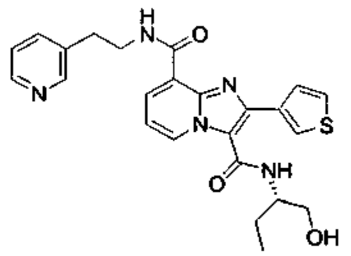
63		568.14	569.0	3.582
64		568.14	569.0	3.576
65		569.13	570.1	2.461
66		569.13	570.1	2.578

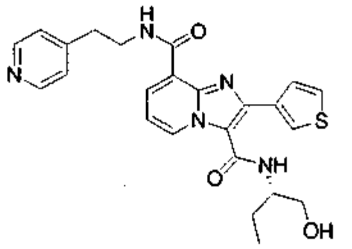
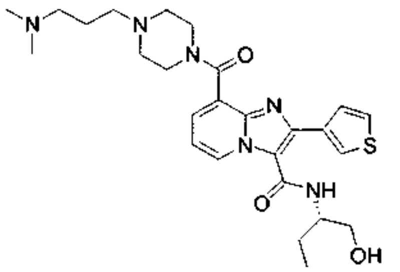
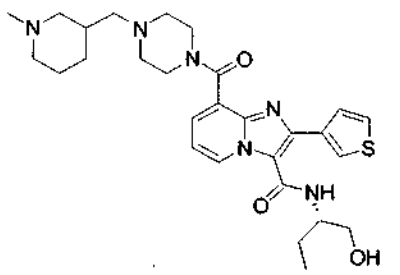
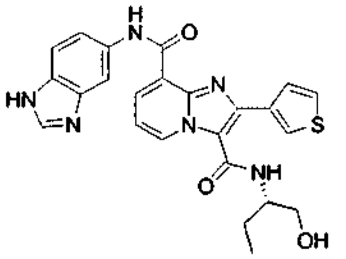
67		569.13	570.1	2.480
68		569.13	570.1	2.477
69		574.18	575.34	4.11
70		616.11	617.27	4.12

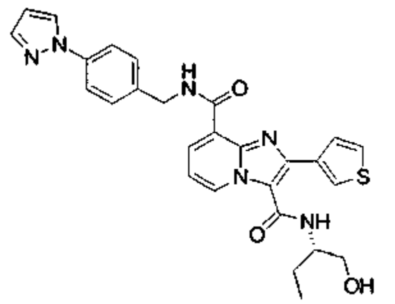
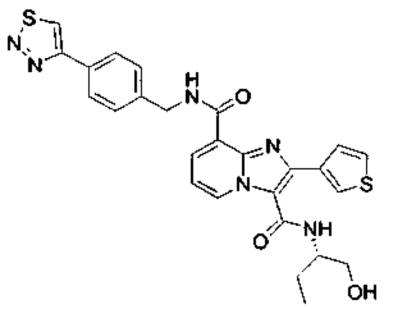
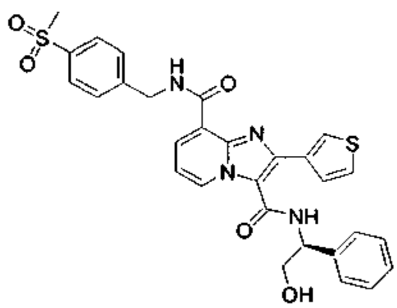
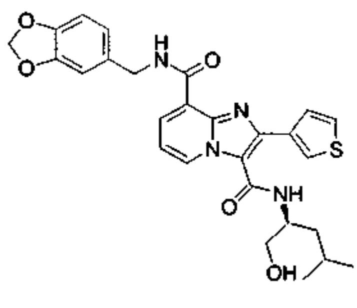
71		545.17	546.1	2.453
72		562.15	563.0	2.976
73		531.15	532.0	2.421
74		484.14	485.1	4.768

75		452.16	453.1	2.625
76		505.19	506.2	2.983
77		504.19	505.1	2.359
78		485.15	486.1	3.511

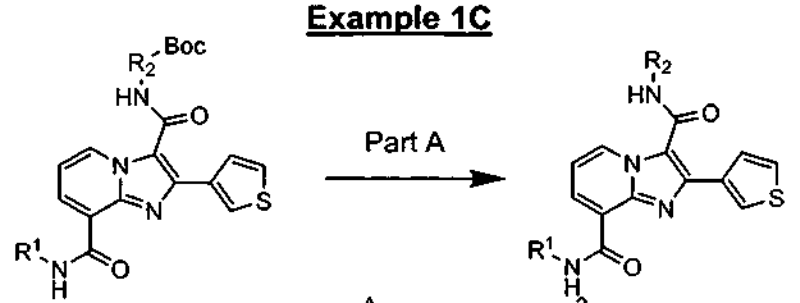
79		551.18	552.1	3.232
80		540.25	541.3	2.154
81		518.21	519.2	2.203
82		489.18	490.1	2.418

83		489.18	490.1	2.299
84		463.17	464.1	2.795
85		477.18	478.1	2.329
86		463.17	464.1	2.790

87		463.17	464.1	2.768
88		512.26	513.3	2.946
89		538.27	539.2	2.191
90		474.15	475.1	3.195

91		514.18	515.1	4.345
92		532.14	533.0	4.424
93		574.13	575.23	4.45
94		520.18	521.1	4.759

Example 1C

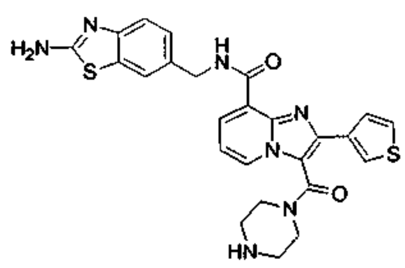


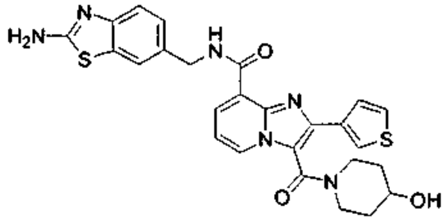
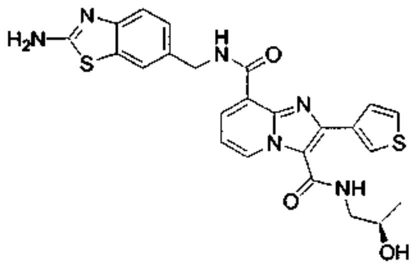
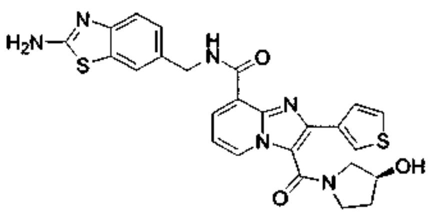
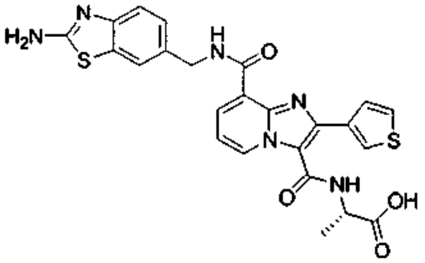
(wherein R^1 is remaining moiety of the Q^A group, and R^2 is the remaining moiety of the Q^B group in formula 1.0)

Part A:

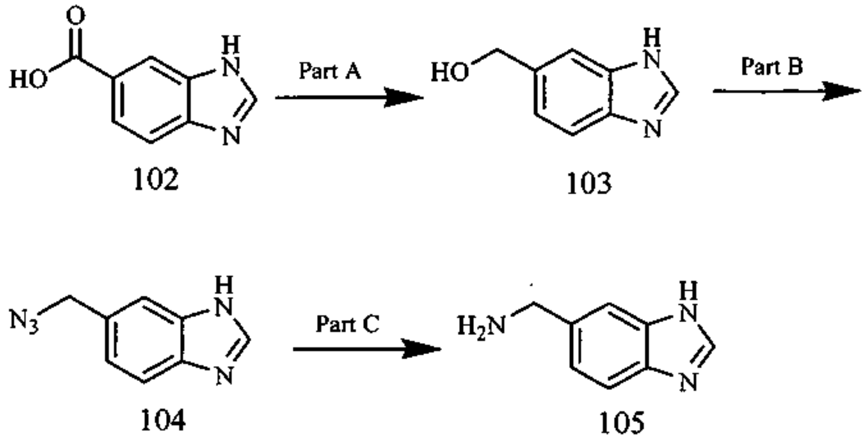
The crude compounds which were synthesized using methods described in **Example 1B**, were dissolved in dioxane (1mL), and a solution of 4 N HCl in dioxane (2mL) and water (0.2 mL) was added 0^0C. The reaction mixture was stirred at room temerature for 3 hours. LC-MS analysis of the reaction indicated that the hydrolysis was complete. The volatiles were removed in Vacuo, acetonitrile was added, concentrated and dried to afford the desired compounds. Purification by Prep. LC and conversion to the hydrochloride salt afforded compounds as white solids. The compounds prepared are in Table 2.

Table 2

Compd No.	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
97		517.14	518.0	2.406

98		532.14	533.0	2.871
99		506.12	507.1	2.940
100		518.12	519.1	2.799
101		520.10	521.0	3.002

Example 1D



102 103 104 105

Part A

Benzimidazole-5-carboxylic acid **102** (1 g, 6.17 mmol) in THF (100 mL) was added 1 N. LAH soln. (13 mL) at 0^{0}C. After the complete addition of LAH soln., reaction mixture was warmed to room temperature and then refluxed for 3 hours. The solution was cooled to 0^{0}C and then excess of LAH is quenched with satd. soln. of Na_2SO_4. Filtered and solid was washed with ethyl acetate. The solution was concentrated to obtain compound **103.**

Part B

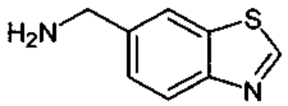
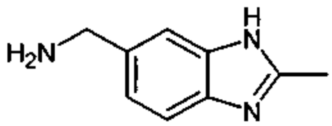
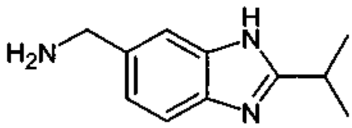
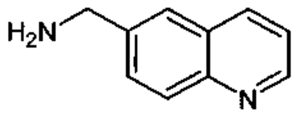
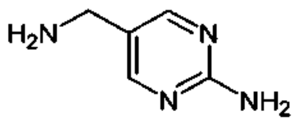
To a solution of 5-(hydroxymethyl)-benzimidazole **103** (0.74 g., 5 mmol) in THF was added DPPA (5.5 mmol) followed by DBU (1.2 mmol). The resulting solution was heated to reflux for 5 hours, cooled to room temperature, and concentrated. The residue was dissolved in ethyl acetate and washed with sodium $NaHCO_3$ solution, brine and dried over anhydrous sodium sulfate. Crude product **104**was purified on silica gel chromatography using Methanol-Chloroform solvents. HPLC-MS t_R = 0.855 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_7N_5$ 173.07, observed LCMS m/z 174.1 (M+H).

Part D

To a stirred solution of 5-(azidomethyl)benzimidazole **104** (0.519 g., 3 mmol) in THF (10 mL), was added Ph_3P (6 mmol) followed by water 0.20 mL and the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was dissolved in ethyl acetate and dry HCl gas was bubbled through the solution. The precipitate was filtered to obtain compound **105**. HPLC-MS t_R = 0.2 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_9N_3$ 147.08, observed LCMS m/z 148.1 (M+H).

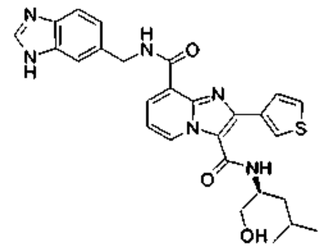
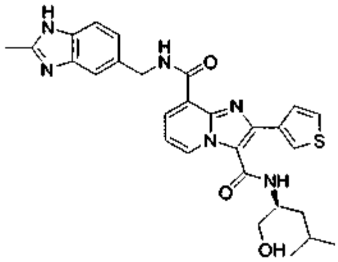
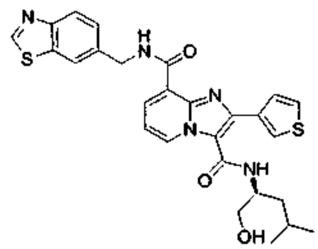
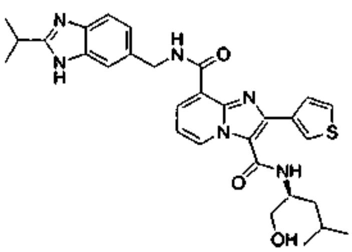
The building blocks in Table 3 are synthesized using above procedures.

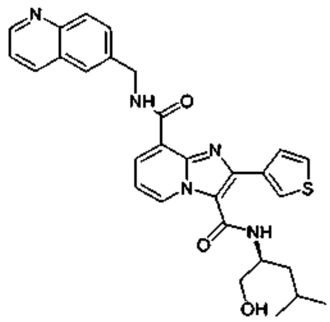
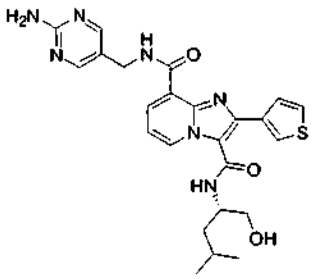
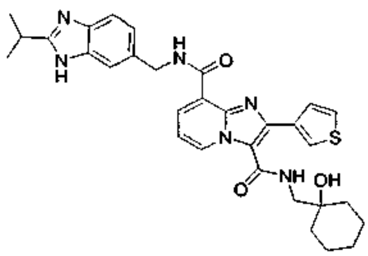
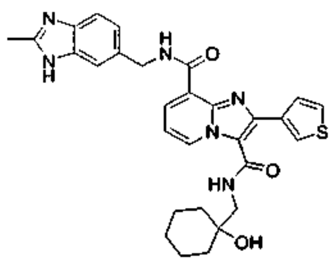
Table 3

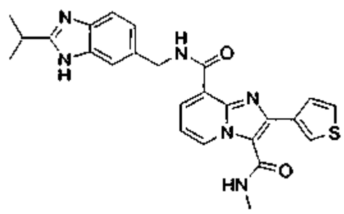
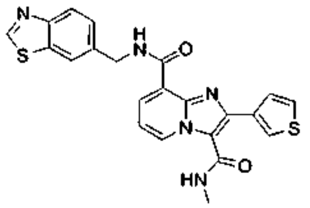
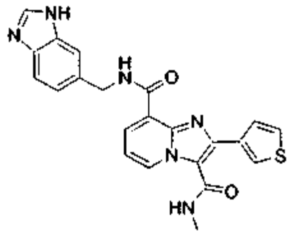
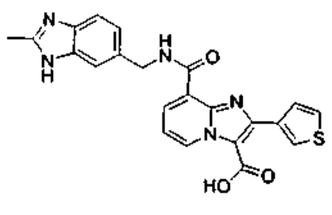
Compound #	Structure	MW calculated	M^++H observed
106		164.04	165.1
107		161.10	162.1
108		189.13	190.1
109		158.08	159.1
110		124.07	125.1

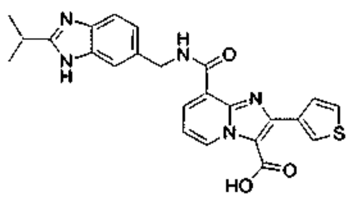
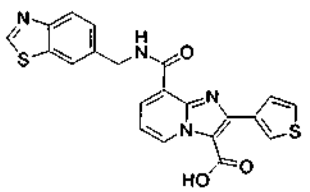
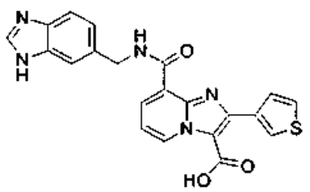
The compounds in Table 4 are synthesized using the building blocks from Table 3 and methods similar to those described in **Example 1B**. Compounds are purified on prep.LC either after the reaction part H or part I in **Example 1B** and converted to their hydrochloride salts.

Table 4

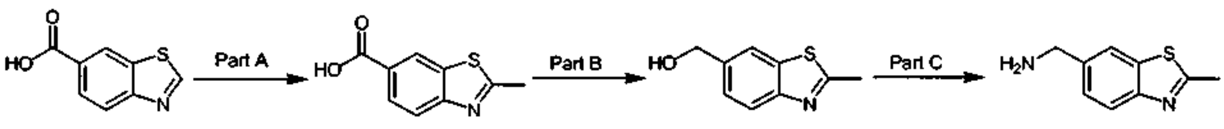
Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
111		516.19	517.1	3.478
112		530.21	531.38	3.75
113		533.16	534.1	4.614
114		558.24	559.32	3.89

115		527.20	528.29	3.61
116		493.19	494.36	3.48
117		570.24	571.33	3.94
118		542.21	543.27	3.69

119		472.17	473.21	3.14
120		447.08	448.16	4.22
121		430.12	431.21	2.8
122		431.11	432.18	2.92

123		459.14	460.2	3.17
124		434.05	435.11	4.28
125		417.09	418.17	2.83

Example 1E



126 127 128 129

Part A

Benzothiazole-6- carboxylic acid **126** (1.79 g., 10 mmol) was suspended in THF (200 mL) and cooled to -78^0 C. n BuLi (2.5 N soln. in Hexane, 10 mL) was added and the reaction mixture was stirred for an hour followed by the addition of MeI (1.2 equiv. 1.7 g.) in 10 mL of THF. The reaction mixture was warmed to room temperature and the stirring was continued overnight. Reaction was cooled to 0^{0}C and then quenced with brine solution and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to yield compound **127**. HPLC-MS t_R = 1.123 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_7NO_2S$ 193.02, observed LCMS m/z 193.9 (M+H).

Part B

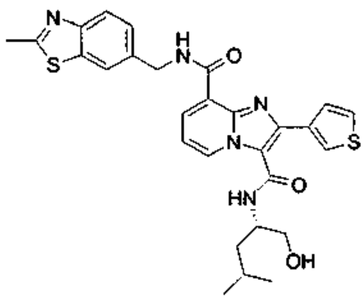
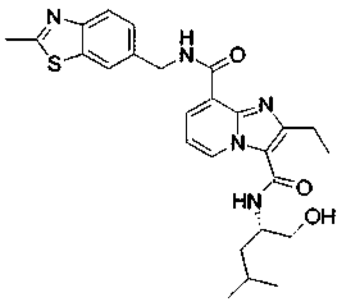
2-Methyl benzothiazole-6-carboxylic acid **127** was converted to its alcohol **128** using the procedure described in **Example 1D.** HPLC-MS t_R = 0.955 min ($UV_{254\ nm}$); mass calculated for formula C_9H_9NOS 179.04, observed LCMS m/z 180.0 (M+H).

Part C

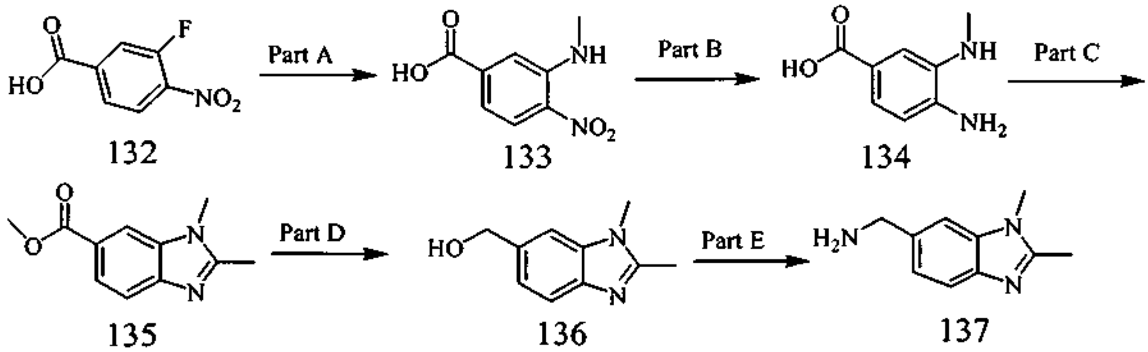
(2-Methyl-benzothiaole-6-yl)-methanol **128** was converted to (2-Methyl-benzothiaole-6-yl)-methylamine **129** using procedures described in **Example 1D**, Part C and Part D HPLC-MS t_R = 0.295 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_{10}N_2S$ 178.06, observed LCMS m/z 179.1 (M+H).

The compounds in Table 5 are made using compound **129** and core **8** according to the methods described in **Example 1B**.

Table 5

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
130		547.17	548.25	5.16
131		493.22	494.28	4.33

Example 1F



Part A

To the solution of 3-fluoro-4-nitrobenzoic acid **132** (1 g,5.40 mmol) was suspended in Ethanol (20 mL) and methylamine (40 wt% in water, 10 mL) was added and refluxed overnight. Reaction mixture was cooled to room tepecrature and concentrated to obtain compound **133**. HPLC-MS t_R = 1.088 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_8N_2O_4$ 196.05, observed LCMS m/z 197.1 (M+H).

Part B

3-methylamino-4-nitro benzoic acid **133** (1 g, 5.10 mmol) was suspended in Ethanol (20 mL) and catalytic amount of 5 % Pd on carbon was added. The reaction flask was sealed with septum, evacuated by applying vacuum and hydrogen balloon was inserted and stirred overnight. The solution was filtered through celite pad and concentrated to yield compound **134**. HPLC-MS t_R = 0.229 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_{10}N_2O_2$ 166.07, observed LCMS m/z 167.1 (M+H).

Part C

4-Amino-3-methylamino benzoic acid **134** was taken in 20 mL of acetic acid and refluxed for overnight. The reaction mixture was cooled and concentrated. The residue was taken in methanol and acetonitrile mixture (1:1) and added (Trimethylsilyl) diazomethane (2 M soln. in hexanes, 10 mmol) at 0^0C. The solution was stirred for 1 hr and concentrated. The crude product was purified on silica column using Methanol/Ethylacetate solvent system. HPLC-MS t_R = 0.797 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{12}N_2O_2$ 204.09, observed LCMS m/z 205.1 (M+H).

Part D

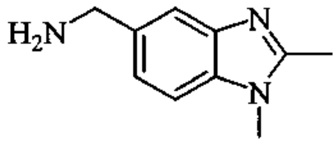
To a suspension of 2,3-Dimethyl-benzimidazole-5-carboxylic acid methyl ester **135** (0.5 g., 2.5 mmol) in 50 mL of DCM was added 3 equivalents of 1 M solution of DIBAL-H at -78^{0}C and the mixture was stirred for 4 hrs. The reaction mixture was warmed to room temperature. The reaction was cooled to 0^0Cquenched by the sequential addition of 1 M sodium hydroxide and 30 % Rochelle salt (10 mL). The mixture was filtered, and the residue was washed with DCM. The filtrate was concentrated to obtain compound **136**. HPLC-MS mass calculated for formula $C_8H_8N_2O$ 148.06, observed LCMS m/z 149.1 (M+H).

Part E

2,3-Dimethyl-3H-benzimidazol-5-yl)-methanol has been converted to the compound **137** using the procedures illustrated in **Example 1D**. Part B and Part C.

HPLC-MS t_R = 0.210 min ($UV_{254\ nm}$); mass calculated for formula C10H13N3 175.11, observed LCMS m/z 176.2 (M+H).

Example 1G



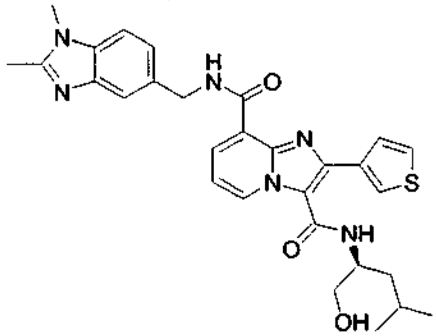
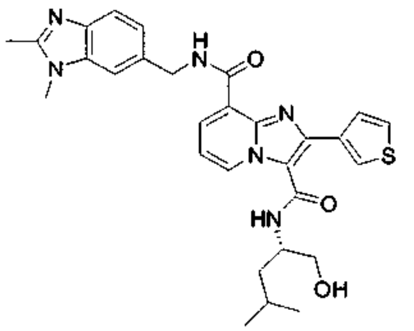
138

(1,2-Dimethyl-1H-benzimidazol-5-yl)-methylamine has been synthesized starting from 4-Fluoro 3 nitro benzoic acid using procedures described in **Example 1F**

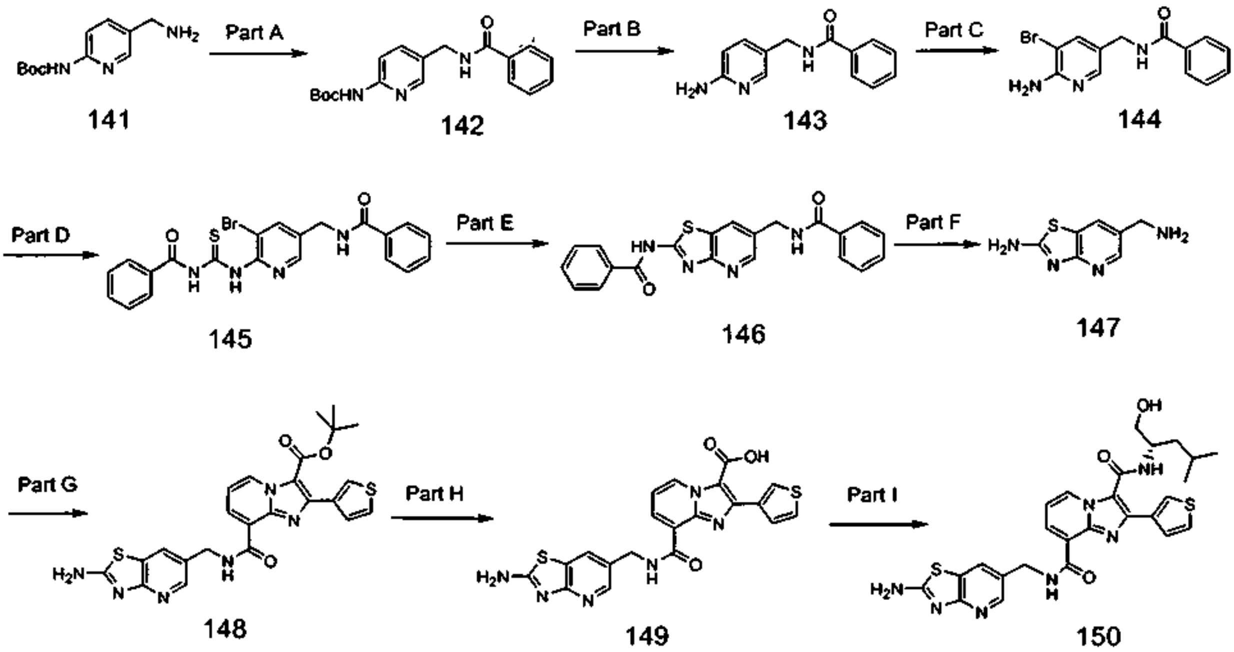
HPLC-MS t_R = 0.177 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_{13}N_3$ 175.11, observed LCMS m/z 176.2 (M+H).

The compounds in Table 6 are made using compounds **137** and **138** and the methods described in **Example 1B.**

Table 6

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
139		544.23	545.31	3.72
140		544.23	545.23	3.41

Example 1H



Part A

The compound **141** (1.0 g, 4.5 mmol) was dissolved in DCM (20 mL) and TEA (1.36 mL, 10 mmol) was added. The mixture was cooled to 0^0C with ice-water bath and benzoyl chloride (0.675 g, 4.8 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 3 hours. The mixture was diluted with EtOAc (200 mL) and washed with H_2O, $NaHCO_3$, and brine and dried over Na_2SO_4. After concentration, the crude residue was purified with short column (silica gel, hexane/EtOAc = 70/30) gave the product **142** (1.31 g). HPLC-MS t_R = 1.48 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{21}N_3O_3$ 327.2, observed LCMS m/z 328.1 (M+H).

Part B

The compound **142** (1.0 g, 3.0 mmol) was dissolved in MeOH (3 mL) and HCl (6N, 5 mL) was added. The mixture was stirred at room temperature for 1 hour and concentrated. The aqueous was treated with $NaHCO_3$ (sat. aq., 30 mL) and extracted with EtOAc. The organics were dried over Na_2SO_4 and concentrated to give the crude product **143**. It was used in the next step without further purification. HPLC-MS t_R = 0.61 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{13}N_3O$ 227.1, observed LCMS m/z 228.1 (M+H).

Part C

The 2-aminopyridine compound **143** (1.14 g, 5 mmol) was dissolved in HOAc (20 mL) and bromine (0.260 mL, 5.0 mmol) was added at room temperature. The mixture was stirred for 1 hour and concentrated. The resulting residue was diluted with Na_2CO_3 (aq.) and extracted with EtOAc. After concentration, the product was purified with column (silica gel, hexane/EtOAc = 40/60) gave the pure product **144** (1.28 g) as white solid. HPLC-MS t_R = 0.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{12}BrN_3O$ 305.0, observed LCMS m/z 306.0 (M+H).

Part D

A mixture of ammonium thiocyanate (0.35 g, 4.3 mmol) and acetone (1.5 mL) was warmed until a clear solution was obtained. Benzoyl chloride (0.53 mL, 4.3 mmol) was then slowly dropped in and the resulting suspension refluxed 5 min. The 2-amino-

3-bromopyridine **144** (1.28 g, 4.3 mmol) in acetone (1.5 mL) was added and the reaction mixture was refluxed for 1 hour. After cooling to room temperature, the solution was poured into water and the the solid was collected by filtration, washed with water, ethyl ether and dried under vacuum. Gave the product **145** (1.15 g) as white solid. HPLC-MS t_R = 1.32 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{17}BrN_4O_2S$ 468.0, observed LCMS m/z 469.0 (M+H).

Part E

The compound **145** (1.15 g, 2.5 mmol) was dissolved in NMP (10 mL) and NaOMe (0.810 g, 15 mmol) was added. The mixture was heated up to 120^{0}C under Ar for 4 hours. After cooling down to room temperature, the mixture was diluted with EtOAc and washed with NH_4Cl (aq.) and brine. After drying over Na_2SO_4, the organics were concentrated and the residue was purified by column (silica gel, hexane/EtOAc = 20/80) gave the compound **146** (0.710 g) as yellowish solid. HPLC-MS t_R = 1.53 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{16}N_4O_2S$ 388.1, observed LCMS m/z 389.0 (M+H).

Part F

Compound **146** (710 mg, 1.8 mmol) was treated with HCl (6N, 5 mL) and heated up to refluxed overnight. After cooling to room temperature, the aqueous was extracted with ethyl ether. The aqueous was concentrated and dried with lyophlization gave the product **147** which was used in the next step directly without further purification. HPLC-MS t_R = 0.18 min ($UV_{254\ nm}$); mass calculated for formula $C_7H_8N_4S$ 180.0, observed LCMS m/z 181.1 (M+H).

Part G

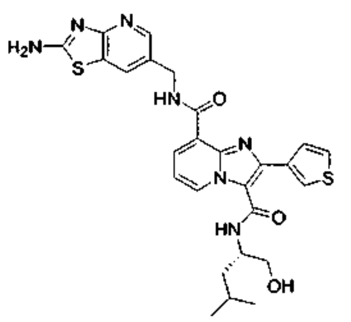
Compound **148** was prepared using the peptide coupling conditions described in **Example 1B** Part F. HPLC-MS t_R = 1.70 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{22}N_6O_3S_2$ 506.1, observed LCMS m/z 507.1 (M+H).

Part H

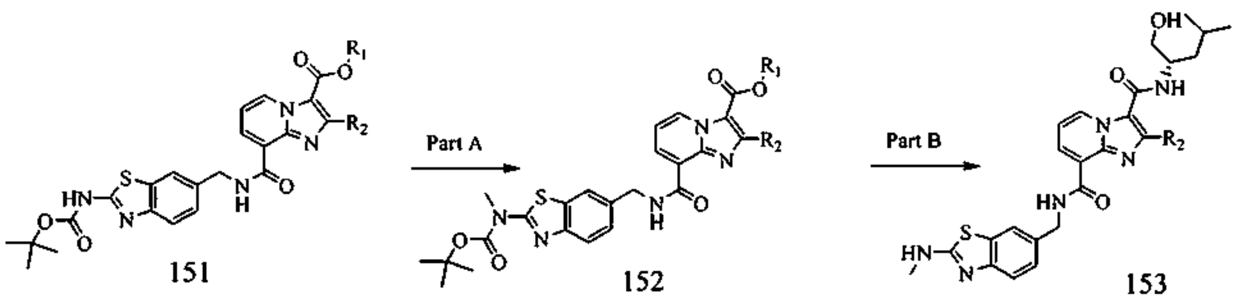
Compound **149** was prepared using the hydrolysis conditions described in **Example 1B** Part H. HPLC-MS t_R = 1.06 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{14}N_6O_3S_2$ 450.0, observed LCMS m/z 451.0 (M+H).

Part I

Compound **150** was prepared using the peptide coupling conditions described in **Example 1B** Part I. HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{27}N_7O_3S_2$ 549.1, observed LCMS m/z 550.0 (M+H).

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
150		549.1	550.0	1.35

Example 2A



R_1 = Ethyl or t-butyl
R_2 = H, Ethyl, 3-thiophene or 2 pyridyl

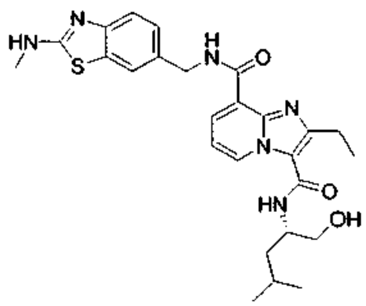
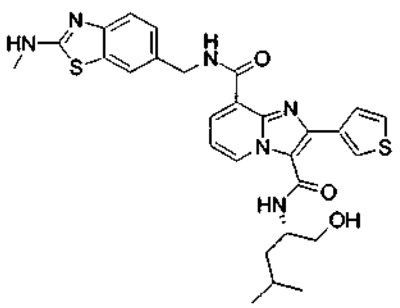
Part A

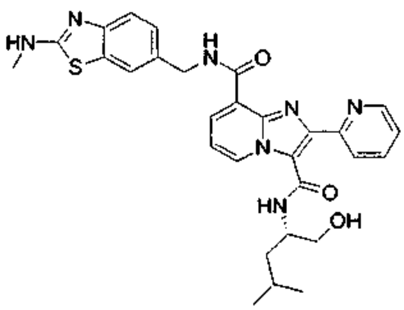
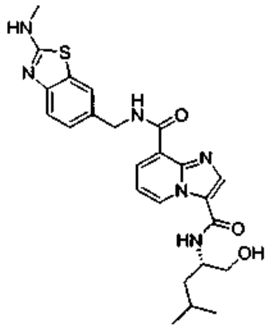
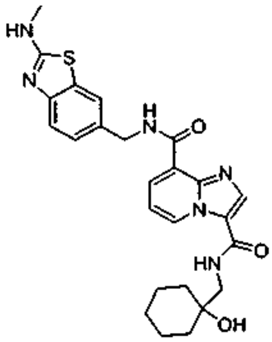
Compounds of structure **151** was synthesized using methods described in **Example 1B** (Part F and G). To a stirred solution of compound **151** (0.064mmol) in anhydrous THF (1 mL) was added the Methanol (1 equivalent), triphenylphosphine (1.5 equivalents) and DIAD (1.5 equivalents) at room temperature. The reaction mixture was continued to stirr at room temperature for 5 hours at which time LC-MS analysis indicated the reaction was complete. The reaction mixture was concentrated and purified using column chromatography.

Part B

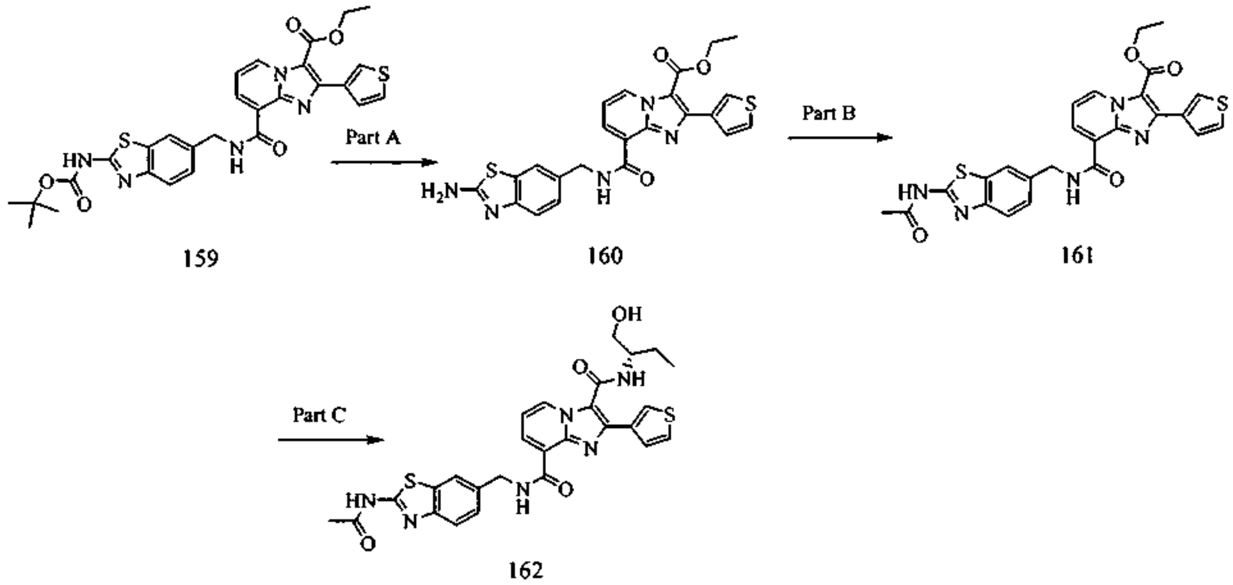
The final compounds in Table 7 are synthesized using the methods described in **Example 1B**.

Table 7

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
154		508.23	509.30	3.24
155		562.18	563.23	3.89

156		557.2	558.1	4.05
157		480.19	481.1	3.147
158		492.19	493.1	3.102

Example 2 B



Part A:

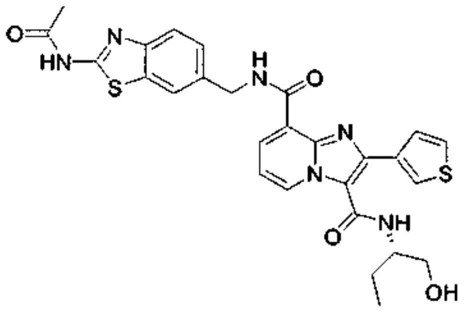
The Boc protecting group in compound **159** was deprotected using conditions described in **Example 1B** (part H).

Part B:

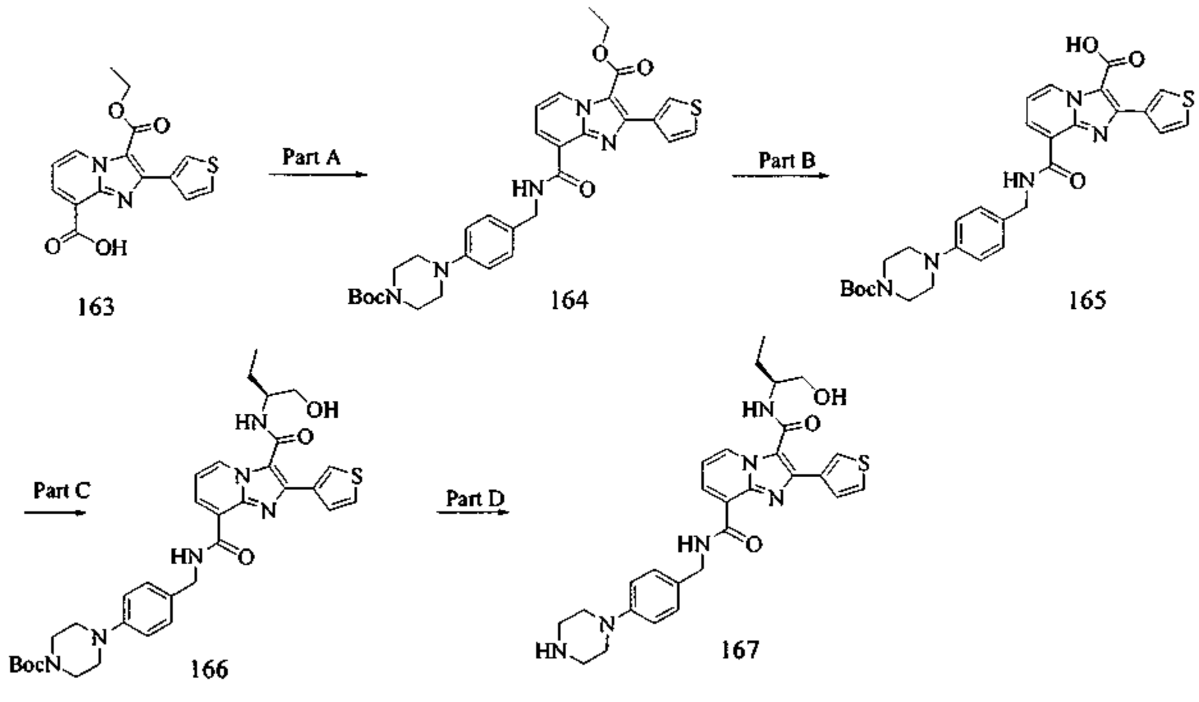
To the stirred solution (0.1 mmol) in DCM (5 mL), DIEA (100 mL, 0.6 mmol) was added followed by the addition of acetyl chloride (0.15 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and the oraganic layer was washed with $NaHCO_3$ soln. Water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the resulting residue was used for the next reaction with out any further purification. HPLC-MS t_R = 1.929 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{21}N_5O_4S_2$ 519.10, observed LCMS m/z 520.0 (M+H).

Part C:

The compound **161** was converted to the final product using methods described in **Example 1B** (Part F and Part I)

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
162		562.15	563.0	3.978

Example 2C



Part A:

2- Thiphene-3-yl-imidazo[1,2-a]pyridine-3,8-dicarboxylic acid **163** (0.05 mmol) dissolved in in dichloromethane (5 mL) and cooled to -20^{0}C. To this (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.2 equivalents, 0.06 mmol) was added. Followed by Diisopropyl ethyl amine (3 equivalents) was added and the solution stirred at – 20^{0}C for 15 minutes. To the activated acid was added with 0.05 mmol solution of Amine (pre dissolved in to DCM or NMP; 0.5 mL). The solution was shaken at -5^{0}C for 14 hrs. LCMS analysis showed the completion of the reaction. HPLC-LC-MS mass calculated for formula $C_{31}H_{35}N_5O_5S$, 589.23; and observe m/z M^++H 590.0

Part B:

8-[4-(4-tert-Butoxycarbomoyl-piperazin-1-yl) -2-thiophen-3yl-imidazo[1,2-a]pyridine-3carboxylic acid ethyl ester **164** (0.040 g) was dissolved in THF:Water (1:!; 5 mL) and LiOH (0.004 g) added and stirred at room temperature for 5 hrs. The solvent was evaporated and neutralized to pH 4 with dil.HCl. Extracted in to EtOAc. EtOAC is evaporated and dried. HPLC LC-MS mass calculated for formula, $C_{29}H_31N_5O_5S$, 561.20; and observed M^++H 562.2

This has been used in the next step with out any further purification.

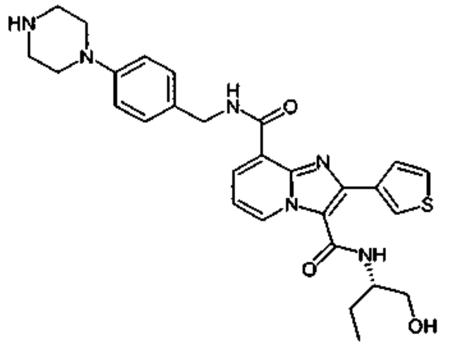
Part C:

To the above solution, one equivalent of (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.05 mmol) was added in each reaction vial followed by diisopropyl ethyl amine (5 equivalents) and S-(S)-(+)-2-amino-1-butanol (0.05 mmol). The reaction mixture stirred at room temperature for overnight. LCMS analysis showed completion of reaction.

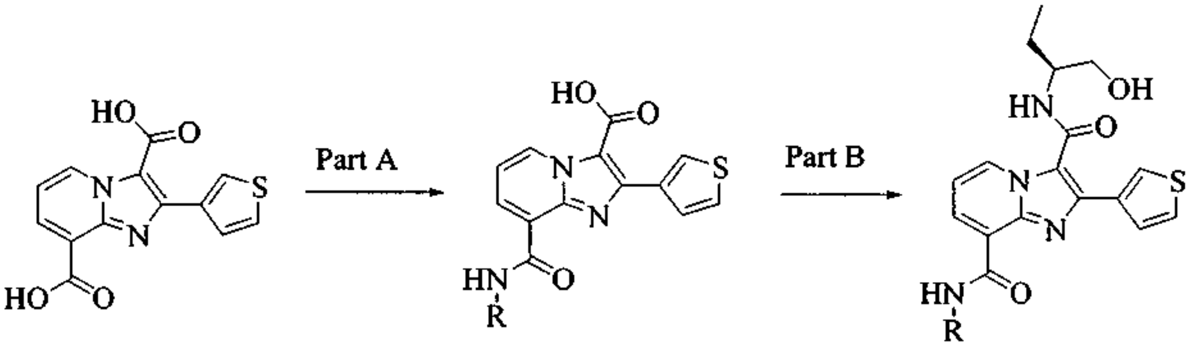
The dichloromethane/N-methylpyrrolidine solution was concentrated under vacuum. Extracted in to ethyl acetate (3X 2mL). The organic extracts were dried under vacuum and re dissolved in methanol-acetonitrile and subjected to Prep. LC purification to get the desired product in 95% purity. HPLC LC-MS mass calculated for molecular formula, $C_{33}H_{40}N_6O_5S$; 632.27, and observed M^++H=637.2

Part D:

The above purified product was treated with 4N hydrochloride in dioxane for 1 hr. The dioxane solution evaporated under vacuum and redissolved in water-acetonitrile lyophilized to get the hydrochloride salt of the title compound.

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
167		532.23	533.1	3.22

Example 3A



7 168 169

Part A:

2- Thiphene-3-yl-imidazo[1,2-a]pyridine-3,8-dicarboxylic acid **7** (0.144 g, 0.5 mmol) dissolved in in dichloromethane (5mL) and cooled to -20^{0}C. To this (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.093 g; 1.2 equivalents; 0.6 mmol) was added. Followed by Diisopropyl ethyl amine (3 equivalents., 0.315 mL) was added and the solution was stirred at – 20^{0}C for 15 minutes.

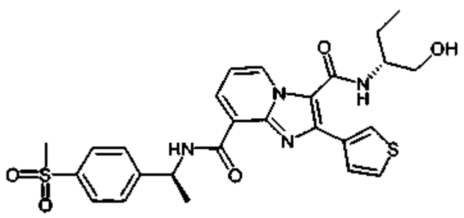
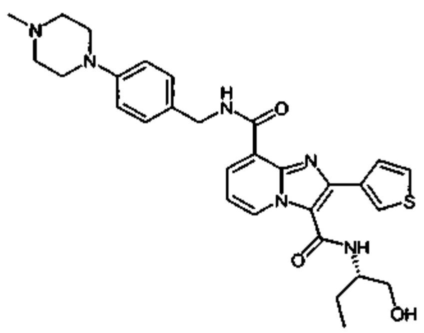
The activated acid was distributed equally in to, 4ml Vials. Each vial was added with 0.025 mmol solution of Amine (pre dissolved in to DCM or NMP; 0.5 mL). The solution was shaken at -5^{0}C for 14 hrs. LCMS analysis showed the completion of the reaction.

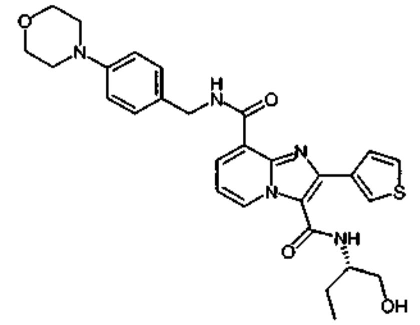
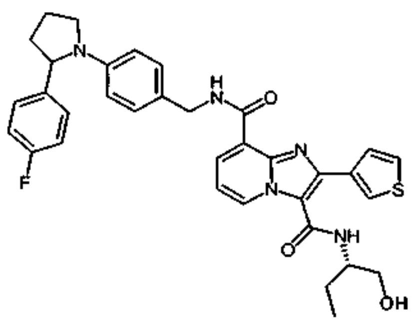
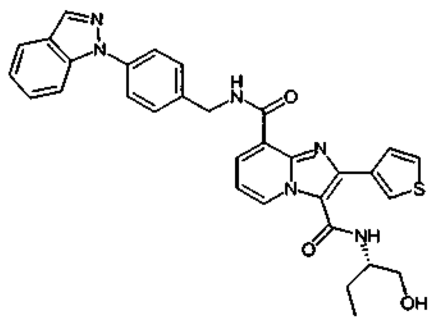
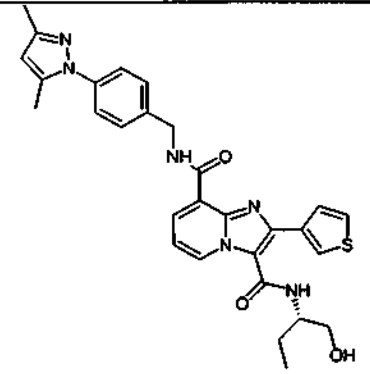
Part B:

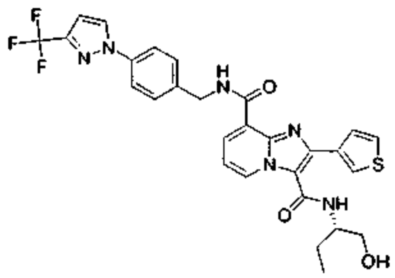
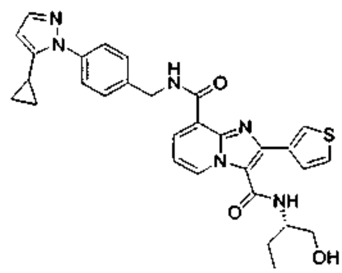
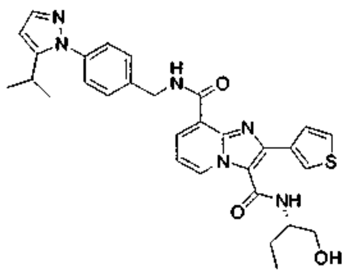
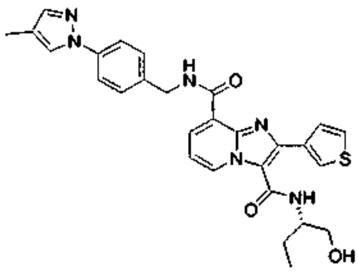
The 8- aralkyl/aryl carbomyl -2-thiophen-3yl-imidazo[1,2-a]pyridine-3-carboxylic acid **168** obtained in the above step was used for this step with out any purification. The reaction mixture was warmed up to room temperature and to the above solution, one equivalent of (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.03 mmol) was added in each reaction vial followed by diisopropyl ethyl amine (5 equivalents) and S-(S)-(+)-2-amino-1-butanol (0.027 mmol). The reaction mixture stirred at room temperature for overnight. LCMS analysis showed completion of reaction.

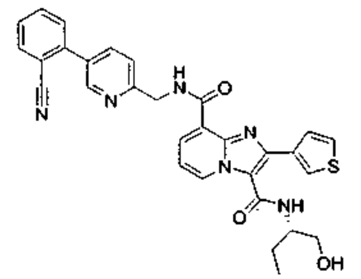
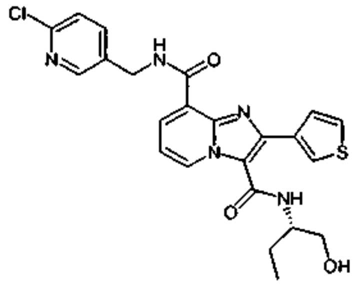
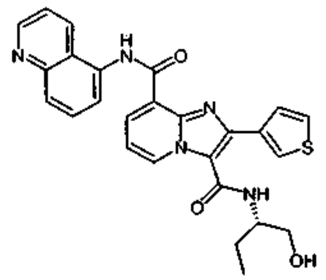
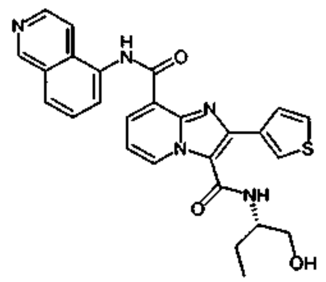
The dichloromethane/N-methylpyrrolidine solution was concentrated under vacuum. Extracted in to ethyl acetate (3X 2mL). The organic extracts were dried under vacuum and re dissolved in methanol-acetonitrile and subjected to Prep. LC purification to get the products in Table 8.

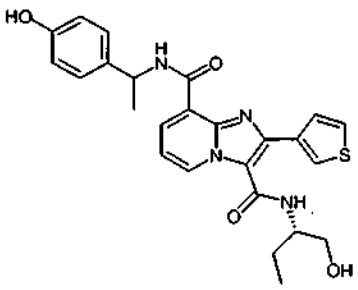
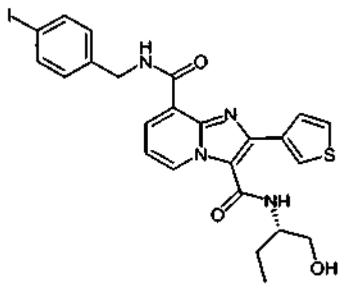
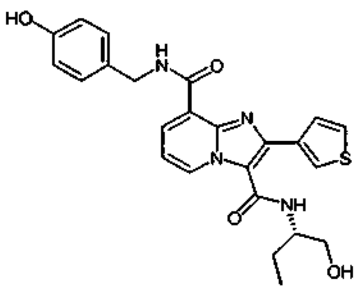
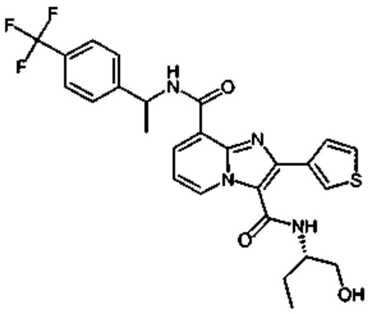
Table 8

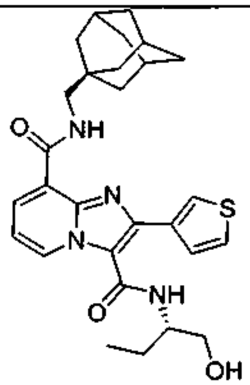
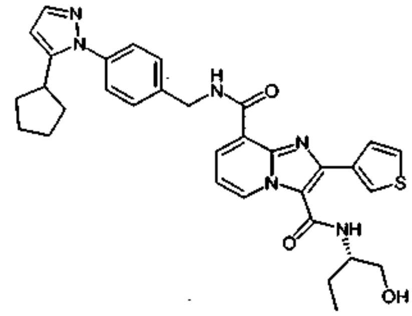
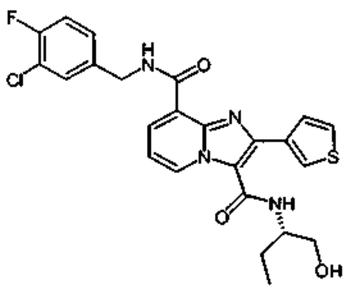
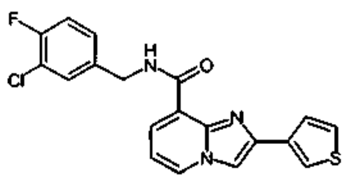
Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
170		540.150	541.2	4.0
171		546.2416	547.2	3.25

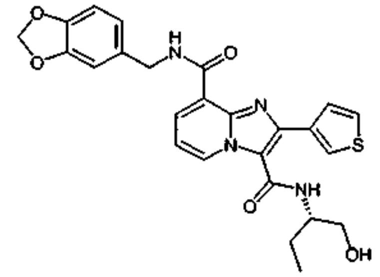
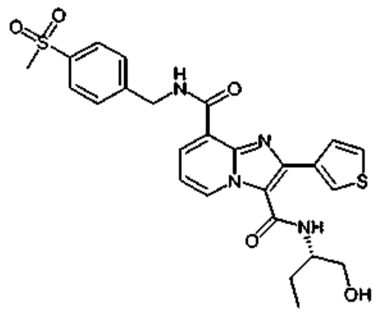
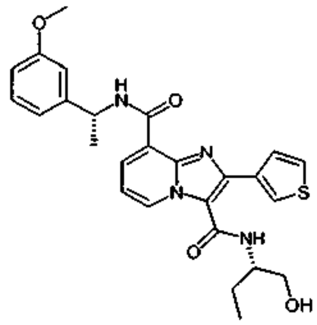
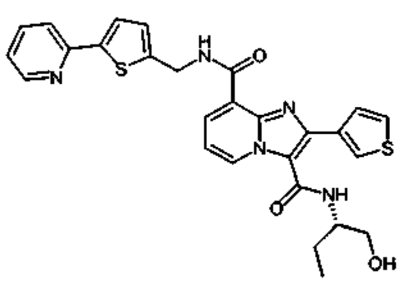
172		533.209	534.1	3.9
173		611.2369	612.20	5.8
174		564.1946	565.1	5.2
175		542.2103	543.1	4.5

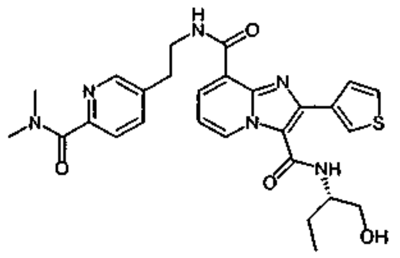
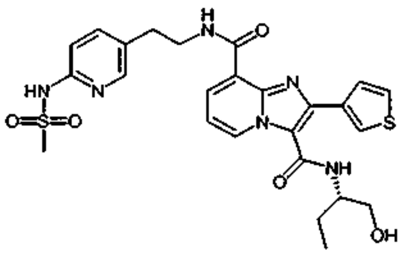
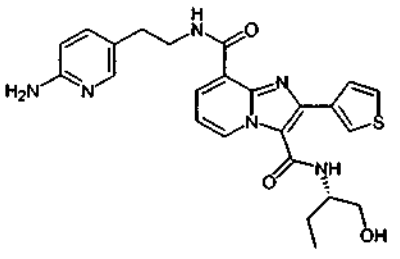
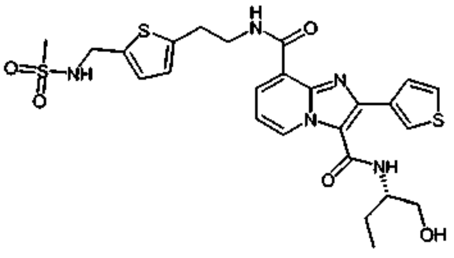
176		582.1664	583.2	5.3
177		554.2103	555.1	4.85
178		556.226	557.2	4.95
179		528.1946	529.2	4.75

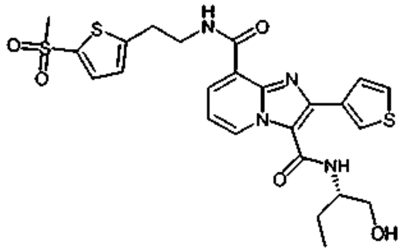
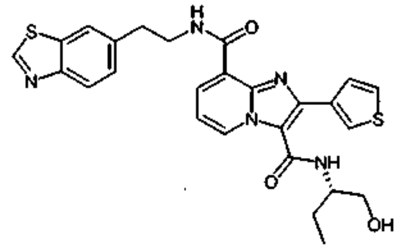
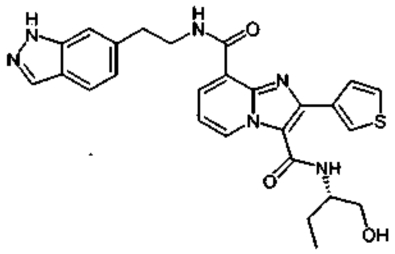
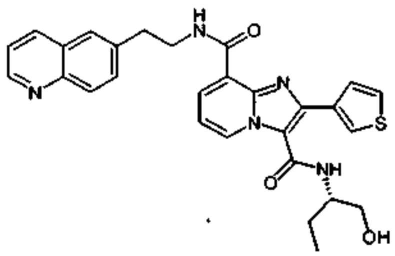
180		550.179	551.2	4.25
181		483.1135	484.1	4.2
182		485.1524	486.1	3.65
183		485.1524	486.1	3.55

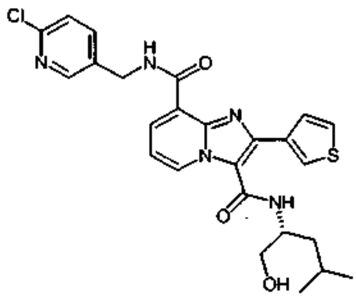
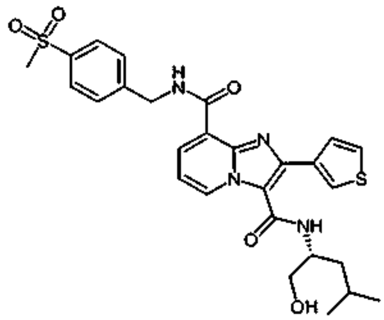
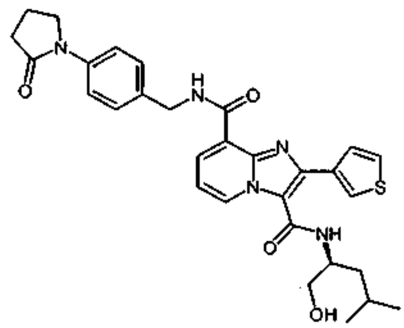
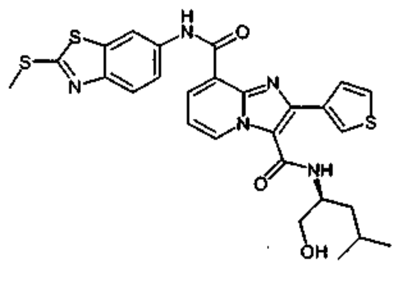
184		478.1677	479.1	3.85
185		574.0538	575.0	5.2
186		464.152	465.1	3.72
187		530.1602	531.0	5.39

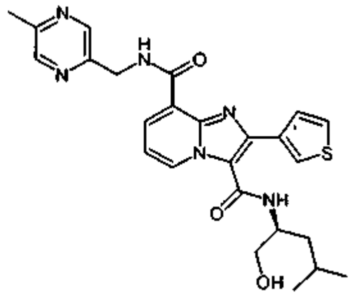
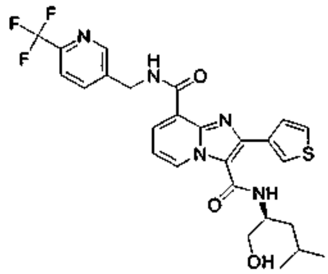
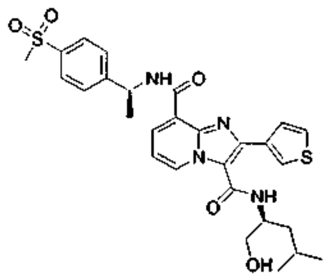
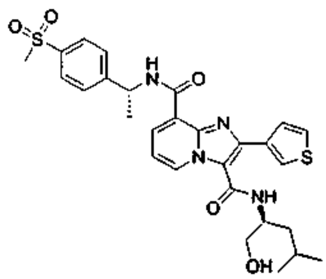
188		506.2354	507.2	5.92
189		582.2416	583.2	5.30
190		500.10	501.1	5.0
191		385.04	386.0	4.25

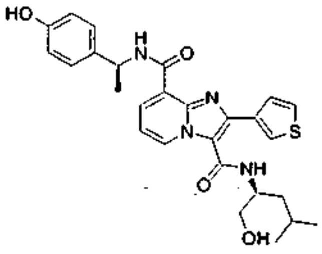
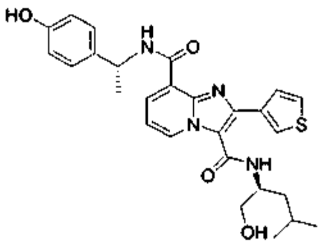
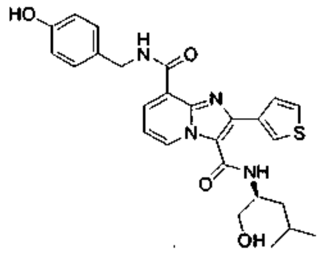
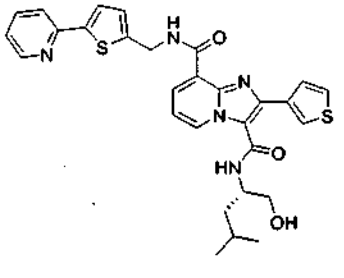
192		492.15	493.1	4.4
193		526.13	527.0	1.5
194		492.18	493.1	4.75
195		531.14	532.0	4.0

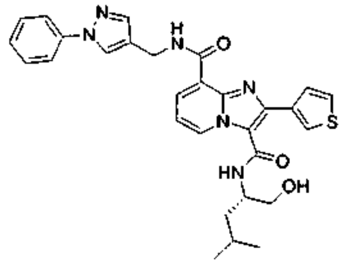
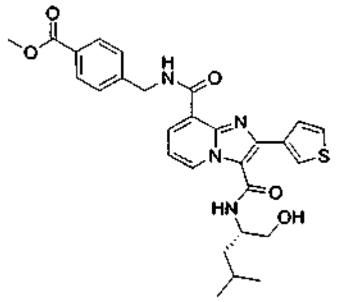
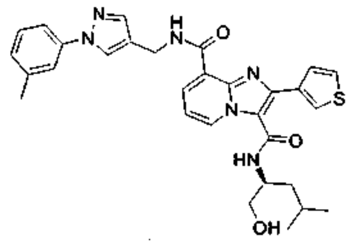
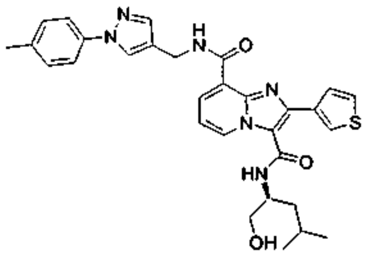
196		534.20	535.2	3.5
197		556.15	557.2	3.5
198		478.17	479.1	2.9
199		575.13	576.1	3.9

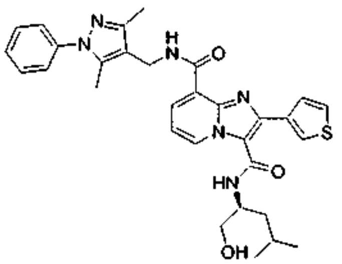
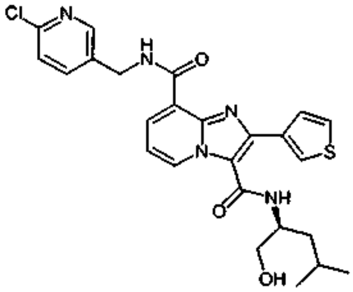
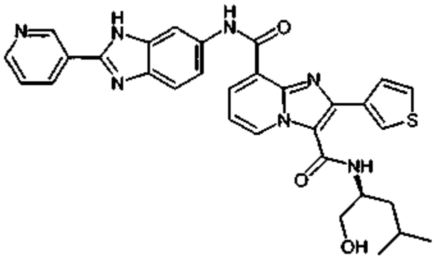
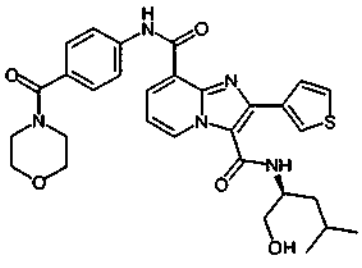
200		546.10	547.0	3.9
201		519.14	520.1	4.25
202		502.17	503.0	3.85
203		513.18	514.1	3.15

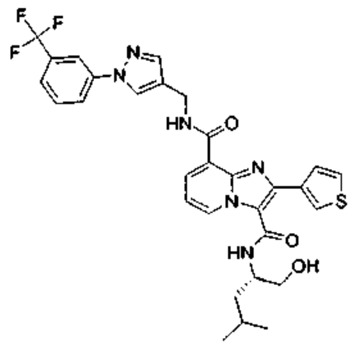
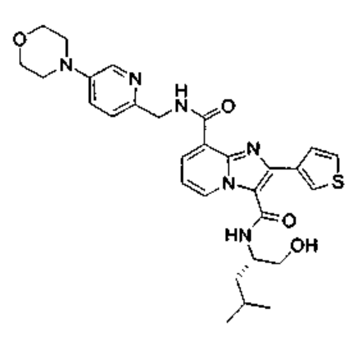
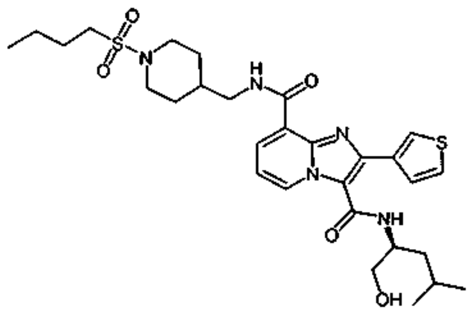
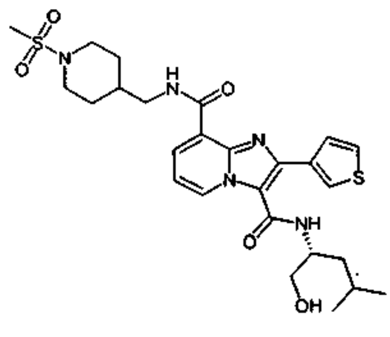
204		511.14	512.0	4.75
205		554.17	555.1	4.4
206		559.23	560.2	4.6
207		565.13	566.0	5.9

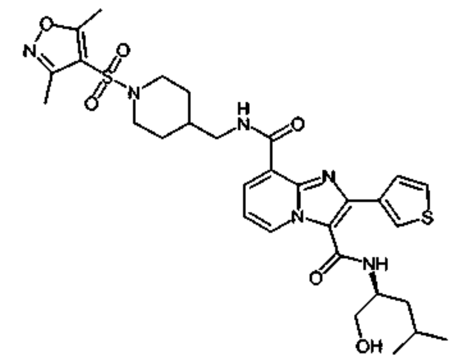
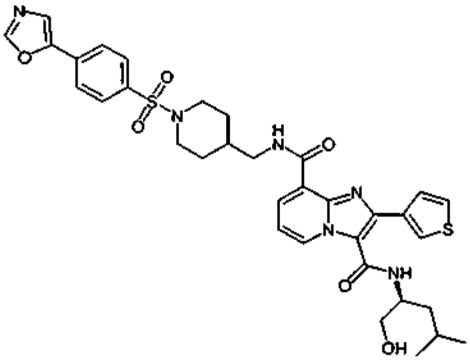
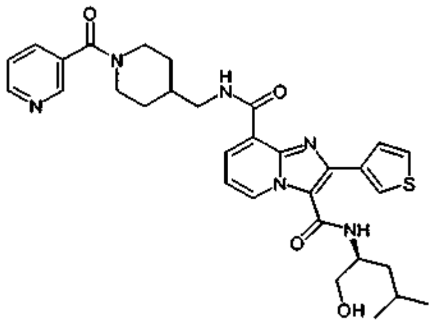
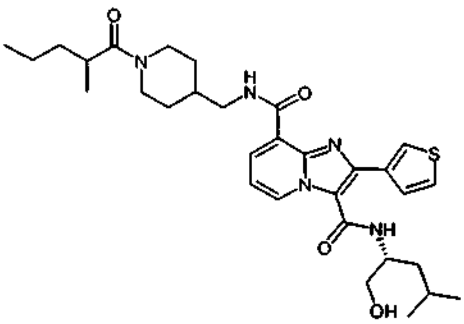
208		492.19	493.1	4.3
209		545.17	546.1	5.0
210		568.18	569.0	4.4
211		568.18	569.0	4.55

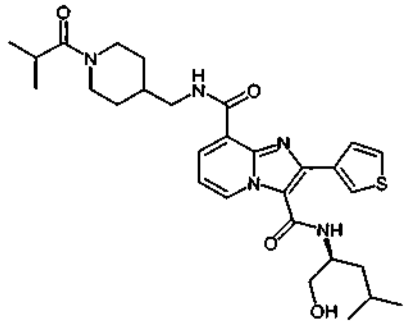
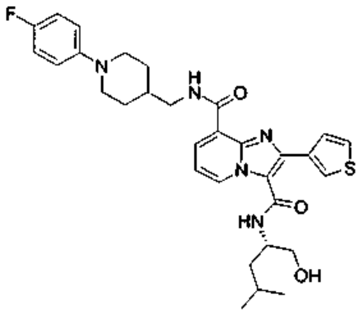
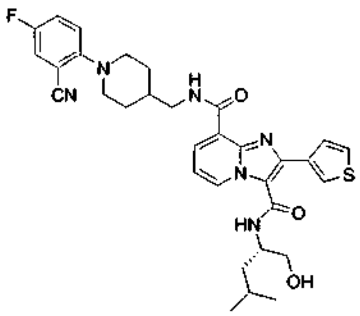
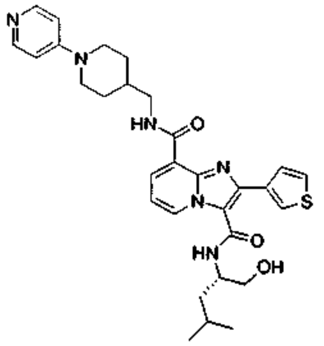
212		506.19	507.0	4.95
213		506.19	507.0	4.74
214		492.18	493.0	4.6
215		559.17	560.0	4.62

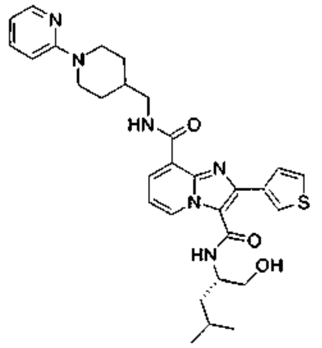
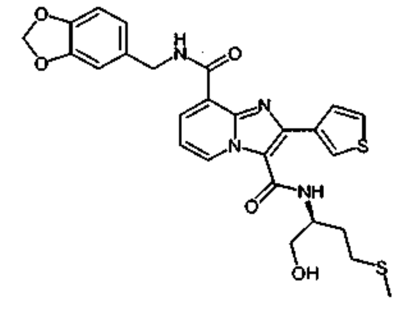
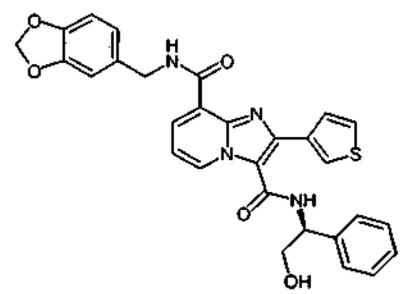
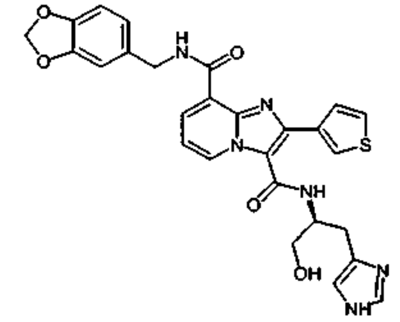
216		542.21	543.0	5.35
217		534.19	535.0	5.39
218		556.23	557.0	5.73
219		556.23	557.0	5.71

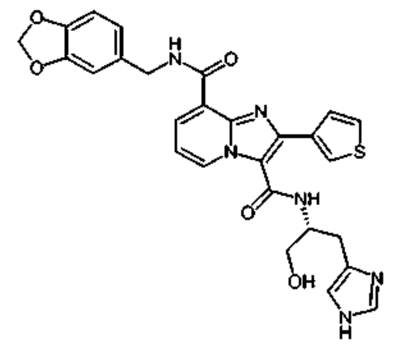
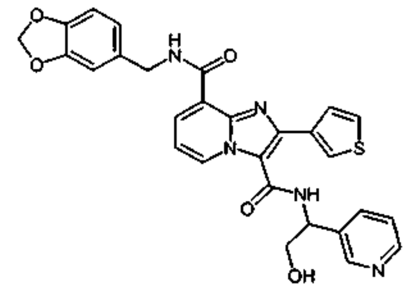
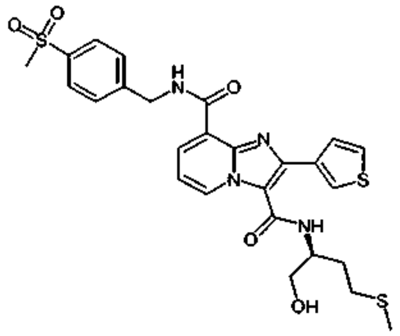
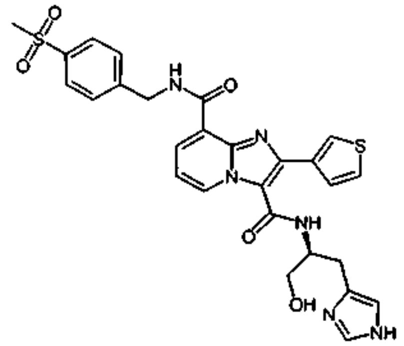
220		570.24	571.0	5.42
221		511.14	512.0	4.75
222		579.21	580.2	4.10
223		575.22	576.2	4.65

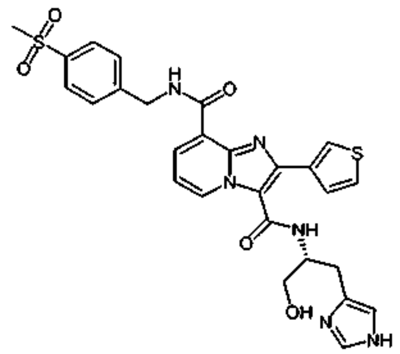
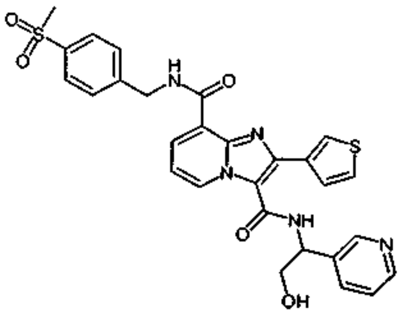
224		610.19	611.0	6.06
225		562.23	563.0	3.77
226		603.25	604.2	5.1
227		561.20	562.2	4.35

228		642.23	643.2	5.0
229		690.23	691.20	4.95
230		588.25	589.2	3.9
231		581.30	581.2	5.15

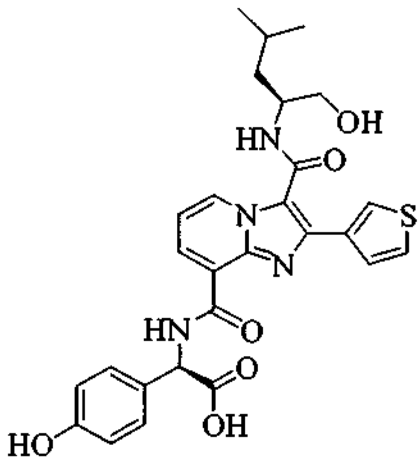
232		553.27	554.2	4.70
233		577.25	578.0	4.35
234		602.24	603	6.12
235		560.25	561.0	3.81

236		560.25	561.0	3.49
237		538.13	539.0	4.5
238		540.14	541.2	4.75
239		544.15	545.0	3.3

240		544.15	545.0	3.3
241		541.14	542.0	3.45
242		572.12	573.1	3.90
243		578.14	579.1	2.75

244		578.14	579.1	2.75
245		575.13	576.1	2.85

Example-3B



246

Part A:

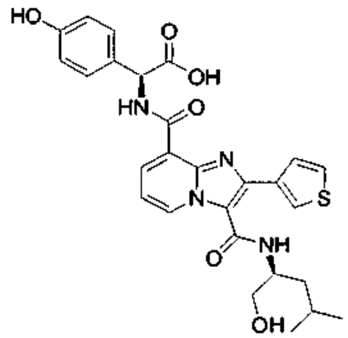
The general procedure used for coupling reaction is as described in preparative **Example 3**-Part A

Part B:

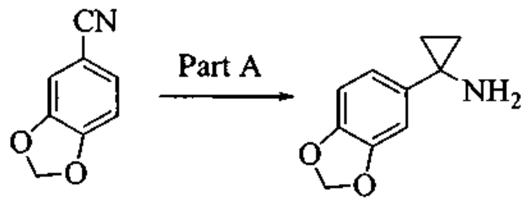
The general procedure used for coupling reaction is as described in preparative **Example 3**-Part B

Part C:

The general procedure used for coupling reaction is as described in preparative **Example 2C**-Part B

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
246		536.17	537.2	4.06

Example 4A

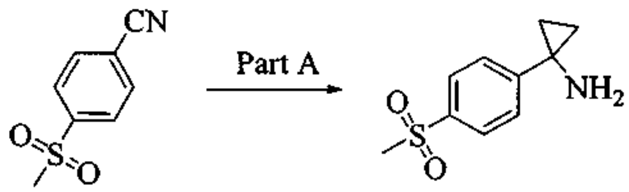


247 248

Part A:

Piperonylonitrile **247** (0.735 g, 0.5 mmol,) was dissolved in dry ether, cooled to – 78^{0}C and kept under inert atmosphere. Ethyl magnesium bromide (1.2 equivalents) was added to the above solution by syringe maintaining the temperature at -78^{0}C. After the addition, the reaction stirred at -78^{0}C for 1 hour and allowed the reaction mixture to warm up to room temperature. Stirring continued at r.t for another 2 hours. LCMS analysis showed the formation of product. The reaction was quenched with water and reaction mixture extracted with ether, Ether layer was washed with water, brine and dried with anhydrous $MgSO_4$.Evaporation of ether gave crude which on passing through the silica gel column eluting with Hexane/Ethyl acetate provided with the product, 1-benzo[1,3]dioxol-5-yl-cyclopropylamine. Calculated M.W.=177.19, and observed M^{+}+H 178.1

Example 4B

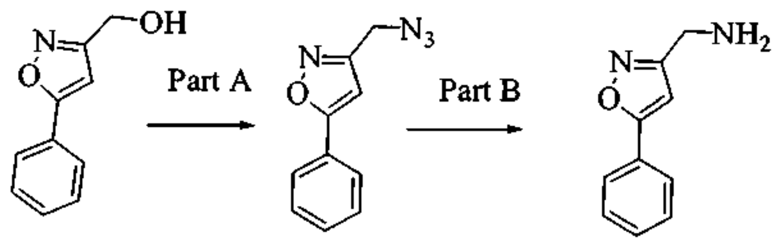


249 250

Part A:

Compound **250** was prepared from **249** using methods described in **Example 4A.** mass calculated for compound **253** is 211.06, observed LCMS m/z 212.21

Example 4C



251 252 253

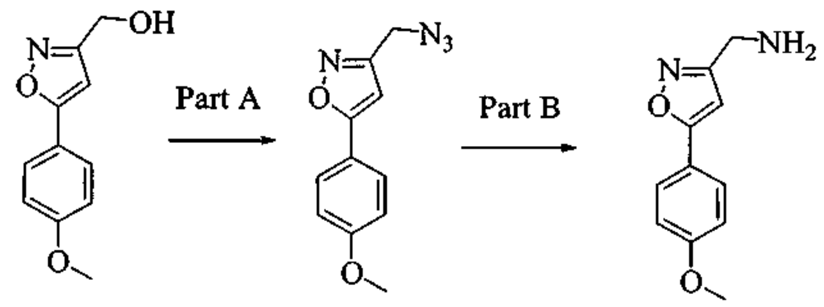
Part A:

(5-Phenyl-isoxazol-3-yl)methanol **251** (0.175 g, 1 mmol) was dissolved in THF (10 mL) and to this , DPPA (1.1 eq, 1.1 mmol) and DBU (1.5 eq, 1.5 mm) was added.and the solution was stirred under reflux for 14 hours. The THF was removed under vacuum and the crude thus obtained showed formation of product from the LCMS analysis. The crude was passed through the silical gel column to give the 3-azido methyl-5-phenyl-isoxazole **252**. mass calculated for compound **252** is 200.19, observed LCMS m/z 201.24.

Part B:

3-azido methyl-5-phenyl-isoxazole **252** obtained in the above step was dissolved in dioxane and resin bound triphenylphosphine (excess) was added and stirred at room temperature. After 2 hours, a mixture of dixane/water (0.50 mL) was added and stirring continued for 2 more hours. Filter off the resin and the evaporated the dioxane under vacuum resulted in the desired amine, (5-Phenyl-isoxazol-3-yl)methylamine **253**,. mass calculated for compound **253** is 174.19, observed LCMS m/z 175.25 which was used in the next step with out purification.

Example 4D



254 255 256

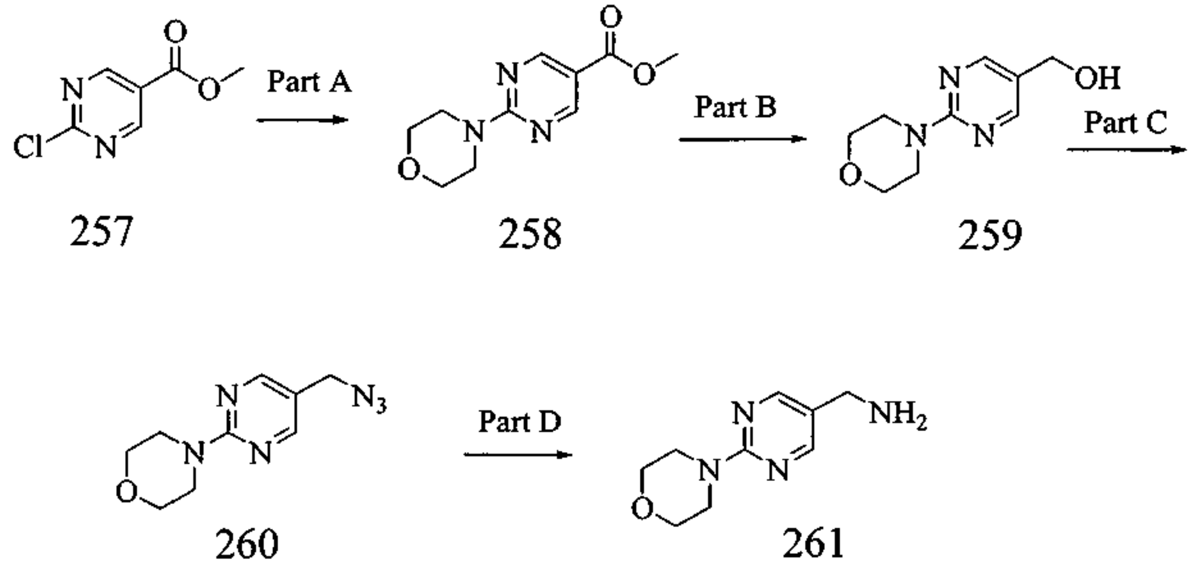
Part A:

Compound **255** was prepared from **254** using methods described in **Example 4C.** mass calculated for compound **255** is 230.08, observed LCMS m/z 239.1

Part B:

Compound **256** was prepared from **255** using methods described in **Example 4C.** mass calculated for compound **256** is 204.1, observed LCMS m/z 205.1

Example 4E



Part A:

2-chloro-5-carboxymethyl pyrimidine **257** (0.5 g) was dissolved in Morpholine and heated at 100°C for 14 hours. Removal of excess morpholine and passing through the column provided the product, 2-morpholino-5-carboxymethylpyrimidine **258**. Mass calculated for compound **258** is 223.22, observed LCMS m/z 224.1

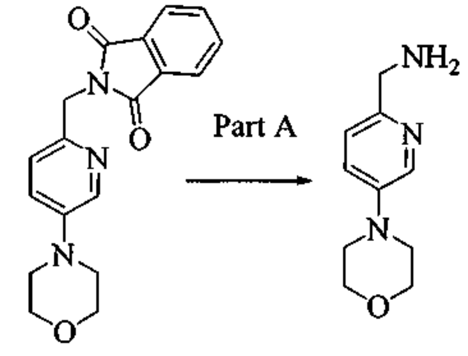
Part B:

2-morpholino-5-carboxymethylpyrimidine **258** (0.4 g) was dissolved in MeOH and $NaBH_4$ (1.5 equivalents) was added and reaction stirred at room temperature for 12 hours. Solvent was evaporated and diluted with ethyl acetate, washed with water, brine, dried over anhydrous magnesium sulfate. Filtered, evaporated and passed through the column to afford the product corresponding alcohol **259**. Mass calculated for compound **259** is 195.21, observed LCMS m/z 196.1

Part C & Part D:

Follwing the general procedure described in the preparative **Example 4C**, Part A and Part B, the title compound was prepared. Mass calculated for compound **261** is 194.23, observed LCMS m/z 195.2

Example 4F



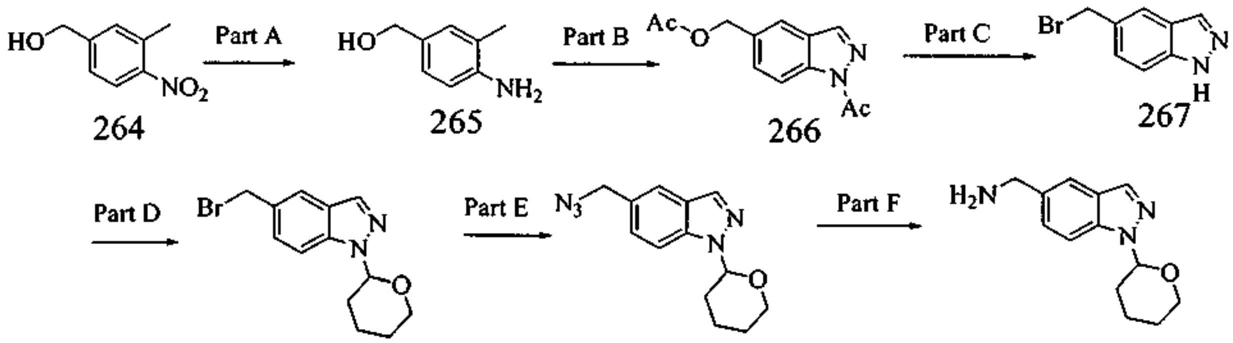
262 263

Part A:

2-(5-Morpholino-4-yl-pyridine-2yl-methyl)isoindole-1,3-dione **262** (0.200 g) was dissolved in methanol and excess hydrazine hydrate was added and refluxed for two hours. After concentration of solvent, the residue was passed through the Prep LC to get the desired product **263**. Mass calculated for compound **263** is 193.24, observed LCMS m/z 194.1

Example 4F

1-(Tetrahydro-pyran-2-yl-1H-indazo-5-yl}-methylamine: synthesized as described in the reference. JOC, 62, 5627(1997).



268 269 270

Part A:

A mixture of 3-methyl -4-nitro benzyl alcohol **264** (2.10 g, 12.6 mmol) and 10% Palladium on carbon (0.2 g) in 25 mL of EtOH was hydrogenated at room temperature. After completion of the reaction, the catalyst was removed by filtration.

The solvent was evaporated and residue dried in a vacuum to give title compound as yellow solid 1.7 g, 97%), ^{1}H NMR ($CDCl_3$), δ 7.06(s,1H),7.03(d, J=8.0 Hz, 1H), 6.66 (d, J=7.7 Hz, 1H), 4.53 (s, 1H), 3.62(br, 2H), 2.17 (s, 3H); mass calculated for compound **265** is 137.17, observed LCMS m/z 138.2 (M+H).

Part B:

A mixture of product **265** from part A (1.65g, 12 mmol), acetic anhydride (3.4 mL, 36 mmol) and potassium acetate (2.37g, 24 mmol) in 50 mL of $CHCl_3$ was stirred at room temperature and then refluxed for 2 hours and stirred at room temperature for overnight. Then n-amyl nitrite (3.2g, 27 mmol) and 18-crown-6 (0.16g, 0.6 mmol) were added and the mixture was heated at reflux for 28 hours. After being cooled to room temperature the reaction mixture was added to acetic anhydride (1 mL) and stirred at room temperature overnight. The reaction mixture diluted with CH_2Cl_2 (50 mL), washed with water, brine and dried (Na_2SO_4) and the solvent evaporated to give dark brown solid. Chromatography (silica gel, 15% EtOAc/Hexane) gve the title product 1.7 g, 58%): ^{1}H NMR ($CDCl_3$) δ 8.44 (d, J=8.8 Hz,1H), 8.13(d,J=0.8Hz,1H), 7.75 (d, J=0.7 Hz, 1H), 7.56(dd,J=8.8,1.5Hz,1H),5.23(s,2H), 2.79(s,3H), 2.12(s,3H), mass calculated for compound **266** is 232.23, observed LCMS m/z 233.2 (M+H).

Part C:

A mixture of the above compound **266** (1.0 g, 4.3 mmol) in 10 mL of 48% HBr was stirred at room temperature for 16 hours. The solid was collected on Buchner funnel, washed with 48% HBr and dried in a vacuum desiccator with P_2O_5 and NaOH to give the title compound as a light tan solid (1.15 g, 92%), which was used in the next step with out further purification. mass calculated for compound **267** is 209.97, observed LCMS m/z 211.2 (M+H).

Part D:

The mixture above compound **267** (1.6g, 5.7 mmol) and 3, 4-dihydro-2H-pyran(1g, 11.3 mmol, 2 equivalents) in THF (40mL) was refluxed for 2 hours and stirred at room temperature for overnight. The reaction mixture diluted to 100 mL with CH_2Cl_2, washed with water, saturated $NaHCO_3$, water, brine and dried over $MgSO_4$ and the solvent evaporated. Chromatography (silica gel, EtOAc/Hexane 0-20%) gave title compound as beige solid (1.3 g, 79%), mass calculated for compound **268** is 293.03, observed LCMS m/z 294.0 (M+H).

Part E:

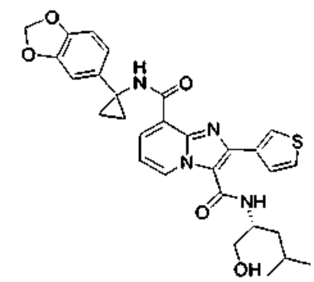
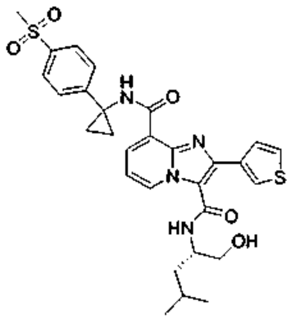
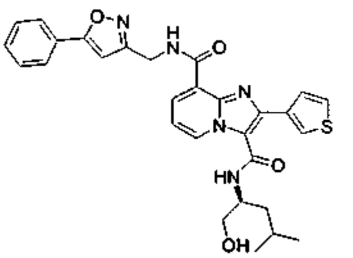
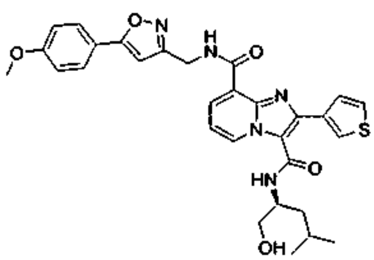
A solution of 5-(Bromomethyl)-1-(2(tetrahydropyranyl) indazole **268** (1 g, 4 mmol) in dry DMF was treated with sodium azide (0.78 g, 12 mmol.) in one portion and heated to 90^{0}C for 30 min. The reaction mixture cooled to room temperature, poured in to water (50 mL) and extracted with ether (150 mL), the organic phase washed with brine, dried over $MgSO_4$, filtered and evaporated to give title compound azide **269**. No further purification is needed. mass calculated for compound **269** is 257.12, observed LCMS m/z 258.2 (M+H).

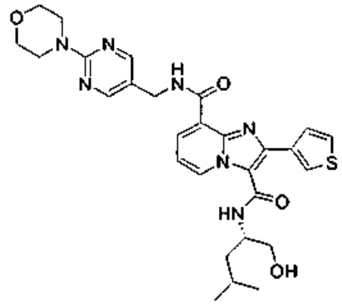
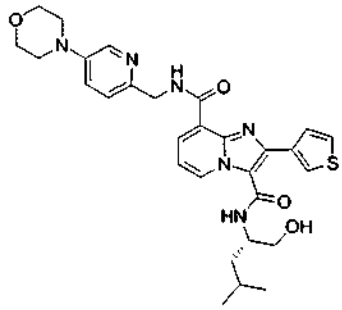
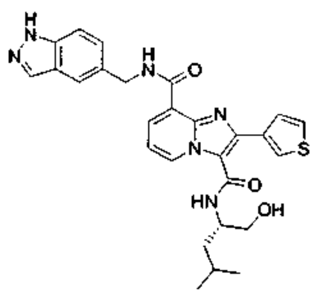
Part F:

A solution of azide **269** from the above step (1g) in THF was cooled to 0^{0}C in ice bath and treated with LAH (10 mL, 1.0 M in THF) via syringe over 10 min. After 1 hour, the reaction mixture was quenched by drop wise addition of 1.0 M solution of NaOH (1.5 mL). The reaction mixture allowed to warm up to room temperature, diluted with EtOAc (60 mL) dried with (Na_2SO_4) and filtered (celite). The organic layer evaporated to give essentially pure amine **270**. mass calculated for compound **270** is 231.13, observed LCMS m/z 232.1 (M+H).

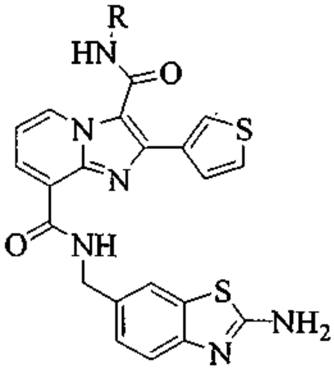
The compounds in Table 9 are made using the methods described in **Example 3** Part A and B.

Table 9

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
271		546.19	547.2	5.58
272		580.18	581.0	4.97
273		543.19	544.0	5.72
274		573.20	574.0	5.67

275		563.23	564.0	4.62
276		562.24	563.0	3.77
277		516.19	517.0	4.46

Example 4H

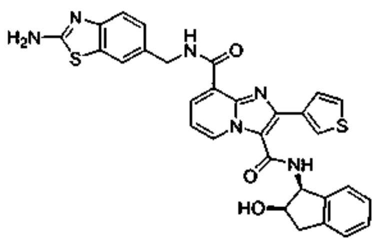
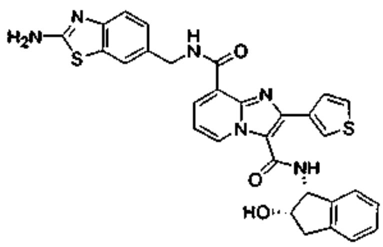


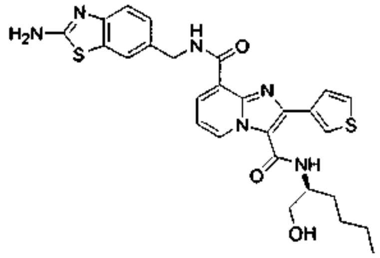
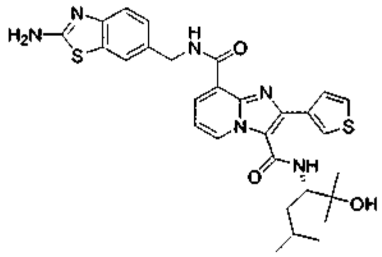
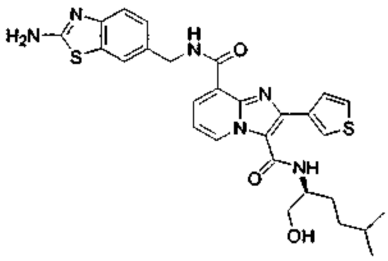
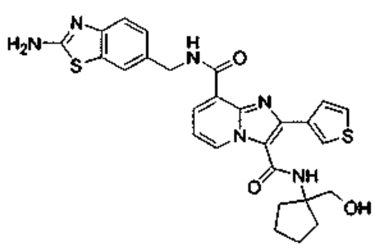
278-289

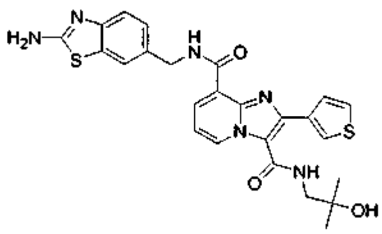
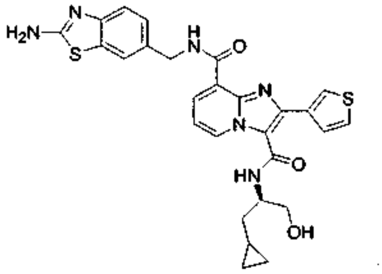
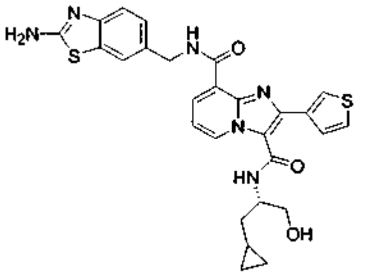
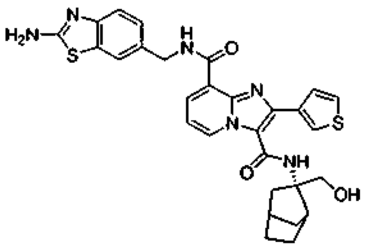
(wherein R is the remaining moiety of the Q^B group in formula 1.0)

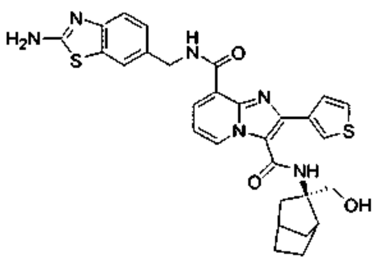
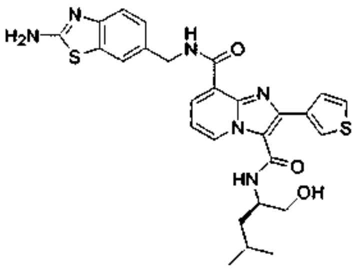
The compounds in Table 10 are made using the methods described in the **Example 3**, parts A and B and **Example 2C** part D.

Table 10

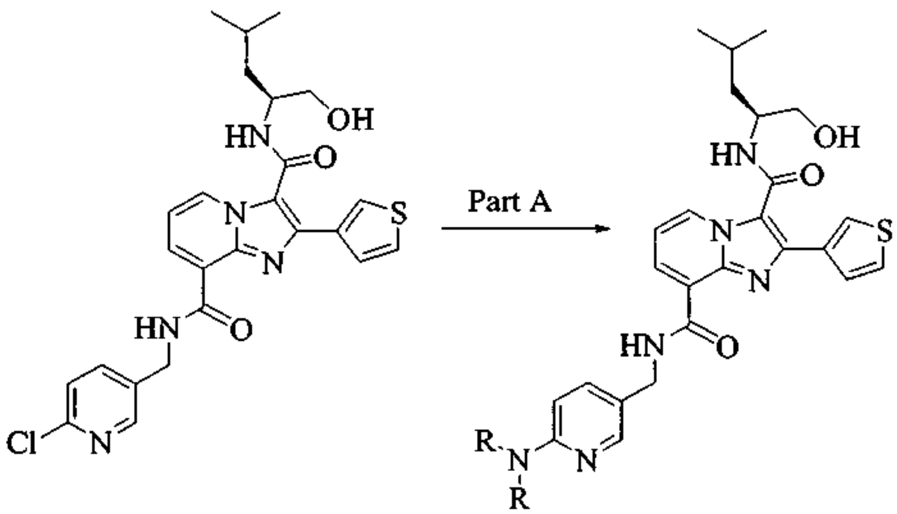
Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
278		580.13	581.0	3.75
279		580.13	581.0	3.75

280		548.16	549.2	3.8
281		576.19	577.2	4.05
282		562.18	563.2	4.17
283		546.15	547.0	3.85

284		520.13	521.0	3.34
285		546.15	546.1	3.45
286		546.15	546.1	3.45
287		572.16	573.1	3.85

288		572.16	573.1	3.87
289		548.16	549.0	5.58

Example 5A



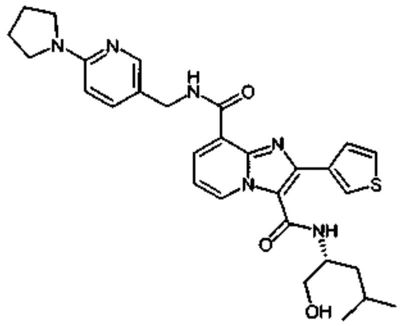
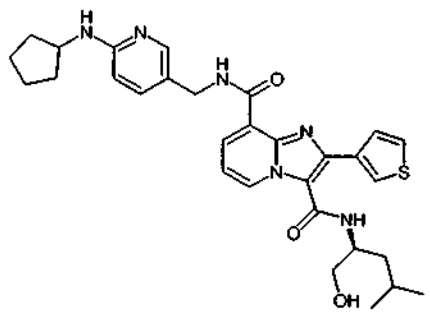
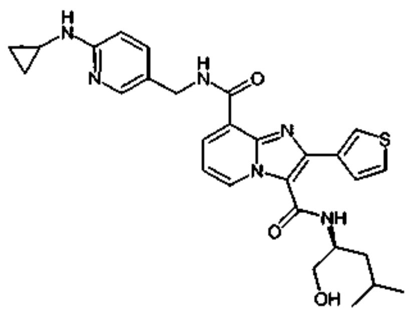
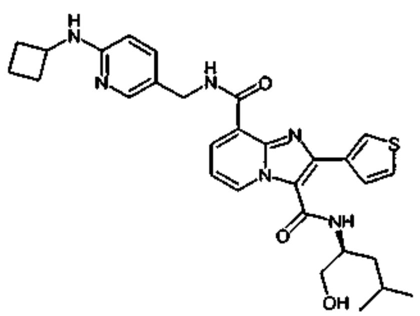
221 290

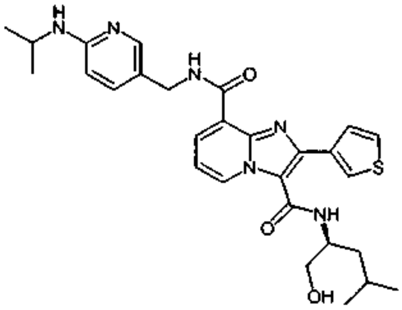
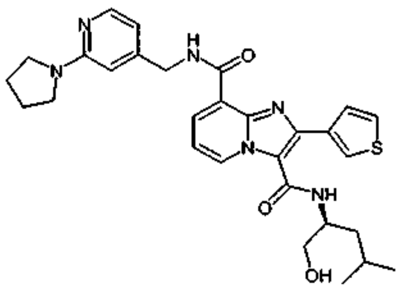
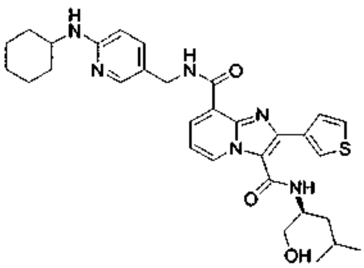
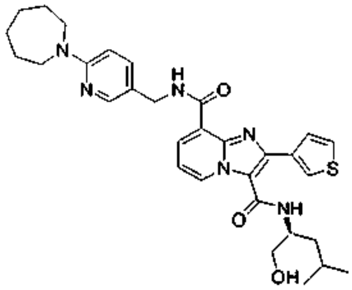
(wherein the R groups are identified in Table 11)

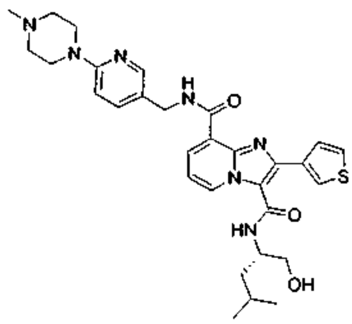
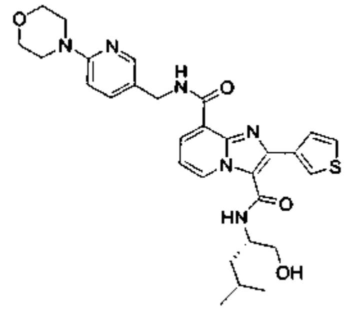
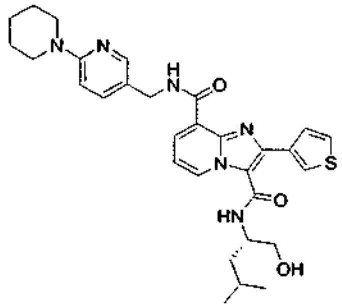
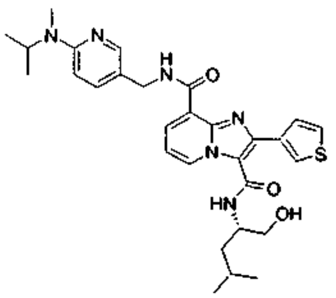
The compound **221** prepared using methods described in **Example 3A** was dissolved in to NMP (5 mL) and distributed equally in to 4 mL vials. The required amine was added in excess and the mixture was heated in a sealed tube at 100^0 C for 72 hours or until LCMS analysis showed the completion of the reaction.

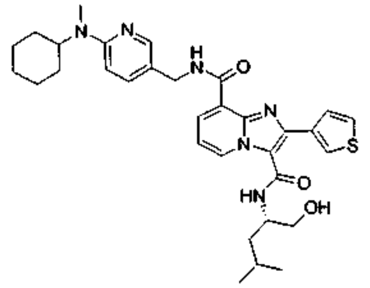
The crude material was subjected to HPLC purification to get pure products in various yields. The products obtained are given in Table 11.

Table 11

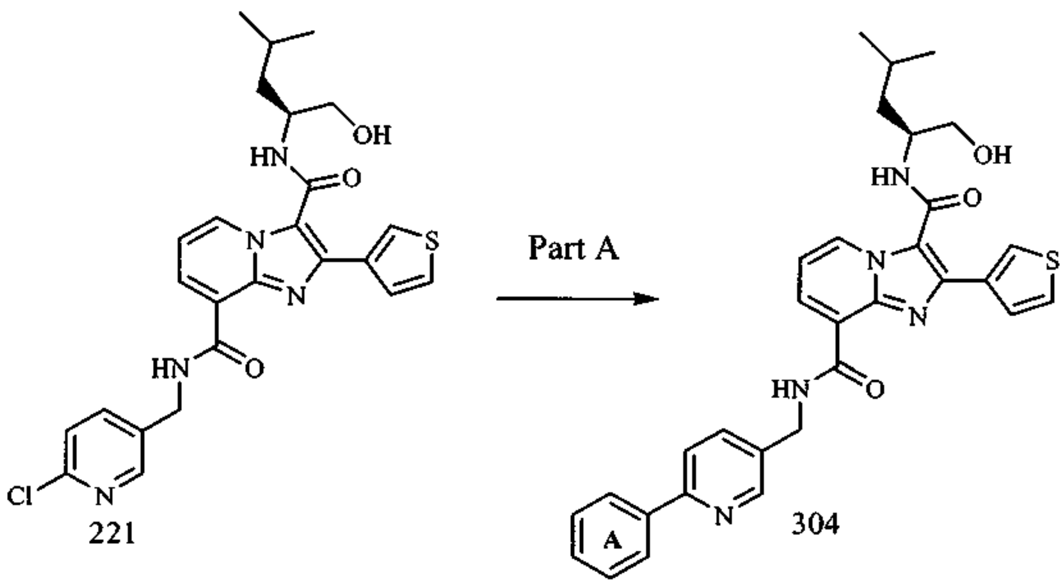
Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
291		546.24	547.2	3.82
292		560.26	561.3	1.32
293		532.23	533.2	1.32
294		546.24	547.2	1.25

295		534.24	535.2	1.25
296		546.24	547.2	3.9
297		574.27	575.2	4.15
298		574.27	575.2	4.0

299		575.27	576.2	3.2
300		562.24	563.2	3.45
301		560.26	561.3	3.8
302		548.26	549.0	4.07

303		588.29	589.0	4.07

Example 5B



221

304

Ring A is phenyl or pyridyl

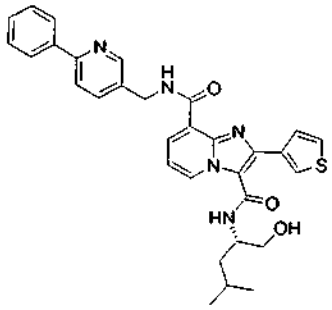
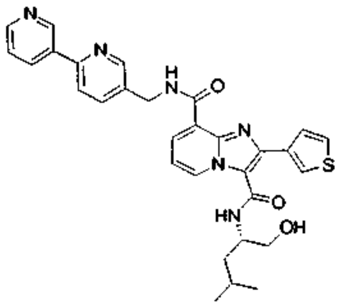
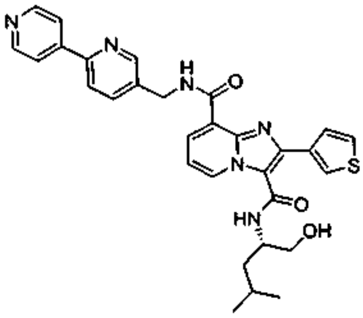
(Ring A is phenyl or pyridyl as identified in Table 12)

Part A:

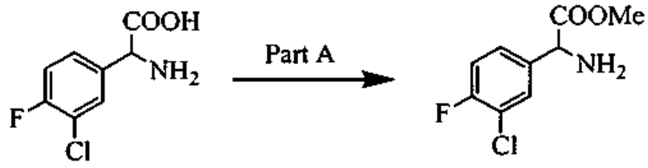
The compound **221** (0.15 mmol) is taken in DMF (1 mL) and added with 0.015 mmol, of $Pd(dppf)_2Cl_2$, appropriate boronic acid (0.18 mmol; 1.2 equivalents) and K_3PO_4 (0. 70mg; 2.5 mmol) were added. The reaction mixture purged with argon and heated at 80 ^{0}C for 14hrs. LC MS analysis showed completion of the reaction.

The reaction mixture poured in to water, extracted with Ethyl acetate. The organic layer washed with brine, dried over anh.$MgSO_4$, filtered, evaporated and subjected to HPLC purification to give the 90% pure title compound. The compounds obtained are identified in Table 12.

Table 12

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
305		553.21	554.0	4.57
306		554.21	555.0	3.79
307		554.21	555.1	3.82

Example 6A

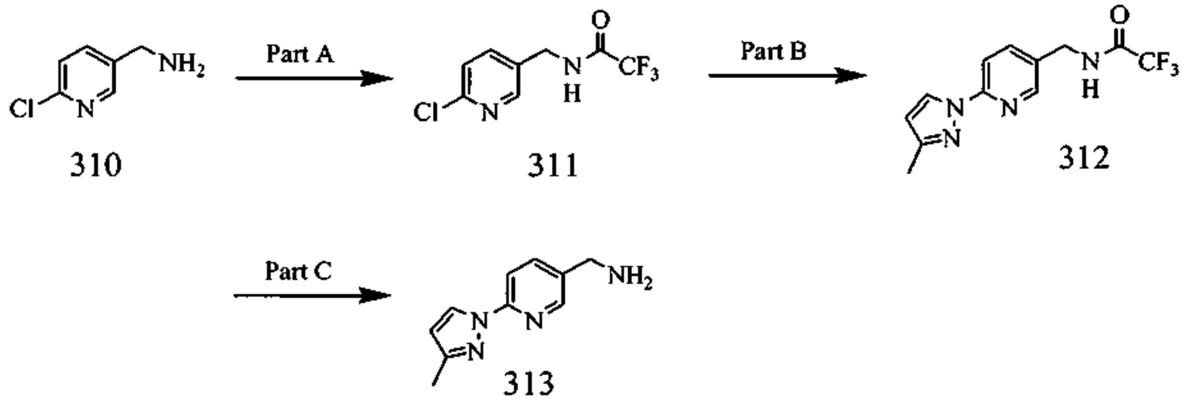


308 309

Part A:

To a solution of compound **308** (0.15 mmol) in acetonitrile (2 mL) and methanol (2 mL) was added (trimethylsilyl)diazomethane (2*M*, 0.11 mL, 0.22 mmol). The reaction mixture was stirred at room temperature for 30 minutes. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo* to afford compound **309** as a white solid. HPLC-MS t_R = 0.82 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_9ClFNO_2$ 217.0, observed LCMS m/z 218.1 (M+H).

Example 6B



310 311 312 313

Part A:

To a solution of 2-chloro-5-aminomethylpyridine **310** (1g, 7.0 mmol) in dichloromethane (20 mL) at 0^0C (ice-bath) was added trifluoroacetic anhydride (1.2 mL, 8.5 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 1 hour. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo* to afford compound **311** (100 % yield) as a white solid. HPLC-MS t_R = 1.37 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_6ClF_3N_2O$ 238.0, observed LCMS m/z 239.0 (M+H).

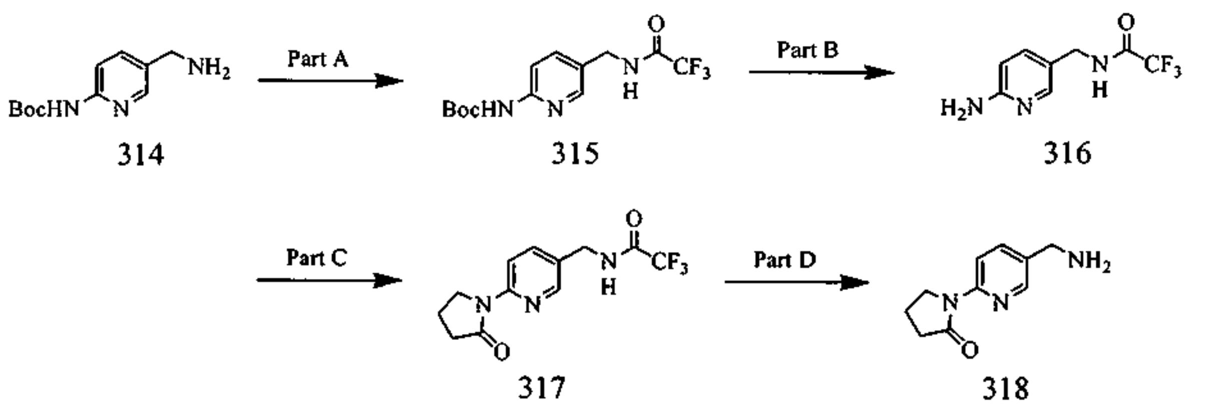
Part B:

A mixture of compound **311** (0.180 g, 0.76 mmol) and 3-methylpyrazole (2 mL) was heated at 110^0 C for 72 hours. Once the reaction mixture was cooled to room temperature, LC-MS analysis indicated that the reaction was complete. The volatiles were removed *in vacuo,* and the crude product was purified by flash column chromatography (SiO_2, ethyl acetate / methanol – 9:1) to afford compound **312** as a white solid (35 % yield). HPLC-MS t_R = 1.57 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{11}F_3N_4O$ 284.1, observed LCMS m/z 285.0 (M+H).

Part C:

A mixture of compound **312** (0.007 g, 0.03 mmol) and NaOH (1*M*, 0.3 mL, 0.3 mmol) in methanol (3 mL) was stirred at room temperature for 16 hours. LC-MS analysis of the reaction indicated that the reaction was incomplete. NaOH (1*M*, 0.6 mL, 0.6 mmol) was added and the reaction mixture heated at 55^0 C for 16 hours. Once the reaction mixture was cooled to room temperature, LC-MS analysis indicated that full hydrolysis had occurred. The volatiles were removed *in vacuo,* and the crude dried to afford compound 30 as white paste (100 % yield). HPLC-MS t_R = 0.72 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_{12}N_4$ 188.1, observed LCMS m/z 189.1 (M+H).

Example 6C



Part A:

Compound **314** was prepared using procedures described in **Example 6B**, Part A. HPLC-MS t_R = 1.59 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{16}F_3N_3O_3$ 319.1, observed LCMS m/z 320.1 (M+H).

Part B:

Compound **316** was prepared using procedures described in **Example 6B**, Part B. HPLC-MS t_R = 0.40 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_8F_3N_3O$ 219.1, observed LCMS m/z 220.1 (M+H).

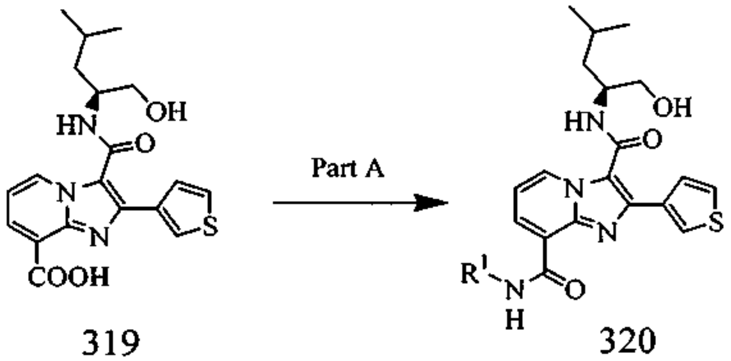
Part C:

A mixture of compound **316** (0.10 g, 0.46 mmol) and vinylacetic acid (5 mL) was heated at 110^0 C for 96 hours. Once the reaction mixture was cooled to room temperature, LC-MS analysis indicated that the reaction was complete. The volatiles were removed *in vacuo*, and the crude was purified by Prep-LC to afford compound **317** as a white solid. HPLC-MS t_R = 0.49 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{12}F_3N_3O_2$ 287.1, observed LCMS m/z 288.1 (M+H).

Part D:

Compound **318** was prepared using procedures described in **Example 6B**, Part C. HPLC-MS t_R = 0.18 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_{13}N_3O$ 191.1, observed LCMS m/z 192.1 (M+H).

Example 6D



319 320

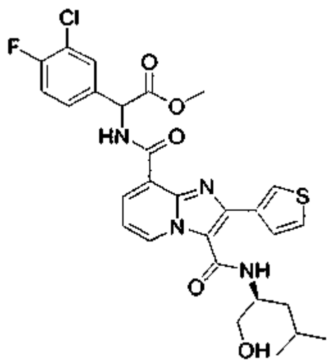
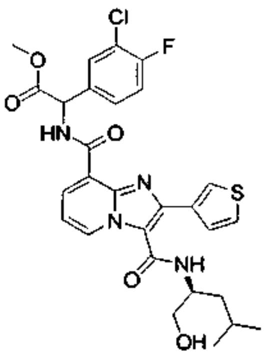
(wherein R^1 is identified in Table 13)

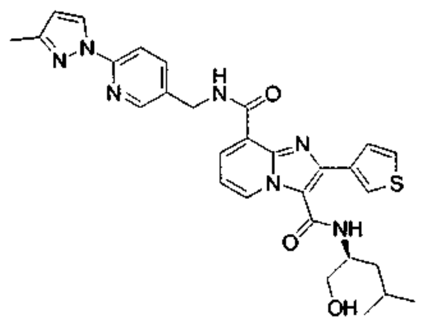
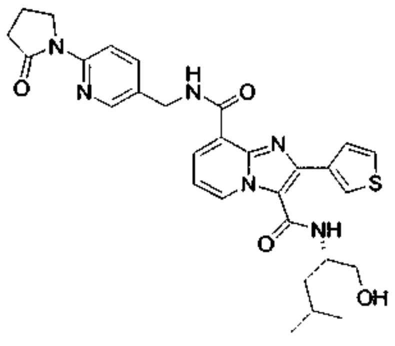
Part A:

Compounds **321** and **322** are isomers and were prepared from compound **309** using the coupling conditions described in **Example 1B**, Part I. Purification by Prep-LC allowed isolation of both diastereomers. Compounds **323** and **324** were prepared from compounds **314** and **318** respectively, using the coupling conditions described in Example 1B, Part I.

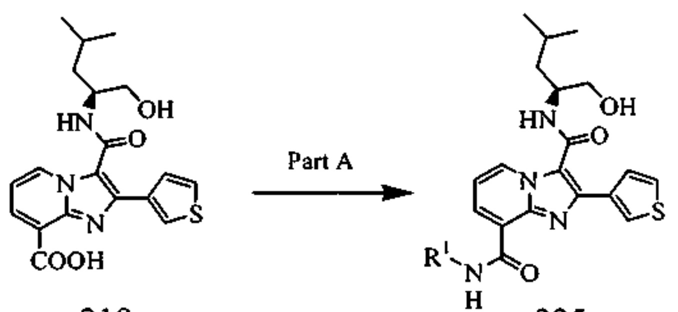
The compounds in Table 13 were synthesized using this procedure.

Table 13

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
321		586.1	587.1	5.98
322		586.1	587.1	6.13

323		557.2	558.2	5.47
324		560.2	561.2	3.49

Example 6E



319 325

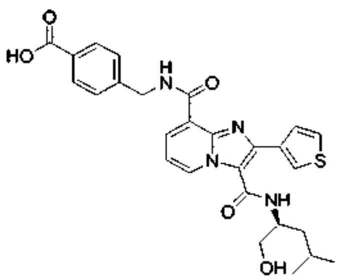
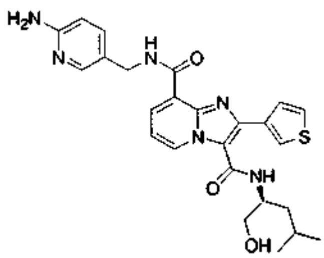
(wherein R[1] is identified in Table 14)

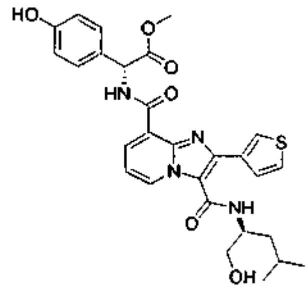
Part A:

To a mixture of compound **319** (0.1 mmol) and HATU (0.046 g, 0.12 mmol) in DMF (2 mL) was added amine building block (1.2 equivalents) and diisopropylamine (3 equivalents). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, ethyl acetate was added, and washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. The crude was redissolved in dioxane (1 mL), and a solution of 4 *N* HCl in dioxane (2 mL) and water (0.2 mL) was added at 0^0C (ice-bath). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, acetonitrile was added, concentrated and dried to afford compounds. Purification by Prep-LC and conversion to the hydrochloride salt afforded compounds as white solids.

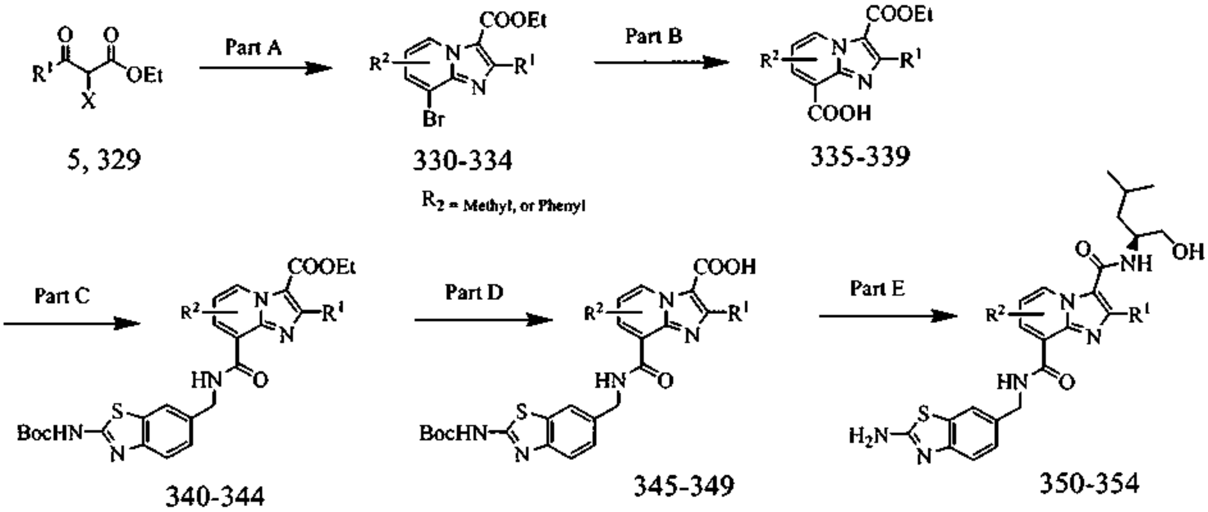
The compounds in Table 14 were synthesized using this procedure.

Table 14

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
326		520.2	521.2	4.53
327		492.2	493.2	3.50

328		550.2	551.2	4.72

Example 7A



(R^1 and R^2 are identified in Table 15)

Compound **5** was prepared using procedures described in **Example 1B**.

Part A:

A mixture of compound **5** (0.148 g, 0.53 mmol) and 2-amino-3-bromo-5-methylpyridine (0.100 g, 0.53 mmol) in ethanol (5 mL) was heated at relux for 60 hours. After cooling to room temperature, the reaction was monitored by LC-MS. The volatiles were removed *in vacuo*, ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. The crude was purified by preparative Thin Layer Chromatography (SiO_2, ethyl acetate / hexanes – 1:1) to afford compound **330** as a white solid. HPLC-MS t_R = 2.25 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{13}BrN_2O_2S$ 363.99, observed LCMS m/z 365.0 (M+H).

Compound **331** was prepared from the reaction of ethyl 2-chloroacetoacetate **332** and 2-amino-3-bromo-5-methylpyridine. HPLC-MS t_R = 1.78 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{13}BrN_2O_2$ 296.0, observed LCMS m/z 297.0 (M+H).

Compound **332** was prepared from the reaction of compound 5 and 2-amino-3-bromo-5-phenylpyridine. HPLC-MS t_R = 2.55 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{15}BrN_2O_2S$ 426.0, observed LCMS m/z 427.0 (M+H).

Compound **333** was prepared from the reaction of ethyl 2-chloroacetoacetate **332** and 2-amino-3-bromo-5-phenylpyridine. HPLC-MS t_R = 2.26 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{15}BrN_2O_2$ 358.0, observed LCMS m/z 359.0 (M+H).

Compound **334** was prepared from the reaction of ethyl 2-chloroacetoacetate **332** and 2-amino-3-bromo-6-methylpyridine. HPLC-MS t_R = 1.61 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{13}BrN_2O_2$ 296.0, observed LCMS m/z 297.0 (M+H).

Part B:

A saturated solution of carbon monoxide in a 20 ml scintillation vial was pre-prepared by adding acetic anhydride (0.032 mL, 0.34 mmol) and diisopropylethylamine (0.046 mL, 0.34 mmol) to a solution of sodium formate (0.034 g, 0.51 mmol) in de-gassed DMF (2 mL). The reaction mixture was stirred at room temperature for 1 hour. In another flask, palladium (II) acetate (0.00113 g, 0.005 mmol) was added to a solution of 1,3-bis(diphenylphosphino)propane (0.00207 g, 0.005 mmol) in de-gassed DMF (2 mL) and stirred at room temperature for 30 minutes. Lithium chloride (0.021 g, 0.51 mmol) was added and the solution sonicated to ensure there was no precipitation. Compound **330** (0.061 g, 0.17 mmol) was added and the reaction mixture quickly transferred to the saturated solution of carbon monoxide. The vial was capped and the reaction mixture heated at 80^{0}C for 16 hours. The vial was cooled to room temperature, and the reaction monitored by LC-MS. The precipitates were removed by filtration, the filtrate concentrated, and the crude re-dissolved in acetonitrile (1 mL). The solution was acidified to p*H* 4.0 with 1.0 *M* HCl, concentrated and dried to afford compound **335** which was used as crude in the next step. HPLC-MS t_R = 1.85 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{14}N_2O_4S$ 330.1, observed LCMS m/z 331.0 (M+H).

Compound **336** was prepared from compound **331**. HPLC-MS t_R = 1.01 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{14}N_2O_4$ 262.1, observed LCMS m/z 263.1 (M+H).

Compound **337** was prepared from compound **332**. HPLC-MS t_R = 2.28 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{16}N_2O_4S$ 392.1, observed LCMS m/z 393.1 (M+H).

Compound **338** was prepared from compound **333**. HPLC-MS t_R = 1.55 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{16}N_2O_4$ 324.1, observed LCMS m/z 325.1 (M+H).

Compound **339** was prepared from compound **334**. HPLC-MS t_R = 0.95 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{14}N_2O_4$ 262.1, observed LCMS m/z 263.2 (M+H).

<u>Part C:</u>

To a mixture of compound **335** (0.1 mmol) and HATU (0.046 g, 0.12 mmol) in DMF (2 mL) was added (6-Aminomethyl-benzothiazol-2-yl)-carbamic acid tert-butyl ester (1.2 equivalents) and diisopropylamine (3 equivalents). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. The crude was purified by preparative Thin Layer Chromatography (SiO_2, ethyl acetate) to afford compound **340** as a white solid. HPLC-MS t_R = 2.40 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{29}N_5O_5S_2$ 591.2, observed LCMS m/z 592.0 (M+H).

Compound **341** was prepared from compound **336**. HPLC-MS t_R = 2.31 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{29}N_5O_5S$ 523.2, observed LCMS m/z 524.2 (M+H).

Compound **342** was prepared from compound **337**. HPLC-MS t_R = 2.50 min ($UV_{254\ nm}$); mass calculated for formula $C_{34}H_{31}N_5O_5S_2$ 653.2, observed LCMS m/z 654.1 (M+H).

Compound **343** was prepared from compound **338**. HPLC-MS t_R = 2.44 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{31}N_5O_5S$ 585.2, observed LCMS m/z 586.2 (M+H).

Compound **344** was prepared from compound **339**. HPLC-MS t_R = 1.54 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{29}N_5O_5S$ 523.2, observed LCMS m/z 524.2 (M+H).

Part D:

A mixture of compound **340** (0.010 g, 0.017 mmol) and LiOH (1*M*, 51 uL, 0.051 mmol) in THF (2 mL) and water (1 mL) was heated at 55^{0}C for 16 hours. LC-MS analysis of the reaction indicated that the reaction was complete. Hexanes (1 mL) were added to form a biphasic solution. The aqueous phase was separated, acidified to p*H* 4.0 with 1*N* HCl, concentrated and lyophilized with acetonitrile and water (1:1) to afford compound **345** as a white solid. HPLC-MS t_R = 1.95 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{25}N_5O_5S_2$ 563.1, observed LCMS m/z 564.1 (M+H).

Compound **346** was prepared from compound **341**. HPLC-MS t_R = 1.74 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{25}N_5O_5S$ 495.2, observed LCMS m/z 496.1 (M+H).

Compound **347** was prepared from compound **342**. HPLC-MS t_R = 2.07 min ($UV_{254\ nm}$); mass calculated for formula $C_{32}H_{27}N_5O_5S_2$ 625.1, observed LCMS m/z 626.0 (M+H).

Compound **348** was prepared from compound **343**. HPLC-MS t_R = 1.93 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{27}N_5O_5S$ 557.2, observed LCMS m/z 558.1 (M+H).

Compound **349** was prepared from compound **344**. HPLC-MS t_R = 1.22 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{25}N_5O_5S$ 495.2, observed LCMS m/z 496.1 (M+H).

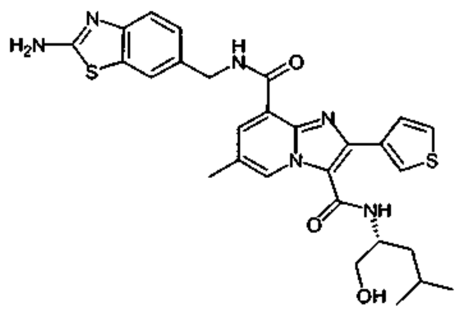
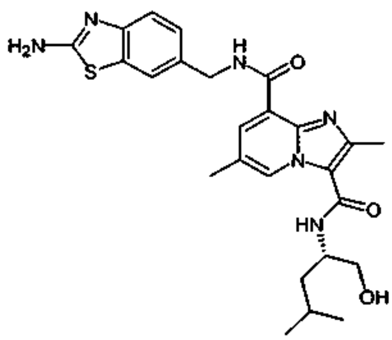
Part E:

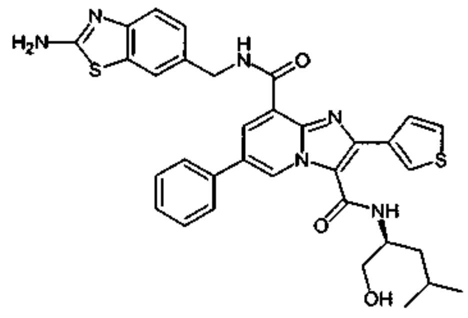
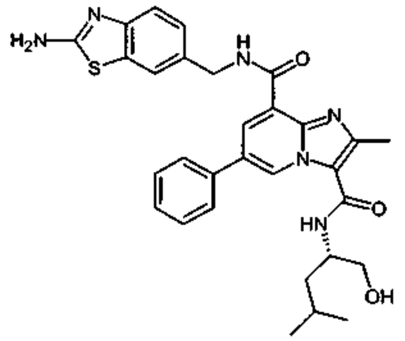
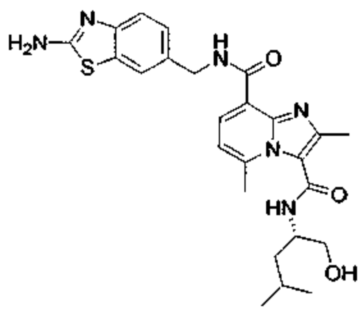
To a mixture of compound **345** (0.1 mmol) and HATU (0.046 g, 0.12 mmol) in DMF (2 mL) was added L-leucinol (1.2 equivalents) and diisopropylamine (3 equivalents). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, ethyl acetate was added, and washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. The crude was redissolved in dioxane (1 mL), and a solution of 4 *N*

HCl in dioxane (2 mL) and water (0.2 mL) was added at 0^{0}C (ice-bath). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that hydrolysis was complete. The volatiles were removed *in vacuo*, acetonitrile was added, concentrated and dried to afford compounds. Purification by Prep-LC and conversion to the hydrochloric salt afforded compounds **350-354** (Table 15) as white solids.

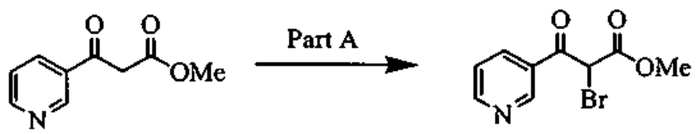
The ligands in Table 15 were synthesized using this procedure.

Table 15

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
350		562.2	563.1	3.93
351		494.2	495.1	2.83

352		624.2	625.2	4.42
353		556.2	557.2	3.72
354		494.2	494.6	2.23

Example 9A

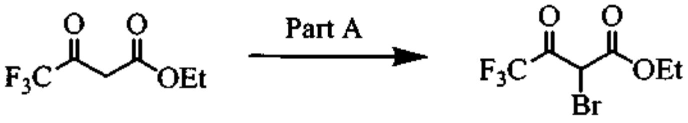


365 366

Part A:

Compound **366** was prepared from methyl nicotinoylacetate **365** using procedures described in Example 1B, Part B. HPLC-MS t_R = 1.15 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_8BrNO_3$ 257.0, observed LCMS m/z 258.0 (M+H).

Example 9B

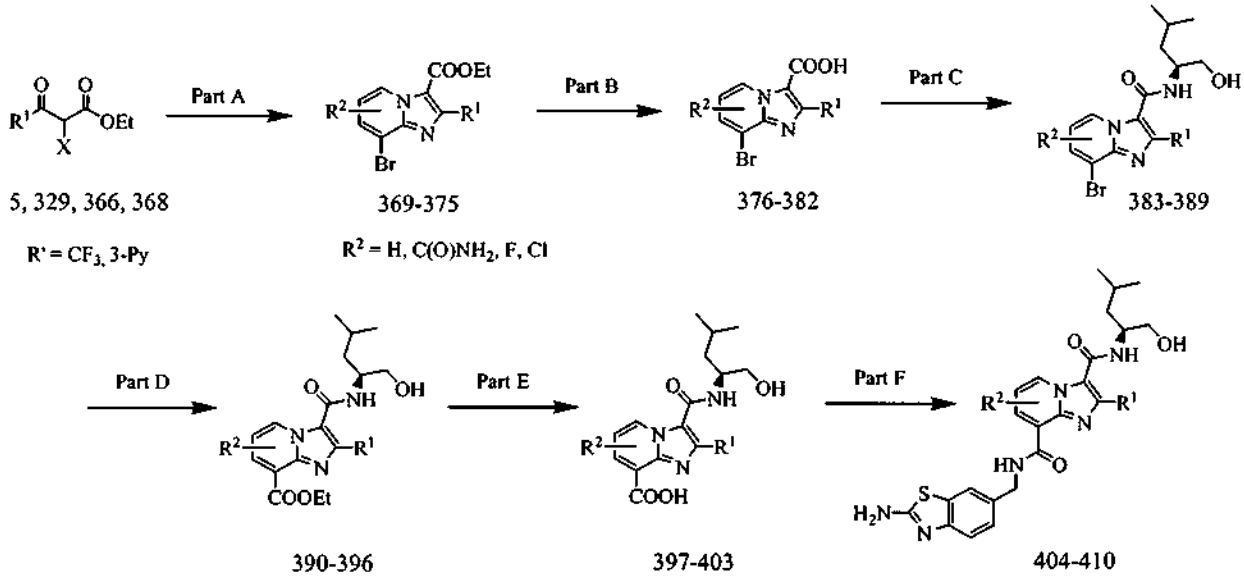


367 368

Part A:

Compound **368** was prepared from ethyl 4,4,4-trifluoroacetoacetate **367** using procedures described in Example 1B, Part B. HPLC-MS t_R = 1.30 min ($UV_{254\ nm}$); mass calculated for formula $C_6H_6BrF_3O_3$ 261.9, observed LCMS m/z 263.0 (M+H).

Example 9C



(wherein R^1 is identified in Table 16)

Compound **5** was prepared using procedures described in **Example 1B**.

Part A:

A mixture of compound **5** (0.148 g, 0.53 mmol) and 2-amino-3-bromo-5-chloropyridine (0.110 g, 0.53 mmol) in ethanol (5 mL) was heated at reflux for 60 hours. After cooling to room temperature, the reaction was monitored by LC-MS. The volatiles were removed *in vacuo*, ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. The crude was purified by preparative Thin Layer Chromatography (SiO_2, ethyl acetate / hexanes – 1:1) to afford compound

369 as a white solid. HPLC-MS t_R = 2.40 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{10}BrClN_2O_2S$ 383.9, observed LCMS m/z 384.9 (M+H).

Compound **370** was prepared from the reaction of ethyl 2-chloroacetoacetate **329** and 2-amino-3-bromo-5-chloropyridine. HPLC-MS t_R = 2.07 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{10}BrClN_2O_2$ 316.0, observed LCMS m/z 317.0 (M+H).

Compound **371** was prepared from the reaction of ethyl 2-chloroacetoacetate **329** and 6-amino-5-bromo-nicotinonitrile. HPLC-MS t_R = 1.74 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{10}BrN_3O_2$ 307.0, observed LCMS m/z 308.0 (M+H).

Compound **372** was prepared from the reaction of compound 5 and 2-amino-3-bromo-5-fluoropyridine. HPLC-MS t_R = 2.29 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{10}BrFN_2O_2S$ 368.0, observed LCMS m/z 369.0 (M+H).

Compound **373** was prepared from the reaction of ethyl 2-chloroacetoacetate **329** and 2-amino-3-bromo-5-fluoropyridine. HPLC-MS t_R = 1.84 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{10}BrFN_2O_2$ 300.0, observed LCMS m/z 301.0 (M+H).

Compound **374** was prepared from the reaction of compound **366** and 2-amino-3-bromo-pyridine. HPLC-MS t_R = 1.11 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{10}BrN_3O_2$ 331.0, observed LCMS m/z 332.0 (M+H).

Compound **375** was prepared from the reaction of compound **367** and 2-amino-3-bromo-pyridine. HPLC-MS t_R = 2.03 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_8BrF_3N_2O_2$ 336.0, observed LCMS m/z 337.0 (M+H).

Part B:

Compound **376** was prepared from compound **369** using procedures described in **Example 7A**, Part D. HPLC-MS t_R = 1.80 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_6BrClN_2O_2S$ 355.9, observed LCMS m/z 357.0 (M+H).

Compound **377** was prepared from compound **370**. HPLC-MS t_R = 1.32 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_6BrClN_2O_2$ 287.9, observed LCMS m/z 289.0 (M+H).

Compound **378** was prepared from compound **371**. HPLC-MS t_R = 0.77 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_8BrN_3O_3$ 297.0, observed LCMS m/z 298.0 (M+H).

Compound **379** was prepared from compound **372**. HPLC-MS t_R = 1.63 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_6BrFN_2O_2S$ 339.9, observed LCMS m/z 340.9 (M+H).

Compound **380** was prepared from compound **373**. HPLC-MS t_R = 1.08 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_6BrFN_2O_2$ 272.0, observed LCMS m/z 273.0 (M+H).

Compound **381** was prepared from compound **374**. HPLC-MS t_R = 1.41min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_8BrN_3O_2$ 317.0, observed LCMS m/z 318.0 (M+H).

Compound **382** was prepared from compound **375**. HPLC-MS t_R = 1.41min ($UV_{254\ nm}$); mass calculated for formula $C_9H_4BrF_3N_2O_2$ 307.9, observed LCMS m/z 309.0 (M+H).

Part C:

To a mixture of compound **376** (0.1 mmol) and HATU (0.046 g, 0.12 mmol) in DMF (2 mL) was added L-Leucinol (1.2 equivalents) and diisopropylamine (3 equivalents). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. The crude was purified by preparative Thin Layer Chromatography (SiO_2, ethyl acetate / methanol – 9:1) to afford compound **383** as a white solid. HPLC-MS t_R = 2.07 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{19}BrClN_3O_2S$ 455.0, observed LCMS m/z 456.0 (M+H).

Compound **384** was prepared from compound **377**. HPLC-MS t_R = 1.70 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{19}BrClN_3O2$ 387.0, observed LCMS m/z 388.0 (M+H).

Compound **385** was prepared from compound **378**. HPLC-MS t_R = 0.69 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{21}BrN_4O_3$ 396.1, observed LCMS m/z 397.1 (M+H).

Compound **386** was prepared from compound **379**. HPLC-MS t_R = 1.90 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{19}BrFN_3O_2S$ 439.0, observed LCMS m/z 440.0 (M+H).

Compound **387** was prepared from compound **380**. HPLC-MS t_R = 1.54 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{19}BrFN_3O_2$ 371.1, observed LCMS m/z 372.0 (M+H).

Compound **388** was prepared from compound **381**. HPLC-MS t_R = 1.27 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{21}BrN_4O_2$ 416.1, observed LCMS m/z 417.1 (M+H).

Compound **389** was prepared from compound **382**. HPLC-MS t_R = 1.72 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{17}BrF_3N_3O_2$ 407.0, observed LCMS m/z 408.0 (M+H).

Part D:

Carbon monoxide (~1.5 mL) was condensed into an evacuated ACE pressure tube (35 mL) at -78^0 C (liquid nitrogen). A solution of compound **383** (0.58 mmol) in ethanol (7 mL) was transferred to the reaction tube, Pd(DPPF)Cl_2.DCM (10 mol %) was added, the pressure tube capped, and the reaction mixture warmed slowly to room temperature and then finally heated at 80^{0}C for 16 hours. The reaction mixture was cooled to 0^0 C (ice-bath), and the pressure released by uncapping the pressure tube. LC-MS analysis of the reaction indicated that the reaction was complete. The precipitates were filtered and the volatiles removed *in vacuo*. The crude was purified by preparative Thin Layer Chromatography (SiO_2, ethyl acetate / methanol – 9:1) to afford compound **390**. HPLC-MS t_R = 1.99 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{24}ClN_3O_4S$ 449.1, observed LCMS m/z 450.1 (M+H).

Compound **391** was prepared from compound **384**. HPLC-MS t_R = 1.46 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{24}ClN_3O_4$ 381.1, observed LCMS m/z 382.1 (M+H).

Compound **392** was prepared from compound **385**. HPLC-MS t_R = 1.06 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{26}N_4O_5$ 390.2, observed LCMS m/z 391.1 (M+H).

Compound **393** was prepared from compound **386**. HPLC-MS t_R = 1.84 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{24}FN_3O_4S$ 433.1, observed LCMS m/z 434.1 (M+H).

Compound **394** was prepared from compound **397**. HPLC-MS t_R = 1.28 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{24}FN_3O_4$ 365.2, observed LCMS m/z 366.1 (M+H).

Compound **395** was prepared from compound **388**. HPLC-MS t_R = 1.14 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{26}N_4O_4$ 410.2, observed LCMS m/z 411.1 (M+H).

Compound **396** was prepared from compound **389**. HPLC-MS t_R = 1.73 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{22}F_3N_3O_4$ 401.2, observed LCMS m/z 402.1 (M+H).

Part E:

Compound **397** was prepared from compound **390** using procedures described in Example 2A, Part D. HPLC-MS t_R = 1.69 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{20}ClN_3O_4S$ 421.1, observed LCMS m/z 422.1 (M+H).

Compound **398** was prepared from compound **391**. HPLC-MS t_R = 1.09 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{20}ClN_3O_4$ 353.1, observed LCMS m/z 354.1 (M+H).

Compound **399** was prepared from compound **392**. HPLC-MS t_R = 0.79 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{22}N_4O_5$ 362.2, observed LCMS m/z 363.1 (M+H).

Compound **400** was prepared from compound **393**. HPLC-MS t_R = 1.52 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{20}FN_3O_4S$ 405.1, observed LCMS m/z 406.1 (M+H).

Compound **401** was prepared from compound **394**. HPLC-MS t_R = 1.00 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{20}FN_3O_4$ 337.1, observed LCMS m/z 338.1 (M+H).

Compound **402** was prepared from compound **395**. HPLC-MS t_R = 1.04 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{22}N_4O_4$ 382.2, observed LCMS m/z 383.1 (M+H).

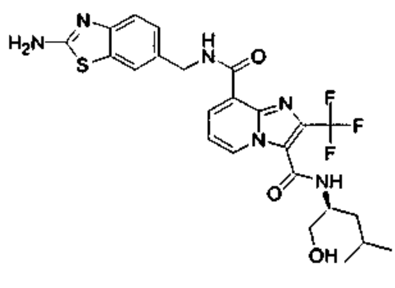
Compound **403** was prepared from compound **396**. HPLC-MS t_R = 1.46 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{18}F_3N_3O_4$ 373.1, observed LCMS m/z 374.0 (M+H).

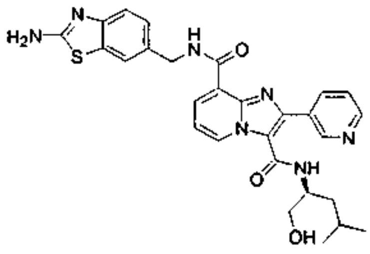
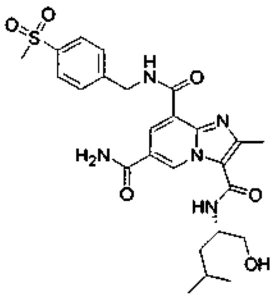
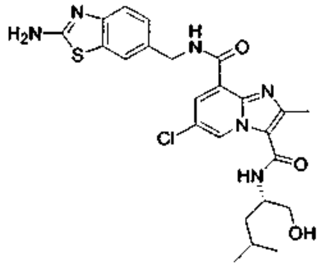
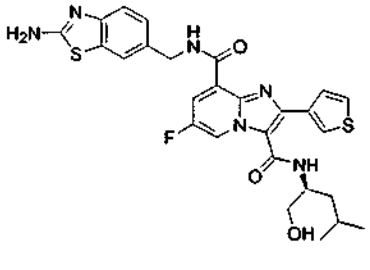
Part F:

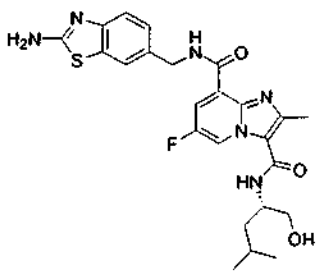
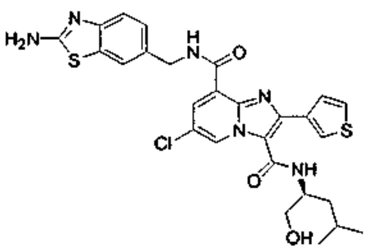
To a mixture of mono-acid (0.1 mmol) and HATU (0.046 g, 0.12 mmol) in DMF (2 mL) was added amine building block (1.2 equivalents) and diisopropylamine (3 equivalents). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, ethyl acetate was added, and washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. For compounds **404-405** and **407-410**, the crude was redissolved in dioxane (1 mL), and a solution of 4 *N* HCl in dioxane (2 mL) and water (0.2 mL) was added at 0^0 C (ice-bath). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that hydrolysis was complete. The volatiles were removed *in vacuo*, acetonitrile was added, concentrated and dried to afford compounds. Purification by Prep-LC and conversion to the hydrochloride salt afforded compounds **404-410** as white solids.

The compounds in Table 16 were synthesized using this procedure.

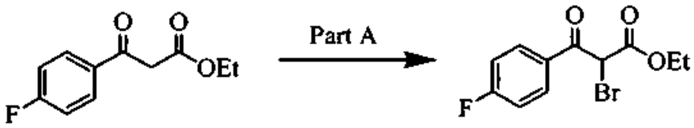
Table 16

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
404		534.2	535.2	3.74

405		543.2	544.2	2.84
406		529.2	530.2	3.5
407		514.2	515.2	3.78
408		566.2	567.2	4.16

409		498.2	499.2	3.51
410		582.1	583.2	4.41

Example 10A

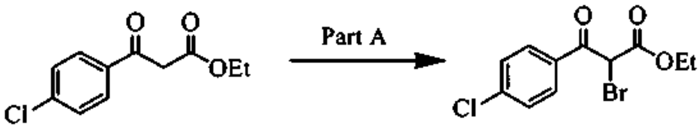


411 412

Part A:

Compound **412** was prepared from ethyl 4-fluorobenzoylacetate **411** using procedures described in **Example 1B**, Part B. HPLC-MS t_R = 1.86 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{10}BrFO_3$ 288.0, observed LCMS m/z 289.0 (M+H).

Example 10B

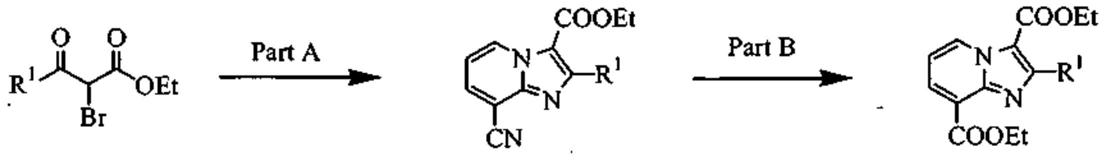


413 414

Part A:

Compound **414** was prepared from ethyl 4-chlorobenzoylacetate **413** using procedures described in Example 1B, Part B. HPLC-MS t_R = 2.04 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{10}BrClO_3$ 304.0, observed LCMS m/z 305.0 (M+H).

Example 10C



357, 412, 414 415-417 418-420

Part A:

A mixture of compound **357** (2 mmol) and 2-amino-3-cyanopyridine (0.200 g, 1.67 mmol) in ethanol (8 mL) was heated at reflux for 60 hours. After cooling to room temperature, the reaction was monitored by LC-MS. The volatiles were removed *in vacuo*, ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. The crude was purified by preparative Thin Layer Chromatography (SiO_2, ethyl acetate / hexanes – 1:1) to afford compound **415** as a white solid. HPLC-MS t_R = 1.92 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{13}N_3O_2$ 291.1, observed LCMS m/z 292.0 (M+H).

Compound **416** was prepared from the reaction of compound **412** and 2-amino-3-cyanopyridine. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{12}FN_3O_2$ 309.1, observed LCMS m/z 310.1 (M+H).

Compound **417** was prepared from the reaction of compound **414** and 2-amino-3-cyanopyridine. HPLC-MS t_R = 2.08 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{12}ClN_3O_2$ 325.1, observed LCMS m/z 326.0 (M+H).

Part B:

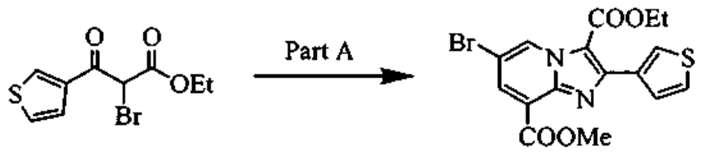
A mixture of compound **415** (0.090 g, 0.31 mmol) and chlorotrimethylsilane (0.393 mL, 3.1 mmol) in ethanol (5 mL) was heated at 60^0 C for 16 hours. After cooling to room temperature, the reaction was monitored by LC-MS. After cooling to room temperature, the reaction was monitored by LC-MS. The volatiles were removed *in vacuo*, ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. The crude was purified by preparative Thin Layer Chromatography (SiO_2, ethyl acetate) to afford compound **418** as a white solid.

HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{18}N_2O_4$ 338.1, observed LCMS m/z 339.1 (M+H).

Compound **419** was prepared from compound **416**. HPLC-MS t_R = 1.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{17}FN_2O_4$ 356.1, observed LCMS m/z 357.1 (M+H).

Compound **420** was prepared from compound **417**. HPLC-MS t_R = 2.16 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{17}ClN_2O_4$ 372.1, observed LCMS m/z 373.0 (M+H).

Example 10D



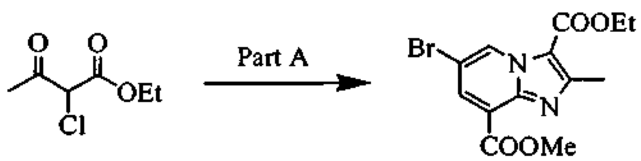
5 421

Compound **5** was prepared using procedures described in **Example 1B**.

Part A:

Compound **421** was prepared from the reaction of compound **5** and methyl 2-amino-5-bromonicotinate using procedures described in **Example 1B**, Part C. HPLC-MS t_R = 2.15 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{13}BrN_2O_4S$ 408.0, observed LCMS m/z 409.0 (M+H).

Example 10E

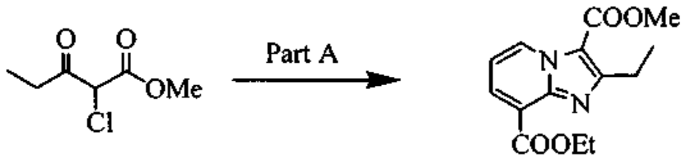


329 422

Part A:

Compound **422** was prepared from the reaction of ethyl 2-chloroacetoacetate **329** and methyl 2-amino-5-bromonicotinate using procedures described in **Example 1B**, Part C. HPLC-MS t_R = 1.72 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{13}BrN_2O_4$ 340.0, observed LCMS m/z 341.0 (M+H).

Example 10F

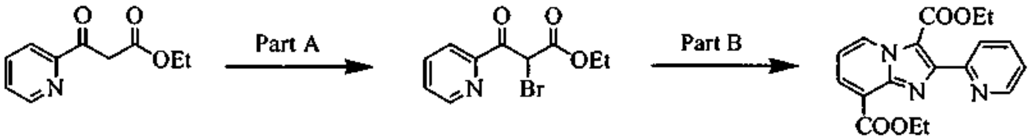


423 424

Part A:

Compound **424** was prepared from the reaction of methyl 2-chloro-3-oxopentanoate **423** and compound 2 using procedures described in **Example 1B**, Part C. HPLC-MS t_R = 1.20 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{16}N_2O_4$ 276.1, observed LCMS m/z 277.1 (M+H).

Example 10G



425 426 427

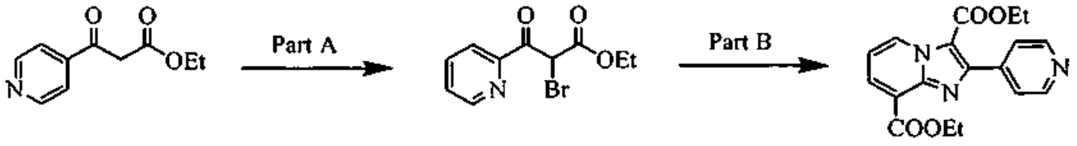
Part A:

Compound **426** was prepared from ethyl picolinoylacetate **425** using procedures described in **Example 1B**, Part B. HPLC-MS t_R = 1.94 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_{10}BrNO_3$ 271.0, observed LCMS m/z 272.0 (M+H).

Part B:

Compound **427** was prepared from the reaction of compound **426** and compound 2 using procedures described in **Example 1B**, Part C. HPLC-MS t_R = 0.67 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{17}N_3O_4$ 339.1, observed LCMS m/z 340.0 (M+H).

Example 10H



428 429 430

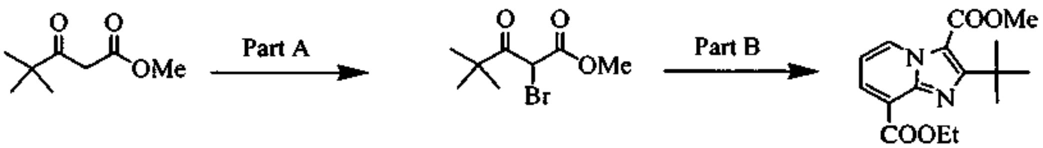
Part A:

Compound **429** was prepared from ethyl isonicotinoylacetate **428** using procedures described in **Example 1B**, Part B. HPLC-MS t_R = 1.49 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_{10}BrNO_3$ 271.0, observed LCMS m/z 272.0 (M+H).

Part B:

Compound **430** was prepared from the reaction of compound **429** and compound 2 using procedures described in **Example 1B**, Part C. HPLC-MS t_R = 0.66 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{17}N_3O_4$ 339.1, observed LCMS m/z 340.0 (M+H).

Example 10I



431 432 433

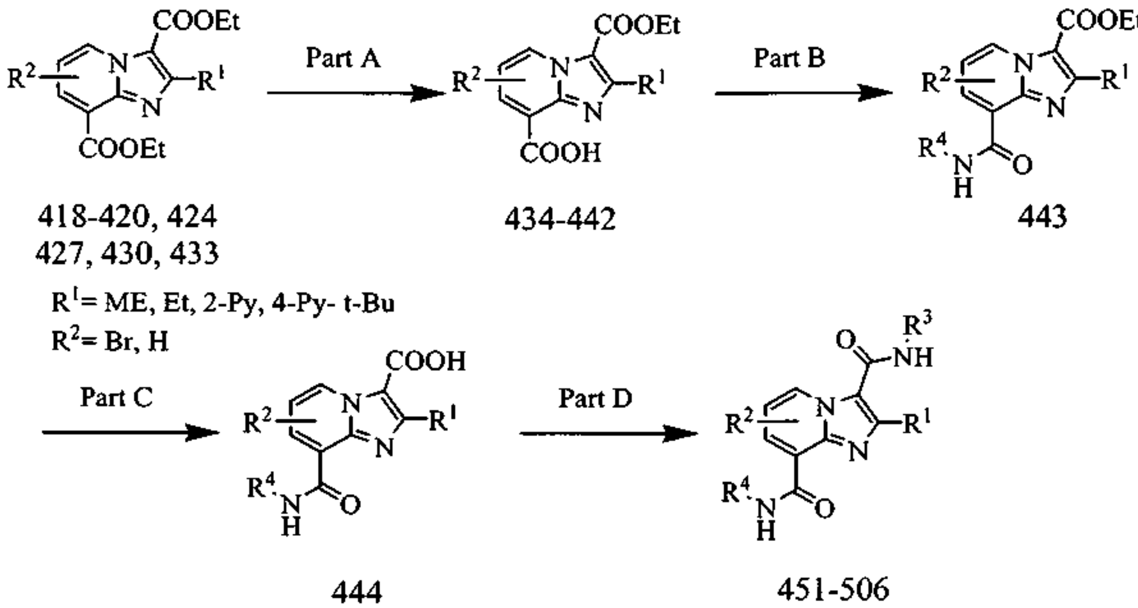
Part A:

Compound **432** was prepared from methyl 4,4-dimethyl-3-oxopentanoate **431** using procedures described in **Example 1B**, Part B. HPLC-MS t_R = 1.70 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_{13}BrO_3$ 236.0, observed LCMS m/z 237.0 (M+H).

Part B:

Compound **433** was prepared from the reaction of compound **432** and compound 2 using procedures described in **Example 1B**, Part C. HPLC-MS t_R = 1.89 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{20}N_2O_4$ 304.1, observed LCMS m/z 305.1 (M+H).

Example 10J:



418-420, 424, 427, 430, 433; 434-442; 443; 444; 451-506

R^1= ME, Et, 2-Py, 4-Py- t-Bu

R^2= Br, H

(wherein R^{1-4} are identified in Table 17)

Part A:

A mixture of compound **418** (0.09 mmol) and LiOH (1*M*, 0.18 mL, 0.18 mmol) in THF (3 mL) and water (1 mL) was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. Hexanes (1 mL) were added to form a biphasic solution. The aqueous phase was separated, acidified to p*H* 4.0 with 1*N* HCl, concentrated and lyophilized with acetonitrile and water (1:1) to afford compound **434** as a white solid (100 % yield). HPLC-MS t_R = 1.74 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{14}N_2O_4$ 310.1, observed LCMS m/z 311.1 (M+H).

Compound **435** was prepared from compound **419**. HPLC-MS t_R = 1.81 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{13}FN_2O_4$ 328.1, observed LCMS m/z 329.0 (M+H).

Compound **436** was prepared from compound **420**. HPLC-MS t_R = 2.01 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{13}ClN_2O_4$ 344.1, observed LCMS m/z 345.0 (M+H).

Compound **437** was prepared from compound **421**. HPLC-MS t_R = 2.08 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{11}BrN_2O_4S$ 394.0, observed LCMS m/z 394.9 (M+H).

Compound **438** was prepared from compound **422**. HPLC-MS t_R = 1.30 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{11}BrN_2O_4$ 326.0, observed LCMS m/z 327.0 (M+H).

Compound **439** was prepared from compound **424**. HPLC-MS t_R = 0.87 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{12}N_2O_4$ 248.1, observed LCMS m/z 249.1 (M+H).

Compound **440** was prepared from compound **427**. HPLC-MS t_R = 1.07 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{13}N_3O_4$ 311.1, observed LCMS m/z 312.0 (M+H).

Compound **441** was prepared from compound **430**. HPLC-MS t_R = 0.95 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{13}N_3O_4$ 311.1, observed LCMS m/z 312.0 (M+H).

Compound **442** was prepared from compound **433**. HPLC-MS t_R = 1.84 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{18}N_2O_4$ 290.1, observed LCMS m/z 291.1 (M+H).

Part B:

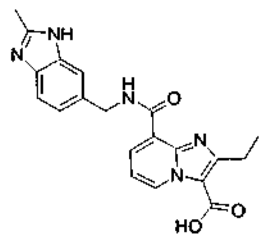
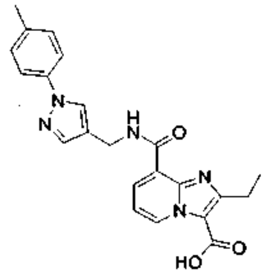
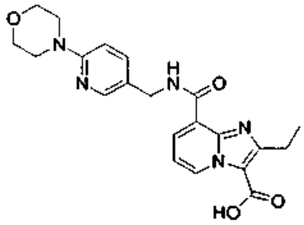
Compounds **443** were prepared using coupling procedures described in **Example 1B**, Part G.

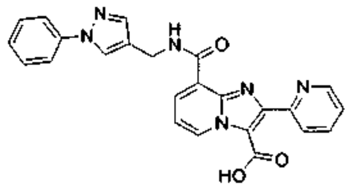
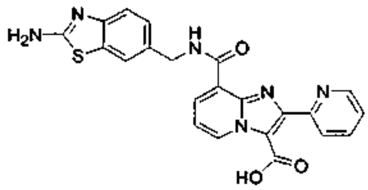
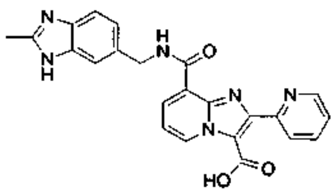
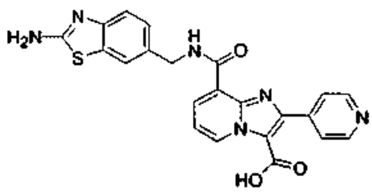
Part C:

The esters were saponified to form compounds **444** using procedures described in **Example 7A**, Part D.

The compounds in Table 17 were synthesized using this procedure.

Table 17

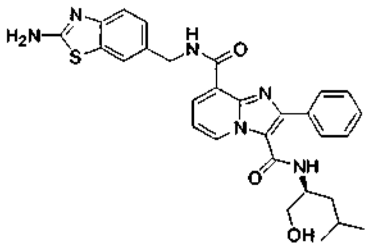
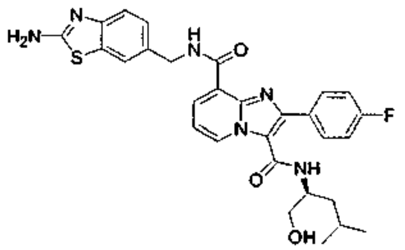
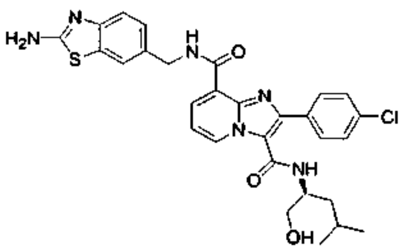
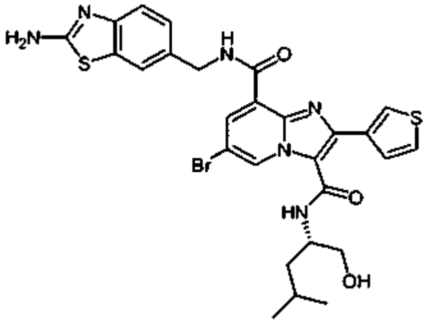
Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
444		377.1	378.1	2.36
445		403.2	404.2	4.20
446		409.2	410.2	2.20

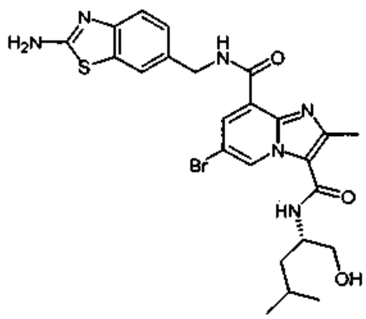
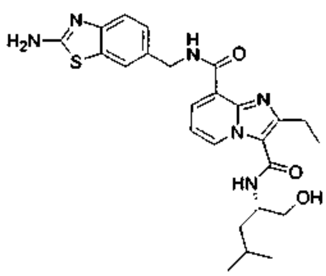
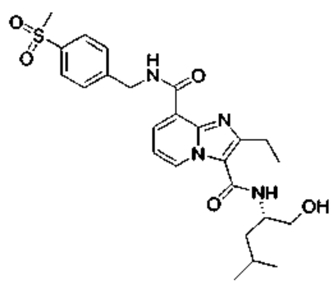
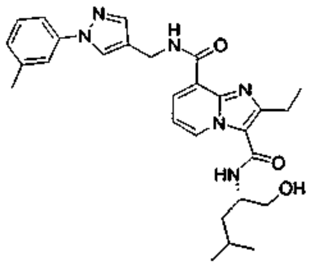
447		438.1	439.1	4.27
448		444.1	445.1	2.74
449		426.1	427.1	2.57
450		444.1	445.1	2.05

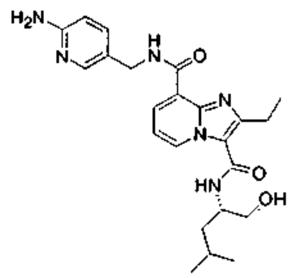
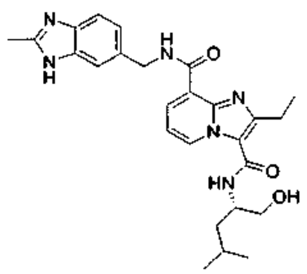
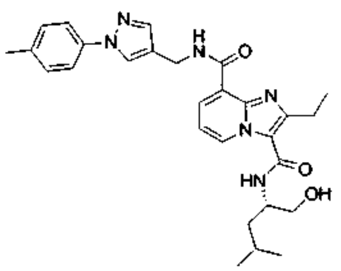
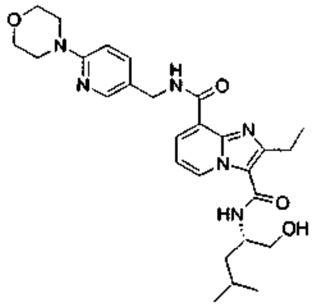
Part D:

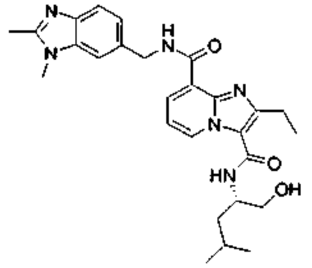
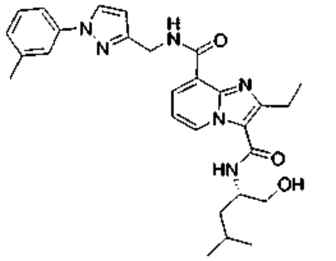
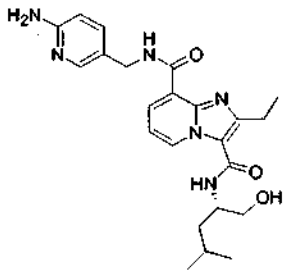
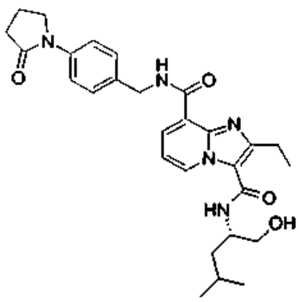
Compounds **451-506** (Table 18) were prepared using procedures described in **Example 6E**, Part A.

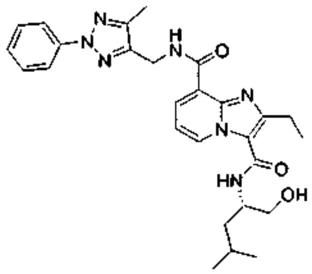
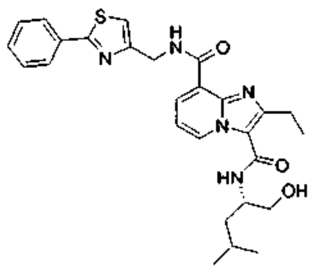
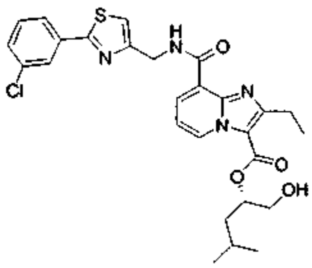
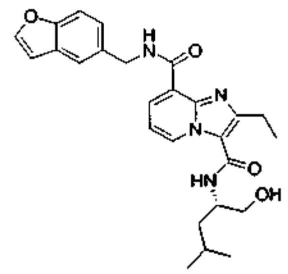
Table 18

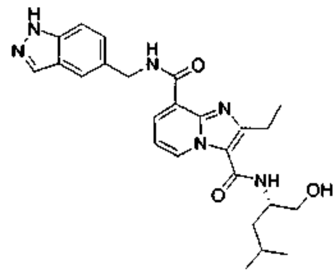
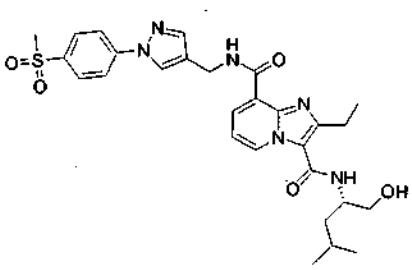
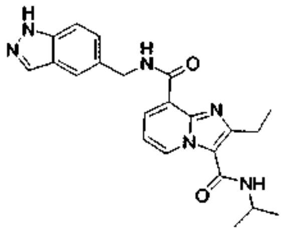
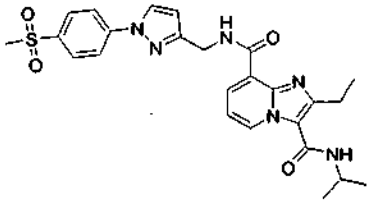
Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
451		542.2	543.1	3.85
452		560.2	561.1	3.95
453		576.2	577.1	4.05
454		626.1	627.0	4.11

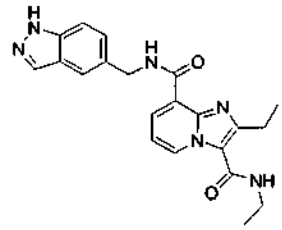
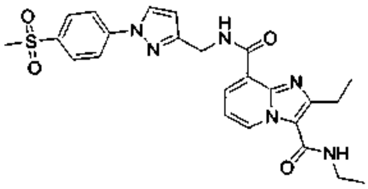
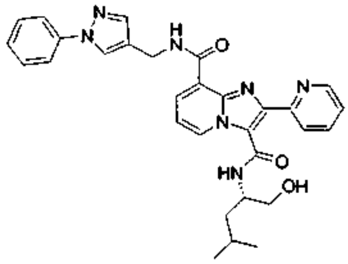
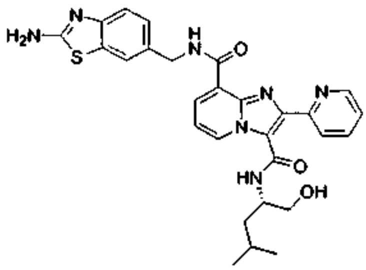
455		558.1	559.0	3.58
456		494.2	495.1	3.17
457		500.2	501.1	3.78
458		502.3	503.3	4.88

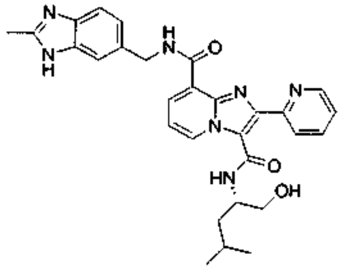
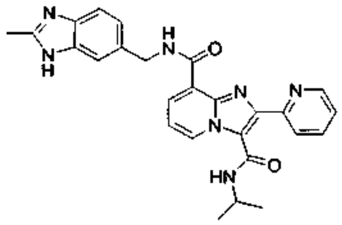
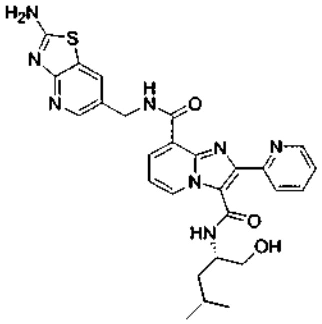
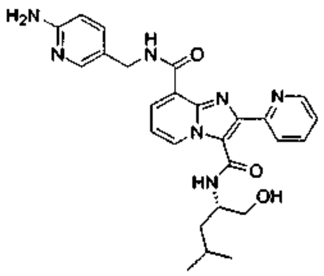
459		438.2	439.2	2.88
460		476.3	477.3	3.01
461		502.3	503.3	4.79
462		508.3	509.3	2.97

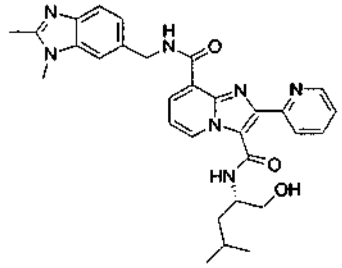
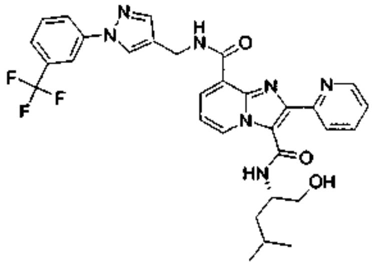
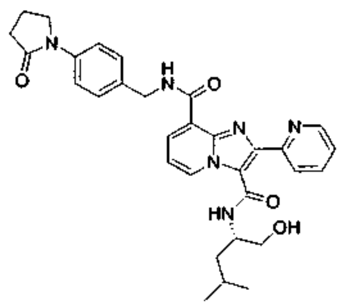
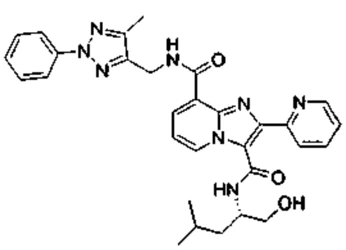
463		490.3	491.3	3.08
464		502.3	503.3	4.88
465		438.2	439.2	2.75
466		505.3	506.3	3.93

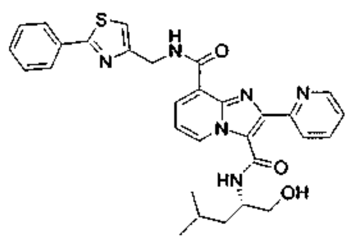
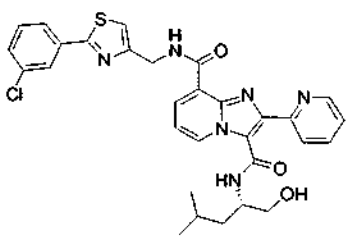
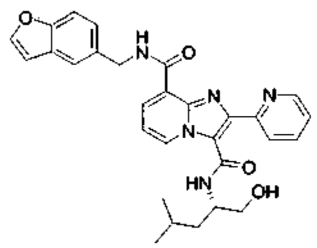
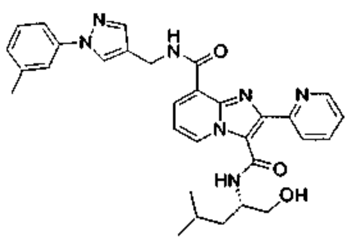
467		503.3	504.3	5.24
468		505.2	506.2	5.11
469		539.2	540.2	5.63
470		462.2	463.2	4.77

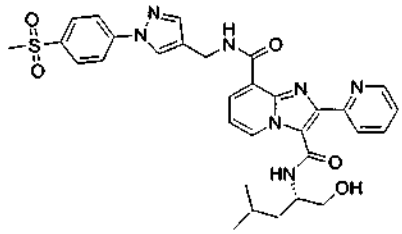
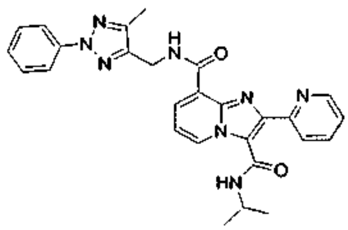
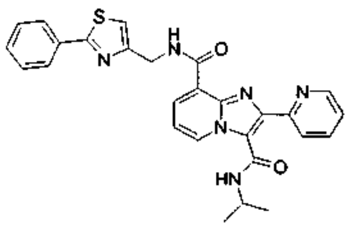
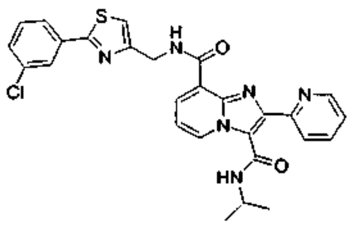
471		462.2	463.2	3.57
472		566.2	567.2	3.77
473		404.2	405.2	3.30
474		508.2	509.2	3.55

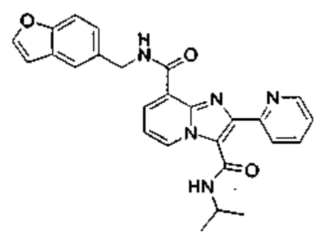
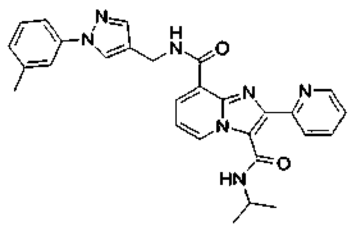
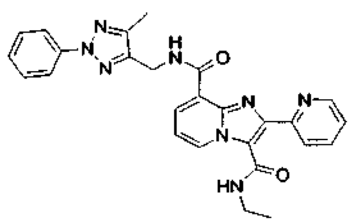
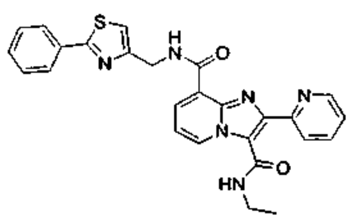
475		390.2	391.2	2.97
476		494.2	495.2	3.25
477		537.2	538.2	5.54
478		543.2	544.2	3.88

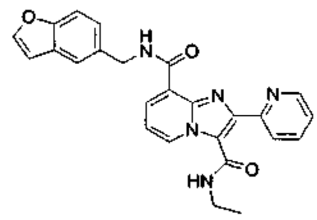
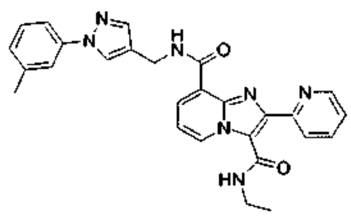
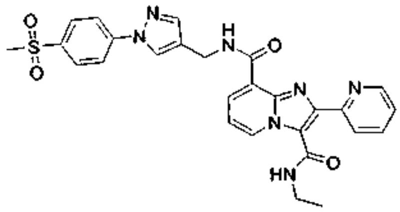
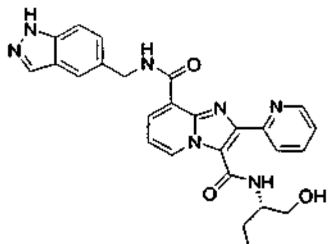
479		525.2	526.2	3.71
480		467.2	468.2	3.78
481		544.2	545.2	3.59
482		487.2	488.2	3.53

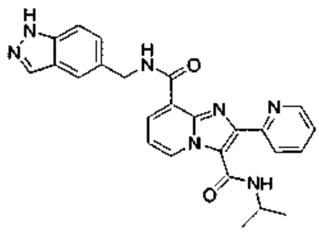
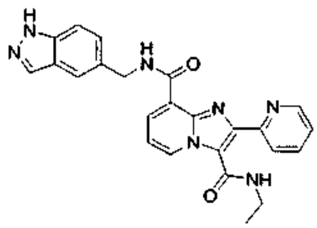
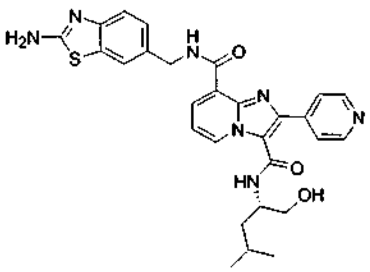
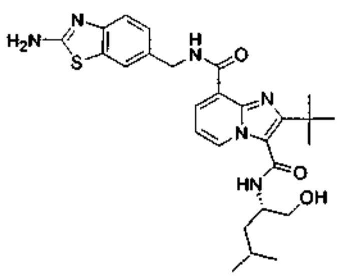
483		539.3	540.3	3.81
484		605.2	606.2	6.16
485		554.3	555.3	4.97
486		552.3	553.3	6.11

487		554.2	555.2	5.98
488		588.2	589.2	6.41
489		511.2	512.2	5.64
490		551.3	552.3	5.74

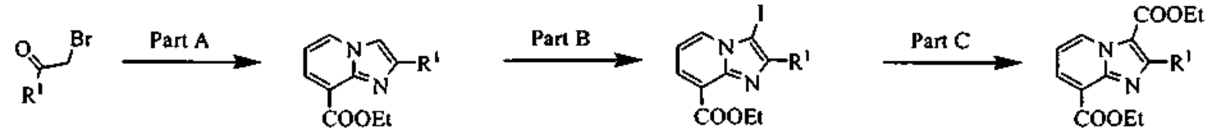
491		615.2	616.2	4.71
492		494.2	495.2	6.44
493		496.2	497.2	6.26
494		530.1	531.1	6.78

495		453.2	454.2	5.91
496		493.2	494.2	6.04
497		480.2	481.2	6.04
498		482.2	483.2	5.89

499		439.2	440.2	5.53
500		479.2	480.2	5.63
501		543.2	544.2	4.49
502		511.2	512.2	4.55

503		453.2	454.2	4.68
504		439.2	440.2	4.30
505		543.2	544.2	2.69
506		522.2	523.2	3.56

Example 11



507-511 512-516 517-521 522-526

Part A:

A mixture of 2-bromo-1-(thienyl)-1-ethanone **507** 0.410 g, 2 mmol) and compound **2** (0.166 g, 1 mmol) in ethanol (5 mL) was heated at reflux for 48 hours. After cooling to room temperature, the reaction was monitored by LC-MS. The volatiles were removed *in vacuo*, ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. The crude was purified by preparative Thin Layer Chromatography (SiO_2, dichloromethane / ethyl acetate – 4:1) to afford compound **512** as a white solid. HPLC-MS t_R = 1.07 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{12}N_2O_2S$ 272.1, observed LCMS m/z 273.0 (M+H).

Compound **513** was prepared from the reaction of chloroacetaldehyde **508** and compound 2. HPLC-MS t_R = 0.21 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_{10}N_2O_2$ 190.1, observed LCMS m/z 191.1 (M+H).

Compound **514** was prepared from the reaction of 3,5-difluorophenacyl bromide **509** and compound 2. HPLC-MS t_R = 1.47 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{12}F_2N_2O_2$ 302.1, observed LCMS m/z 303.1 (M+H).

Compound **515** was prepared from the reaction of 2-fluorophenacyl bromide **510** and compound 2. HPLC-MS t_R = 1.19 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{13}FN_2O_2$ 284.1, observed LCMS m/z 285.0 (M+H).

Compound **516** was prepared from the reaction of 3-fluorophenacyl bromide **511** and compound 2. HPLC-MS t_R = 1.19 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{13}FN_2O_2$ 284.1, observed LCMS m/z 285.0 (M+H).

Part B:

Compound **512** (0.100 g, 0.37 mmol) was dissolved in ethanol (5 mL). To this solution was added *N*-iodosuccinimide (0.125 g, 0.56 mmol) and the reaction mixture stirred at room temperature for 1 hour. The reaction was monitored by LC-MS. If necessary, excess *N*-iodosuccinimide (0.0832 g, 0.37 mmol) was added and the reaction mixture stirred for an additional hour. The volatiles were removed *in vacuo*. Ethyl acetate was added and the organic solution was washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated to afford compound **517**, which was taken forward as crude to the next step. HPLC-MS t_R = 1.98 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{11}IN_2O_2S$ 398.0, observed LCMS m/z 399.0 (M+H).

Compound **518** was prepared from the reaction of compound **513** and *N*-bromosuccinimide. HPLC-MS t_R = 0.64 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_9BrN_2O_2$ 268.0, observed LCMS m/z 269.0 (M+H).

Compound **519** was prepared from the reaction of compound **514** and *N*-iodosuccinimide. HPLC-MS t_R = 2.14 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{11}F_2IN_2O_2$ 428.0, observed LCMS m/z 429.0 (M+H).

Compound **520** was prepared from the reaction of compound **515** and *N*-iodosuccinimide. HPLC-MS t_R = 1.64 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{12}FIN_2O_2$ 410.0, observed LCMS m/z 411.0 (M+H).

Compound **521** was prepared from the reaction of compound **516** and *N*-iodosuccinimide. HPLC-MS t_R = 1.98 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{12}FIN_2O_2$ 410.0, observed LCMS m/z 411.0 (M+H).

Part C:

To a mixture of compound **517** (0.063 g, 0.16 mmol), molybdenum hexacarbonyl (0.084 g, 0.32 mmol), diisopropylethylamine (0.030 mL, 0.18 mmol) in ethanol (3 mL) was added Pd(DPPF)Cl_2.DCM (10 mol %). The reaction vessel was flushed with argon, capped and heated at 80^0 C for 16 hours. After cooling to room temperature, the reaction was shown to be incomplete by LC-MS. Excess molybdenum hexacarbonyl (0.084 g, 0.32 mmol) was added and the reaction mixture heated for another 16 hours. The precipitates were removed by filtration, the filtrate concentrated and purified by preparative thin layer chromatography (SiO_2, dichloromethane / ethyl acetate – 15:1) to afford compound **522** as a yellow solid. HPLC-MS t_R = 2.05 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{16}N_2O_4S$ 344.1, observed LCMS m/z 345.1 (M+H).

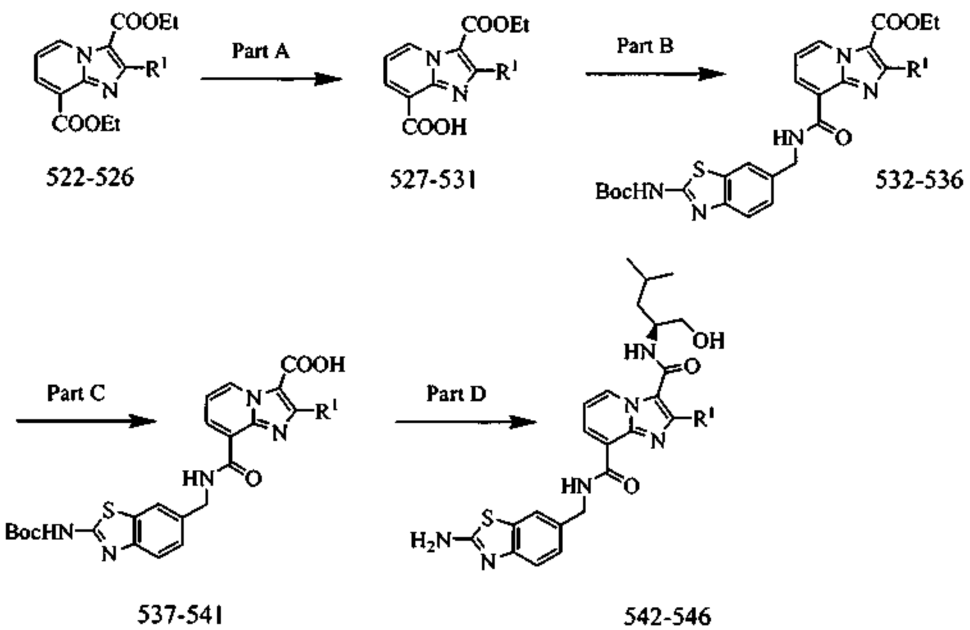
Compound **523** was prepared from compound **518**. HPLC-MS t_R = 1.22 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{14}N_2O_4$ 262.1, observed LCMS m/z 263.1 (M+H).

Compound **524** was prepared from compound **519**. HPLC-MS t_R = 2.83 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{16}F_2N_2O_4$ 374.1, observed LCMS m/z 375.1 (M+H).

Compound **525** was prepared from compound **520**. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{17}FN_2O_4$ 356.1, observed LCMS m/z 357.1 (M+H).

Compound **526** was prepared from compound **521**. HPLC-MS t_R = 2.74 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{17}FN_2O_4$ 356.1, observed LCMS m/z 357.1 (M+H).

Example 11B



(wherein R^1 is identified in Table 19)

Part A:

Compound **527** was prepared from the saponification of compound **522** using procedures described in Example 5K, Part A. HPLC-MS t_R = 1.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{12}N_2O_4S$ 316.1, observed LCMS m/z 317.1 (M+H).

Compound **528** was prepared from compound **523**. HPLC-MS t_R = 0.77 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{10}N_2O_4$ 234.1, observed LCMS m/z 235.1 (M+H).

Compound **529** was prepared from compound **524**. HPLC-MS t_R = 2.63 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{12}F_2N_2O_4$ 346.1, observed LCMS m/z 347.0 (M+H).

Compound **530** was prepared from compound **525**. HPLC-MS t_R = 1.78 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{13}FN_2O_4$ 328.1, observed LCMS m/z 329.0 (M+H).

Compound **531** was prepared from compound **526**. HPLC-MS t_R = 2.46 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{13}FN_2O_4$ 328.1, observed LCMS m/z 329.0 (M+H).

Part B:

Compound **532** was prepared from the coupling of compound **527** and (6-aminomethyl-benzothiazol-2-yl)-carbamic acid *tert*-butyl ester using procedures described in **Example 3A,** Part C. HPLC-MS t_R = 2.33 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{27}N_5O_5S_2$ 577.1, observed LCMS m/z 578.0 (M+H).

Compound **533** was prepared from compound **528**. HPLC-MS t_R = 2.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{25}N_5O_5S$ 495.2, observed LCMS m/z 496.1 (M+H).

Compound **534** was prepared from compound **529**. HPLC-MS t_R = 2.42 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{27}F_2N_5O_5S$ 607.2, observed LCMS m/z 608.0 (M+H).

Compound **535** was prepared from compound **530**. HPLC-MS t_R = 2.33 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{28}FN_5O_5S$ 589.2, observed LCMS m/z 590.0 (M+H).

Compound **536** was prepared from compound **531**. HPLC-MS t_R = 3.63 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{28}FN_5O_5S$ 589.2, observed LCMS m/z 590.0 (M+H).

Part C:

Compound **537** was prepared from the saponification of compound **532** using procedures described in Example 3A, Part D. HPLC-MS t_R = 1.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{23}N_5O_5S_2$ 549.1, observed LCMS m/z 550.0 (M+H).

Compound **538** was prepared from compound **533**. HPLC-MS t_R = 1.64 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{21}N_5O_5S$ 467.1, observed LCMS m/z 468.1 (M+H).

Compound **539** was prepared from compound **534**. HPLC-MS t_R = 1.99 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{23}F_2N_5O_5S$ 579.1, observed LCMS m/z 580.0 (M+H).

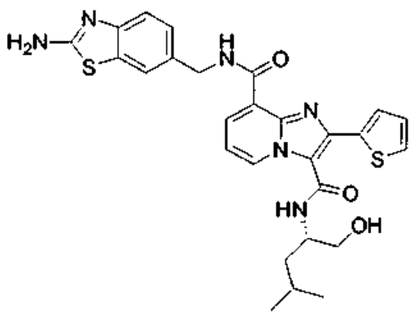
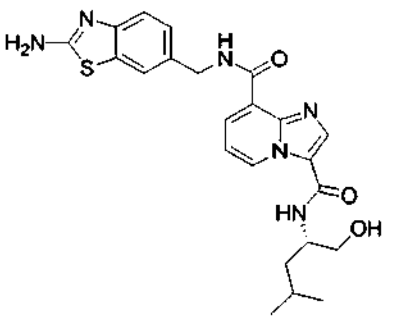
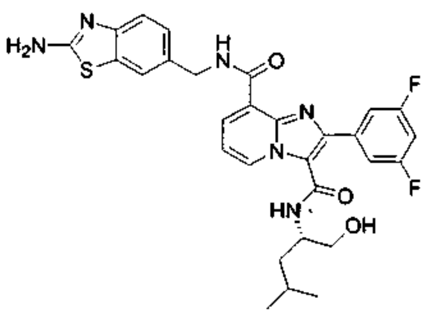
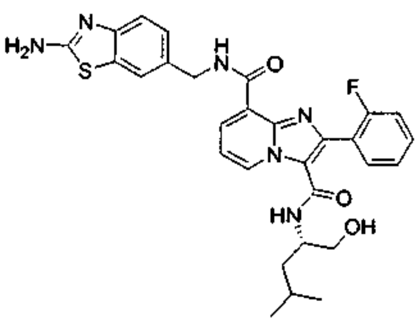
Compound **540** was prepared from compound **535**. HPLC-MS t_R = 1.90 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{24}FN_5O_5S$ 561.1, observed LCMS m/z 562.0 (M+H).

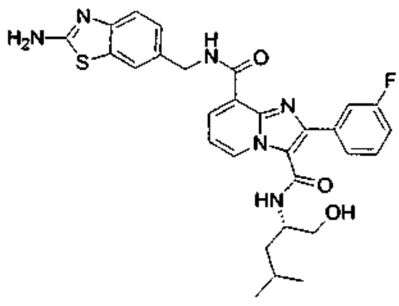
Compound **541** was prepared from compound **536**. HPLC-MS t_R = 1.95 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{24}FN_5O_5S$ 561.1, observed LCMS m/z 562.0 (M+H).

Part D:

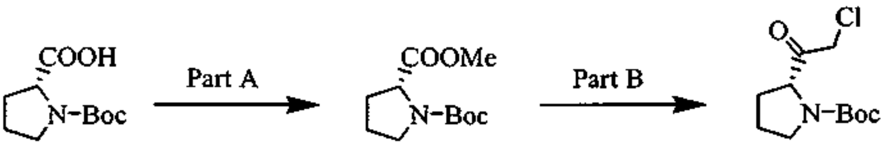
Compounds **542-546** (Table 19) were prepared using coupling procedures described in **Example 7A,** Part E.

Table 19

compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
542		548.2	549.2	3.81
543		466.2	467.2	3.01
544		578.2	579.2	4.07
545		560.2	561.1	3.66

546		560.2	561.0	3.76

Example 12A



547 548 549

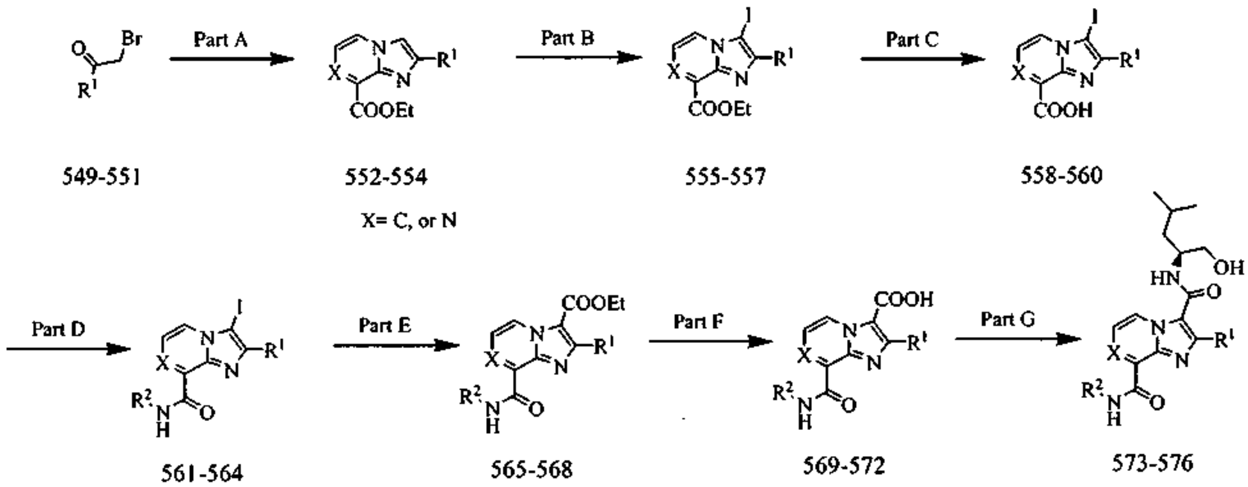
Part A:

To a solution of Boc-D-proline **547** (25.0 g, 0.116 mol) in methanol (50 mL) and acetonitrile (50 mL) was added (trimethylsilyl)diazomethane (2*M*, 116 mL, 0.232 mol), and the reaction mixture stirred at room temperature for 16 hours. The reaction was monitored by Thin Layer Chromatography (hexanes / ethyl acetate – 4:1). Acetic acid (5 mL) was added to quench the excess (trimethylsilyl)diazomethane. The volatiles were removed *in vacuo*, and the crude product purified by flash column chromatography to afford compound **548** as a colorless oil.

Part B:

A fresh solution of lithium diisopropylamide (LDA) was prepared by adding *n*-butyllithium (2.5*M*, 87 mL, 0.218 mol) to a stirred solution of diisopropylamine (32 mL, 0.229 mol) in THF (50 mL) at -78^0 C, under an inert atmosphere. The LDA solution was warmed to -20^0 C (salt ice-bath) with stirring for 1 hour. Chloroiodomethane (16 mL, 0.218 mol) was added to a solution of compound **548** (10.0 g, 0.044 mol) in THF (50 mL), and cooled to -78^0 C. The LDA solution was transferred *via* cannula to the reaction mixture over a period of 90 minutes, and then the mixture was stirred for an additional 1 hour at -78^0 C. A solution of acetic acid (7.5 mL) in THF (20 mL) was added slowly to the reaction, maintaining the temperature below -70^0 C. The reaction mixture was stirred for an additional 10 minutes at -70^0 C and then warmed to room temperature. Ethyl acetate (100 mL) was added and the precipitates removed by filtration. The filtrate was washed with water (x1), saturated Na_2HPO_4 (x1), saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. The crude was purified by flash column chromatography (SiO_2, hexanes / ethyl acetate – 4:1) to afford compound **549** as a deep red oil.

Example 12B



Part A:

Compound **552** was prepared from the reaction of (R)-1-boc-2-(2'-chloroacetyl)-pyrrolidine **549** and compound 2 using procedures described in **Example 11A**, Part A. HPLC-MS t_R = 0.63 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{25}N_3O_4$ 359.2, observed LCMS m/z 360.1 (M+H).

Compound **553** was prepared from the reaction of (S)-1-boc-2-(2'-chloroacetyl)-pyrrolidine **550** and compound 2. HPLC-MS t_R = 0.68 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{25}N_3O_4$ 359.2, observed LCMS m/z 360.2 (M+H).

Compound **554** was prepared from the reaction of 1-bromo-2-butanone **551** and methyl 3-amino-2-pyrazolecarboxylate. HPLC-MS t_R = 0.73 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{13}N_3O_2$ 219.1, observed LCMS m/z 220.1 (M+H).

Part B:

Compound **555** was prepared from compound **552** using procedures described in Example 6A, Part B. HPLC-MS t_R = 1.60 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{24}IN_3O_4$ 485.1, observed LCMS m/z 486.0 (M+H).

Compound **556** was prepared from compound **553**. HPLC-MS t_R = 1.67 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{24}IN_3O4$ 485.1, observed LCMS m/z 486.0 (M+H).

Compound **557** was prepared from compound **554**. HPLC-MS t_R = 1.45 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{12}IN_3O_2$ 345.0, observed LCMS m/z 346.0 (M+H).

Part C:

Compound **558** was prepared from the saponification of compound **555** using procedures described in Example 5K, Part A. HPLC-MS t_R = 1.42 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{20}IN_3O_4$ 457.0, observed LCMS m/z 458.0 (M+H).

Compound **559** was prepared from compound **556**. HPLC-MS t_R = 1.42 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{20}IN_3O_4$ 457.0, observed LCMS m/z 458.0 (M+H).

Compound **560** was prepared from compound **557**. HPLC-MS t_R = 0.79 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_8IN_3O_2$ 317.0, observed LCMS m/z 318.0 (M+H).

Part D:

Compounds **561** was prepared from the coupling of compound **558** and (6-aminomethyl-benzothiazol-2-yl)-carbamic acid *tert*-butyl ester using procedures described in Example 3A, Part C. HPLC-MS t_R = 2.31 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{35}IN_6O_5S$ 718.0, observed LCMS m/z 719.0 (M+H).

Compound **562** was prepared from the coupling of compound **558** and (6-aminomethyl-benzothiazol-2-yl)-carbamic acid *tert*-butyl ester. HPLC-MS t_R = 2.33 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{35}IN_6O_5S$ 718.0, observed LCMS m/z 719.0 (M+H).

Compound **563** was prepared from the coupling of compound **559** and 1-(4-aminomethylphenyl)pyrrolidin-2-one. HPLC-MS t_R = 2.00 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{32}IN_5O_4$ 629.1, observed LCMS m/z 630.0 (M+H).

Compound **564** was prepared from the coupling of compound **560** and (6-aminomethyl-benzothiazol-2-yl)-carbamic acid *tert*-butyl ester. HPLC-MS t_R = 1.92 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{23}IN_6O_3S$ 578.1, observed LCMS m/z 579.0 (M+H).

Part E:

Compound **565** was prepared from compound **561** using carbonylation procedures described in Example 6A, Part C. HPLC-MS t_R = 2.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{33}H_{40}N_6O_7S$ 664.3, observed LCMS m/z 665.2 (M+H).

Compound **566** was prepared from compound **562**. HPLC-MS t_R = 2.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{33}H_{40}N_6O_7S$ 664.3, observed LCMS m/z 665.2 (M+H).

Compound **567** was prepared from compound **563**. HPLC-MS t_R = 2.06 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{37}N_5O_6$ 575.3, observed LCMS m/z 576.2 (M+H).

Compound **568** was prepared from compound **564**. HPLC-MS t_R = 2.03 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{28}N_6O_5S$ 524.2, observed LCMS m/z 525.1 (M+H).

Part F:

Compound **569** was prepared from the saponification of compound **565** using procedures described in **Example 7A**, Part D. HPLC-MS t_R = 1.95 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{36}N_6O_7S$ 636.2, observed LCMS m/z 637.2 (M+H).

Compound **570** was prepared from compound **566**. HPLC-MS t_R = 1.94 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{36}N_6O_7S$ 636.2, observed LCMS m/z 637.1 (M+H).

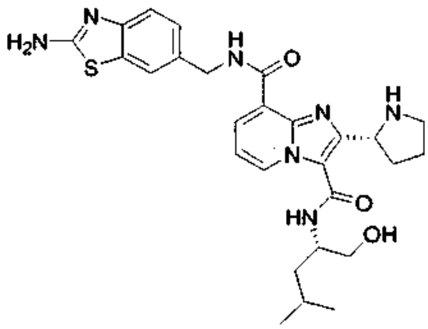
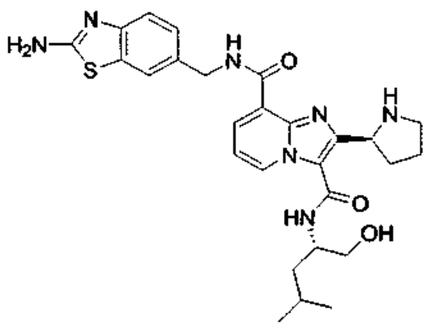
Compound **571** was prepared from compound **567**. HPLC-MS t_R = 1.59 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{33}N_5O_6$ 547.2, observed LCMS m/z 548.2 (M+H).

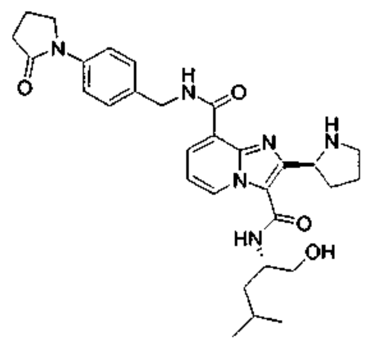
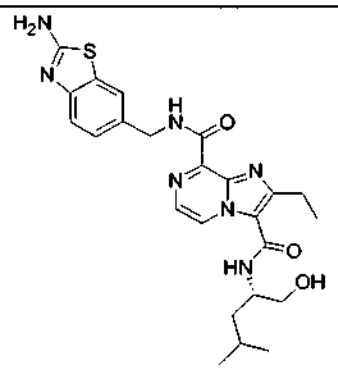
Compound **572** was prepared from compound **568**. HPLC-MS t_R = 1.61 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{24}N_6O_5S$ 496.2, observed LCMS m/z 497.0 (M+H).

Part G:

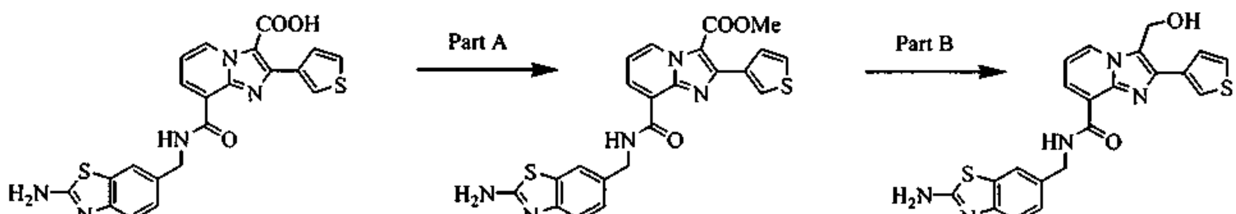
Compounds **573-576** (Table 20) were prepared using coupling procedures described in **Example 7A**, Part E.

Table 20

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
573		535.2	536.2	2.62
574		546.3	547.3	3.21

575		535.2	536.2	2.58
576		495.2	496.1	2.80

Example 13



11 577 578

Compound 11 was prepared using procedures described in **Example 1B**, Part A-H.

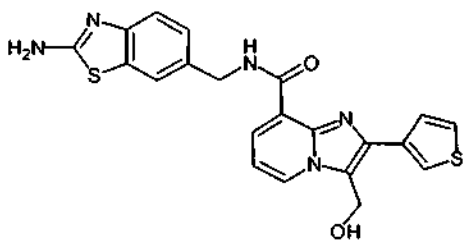
Part A:

To a solution of compound **11** (0.15 mmol) in acetonitrile (2 mL) and methanol (2 mL) was added (trimethylsilyl)diazomethane (2*M*, 0.11 mL, 0.22 mmol). The reaction mixture was stirred at room temperature for 30 minutes. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo* to afford compound **577** (100 % yield). HPLC-MS t_R = 3.80 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{17}N_5O_3S_2$ 463.1, observed LCMS m/z 464.0 (M+H).

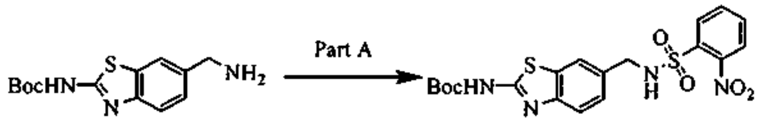
Part B:

Compound **577** (0.010 g, 0.02 mmol) was dissolved in a mixture of THF (0.5 mL) and methanol (0.5 mL). Lithium borohydride (0.0014 g, 0.07 mmol) was added, and the reaction mixture heated at 55^0 C for 1 hour. On cooling to room temperature, the reaction was monitored by LC-MS. The volatiles were removed *in vacuo*. Ethyl acetate was added, and the organic solution washed with saturated $NaHCO_3$ (x1), brine (x1), dried over magnesium sulfate and concentrated to afford compound **578** which was purified by PrepLC.

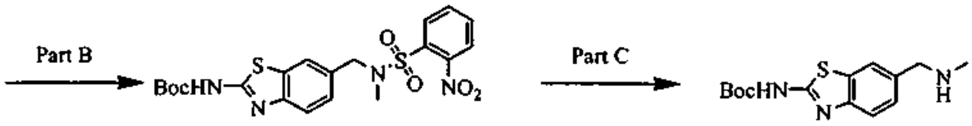
The following ligand was synthesized using this procedure:

compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
578		435.1	436.0	2.51

Example 14A



579 580



581 582

Part A:

(6-aminomethyl-benzothiazol-2-yl)-carbamic acid *tert*-butyl ester **579** (0.100 g, 0.36 mmol) was dissolved in a mixture of dichloromethane (6 mL) and pyridine (2 mL). 2-Nitrobenzenesulfonyl chloride (0.087 g, 0.4 mmol) was added, and the reaction mixture stirred at room temperature for 4 hours. The reaction was monitored by LC-MS. The volatiles were removed *in vacuo*. Ethyl acetate was added, and the organic solution washed with saturated $NaHCO_3$ (x1), brine (x1), dried over magnesium sulfate and concentrated to afford compound **580** which was taken forward as crude to the next step. HPLC-MS t_R = 1.86 min ($UV_{254\ nm}$); mass calculated for formula C19H20N4O6S2 464.1, observed LCMS m/z 465.0 (M+H).

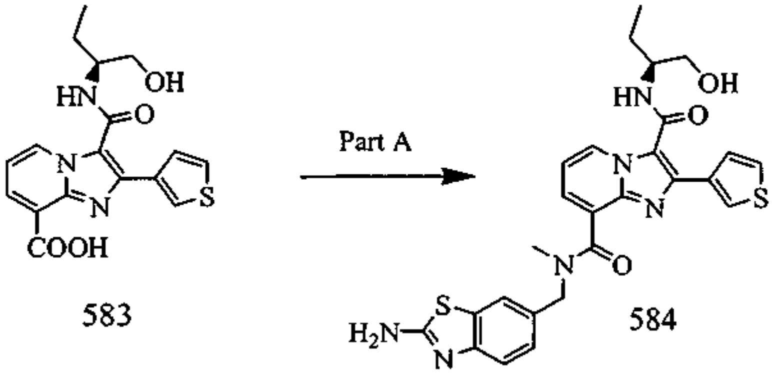
Part B:

A mixture of compound **580** (0.36 mmol), potassium carbonate (50 mg, 0.36 mmol) and iodomethane (0.051 g, 0.36 mmol) in DMF (2 mL) was stirred at room temperature for 16 hours. The reaction was monitored by LC-MS. The volatiles were removed *in vacuo*. Ethyl acetate was added, and the organic solution washed with brine (x1), dried over magnesium sulfate and concentrated to afford compound **581** which was taken forward as crude to the next step. HPLC-MS t_R = 2.15 min ($UV_{254\ nm}$); mass calculated for formula C20H22N4O6S2 478.1, observed LCMS m/z 479.0 (M+H).

Part C:

A mixture of compound **581** (0.030 g, 0.06 mmol), potassium carbonate (0.0095 g, 0.07 mmol) and benzenethiol (0.007 mL, 0.075 mmol) in DMF (2 mL) was stirred at room temperature for 16 hours. The reaction was monitored by LC-MS. Excess benzenthiol (0.014 mL, 0.15 mmol) was added and the reaction mixture stirred at room temperature for an addition 16 hours. The volatiles were removed *in vacuo* to afford compound **582** which was taken forward as crude to the next step. HPLC-MS t_R = 1.17 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{19}N_3O_2S$ 293.1, observed LCMS m/z 294.1 (M+H).

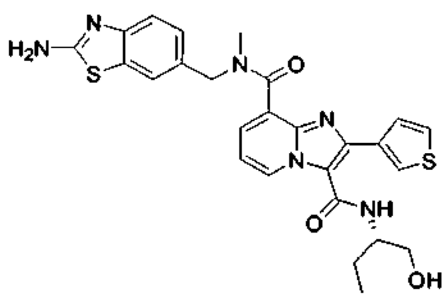
Example 14B



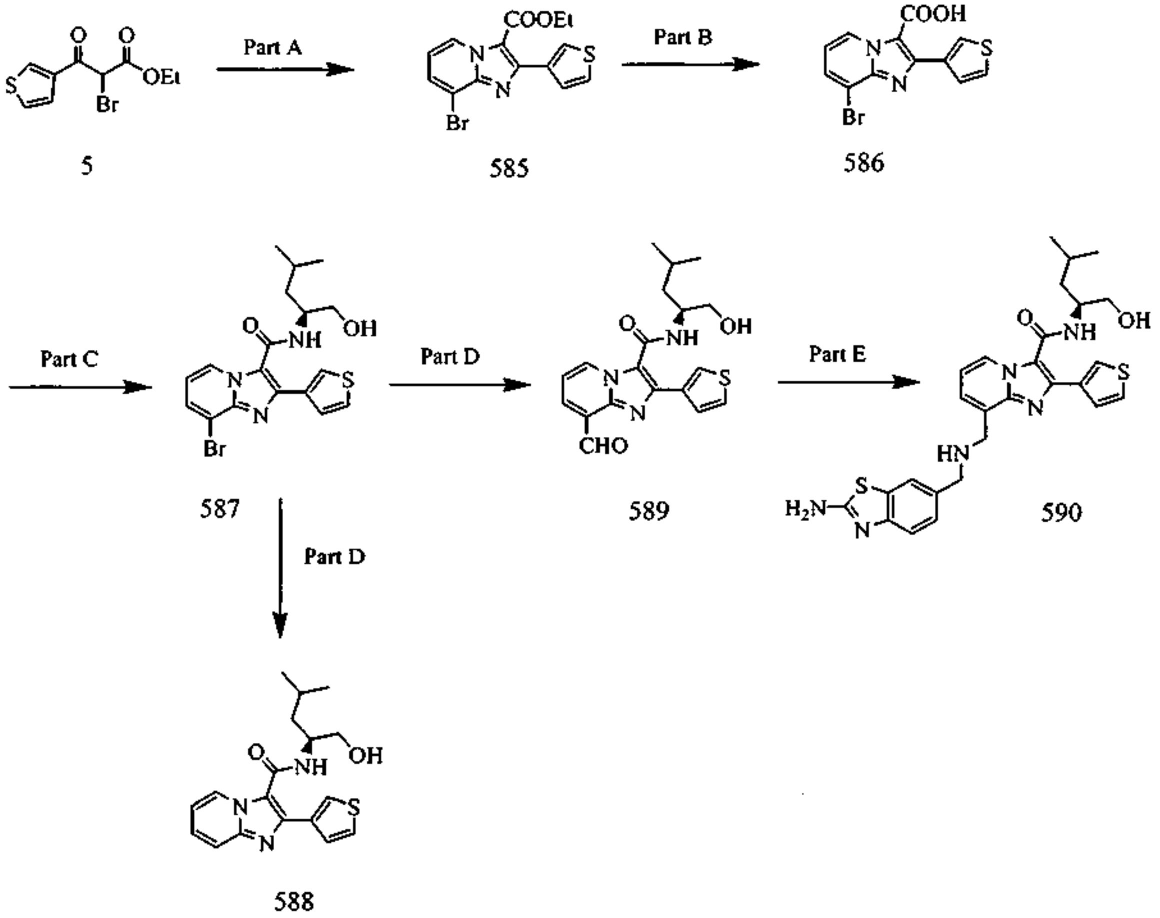
Compound **583** was prepared using procedures described in **Example 13**, Part A-D. **Example 6.** HPLC-MS t_R = 0.99 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{17}N_3O_4S$ 359.1, observed LCMS m/z 360.1 (M+H).

Part A:

Compound **584** was prepared using the coupling procedures described in **Example 6D**, Part A.

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
584		534.2	535.1	3.32

Example 15



Compound **5** was prepared using procedures described in **Example 1B.**

Part A:

Compound **585** was prepared from compound 5 and 2-amino-3-bromopyrdine using procedures described **in Example 7A**, Part A. HPLC-MS t_R = 2.10 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{11}BrN_2O_2S$ 350.0, observed LCMS m/z 351.0 (M+H).

Part B:

Compound **586** was prepared from compound **585** using procedures described in **Example 7A**, Part D. HPLC-MS t_R = 1.47 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_7BrN_2O_2S$ 321.9, observed LCMS m/z 322.9 (M+H).

Part C:

Compound **587** was prepared from compound **586** using procedures described in **Example 9C**, Part C. HPLC-MS t_R = 1.71 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{20}BrN_3O_2S$ 421.0, observed LCMS m/z 422.0 (M+H).

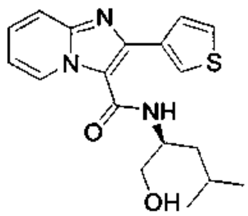
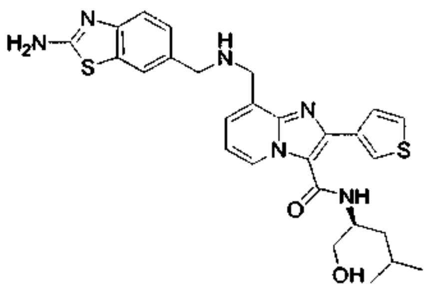
Part D:

Compound **587** (0.022 g, 0.052 mmol) was dissolved in a mixture of DMF (1 mL) and THF (2 mL). *n*-Butyllithium (2.5*M*, 0.053 mL, 0.16 mmol) was added, and the reaction mixture stirred at room temperature for 1 hour. The reaction was monitored by LC-MS, indicating formation of the desired aldehyde, but also de-bromination side product. The volatiles were removed *in vacuo*. Ethyl acetate was added, and the organic solution washed with saturated $NaHCO_3$ (x1), brine (x1), dried over magnesium sulfate and concentrated to afford a mixture of compounds **588**and **589** which were taken forward to the next step.

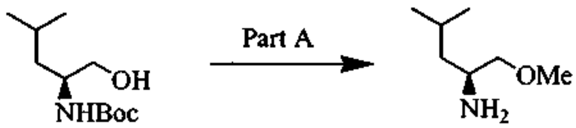
Part E:

Compound **589** (0.052 mmol) was dissolved in 1,2-dichloroethane (2 mL). (6-aminomethyl-benzothiazol-2-yl)-carbamic acid *tert*-butyl ester **578** (0.022 g, 0.078 mmol), acetic acid (0.200 mL) and sodium triacetoxyborohydride (0.0121 g, 0.06 mmol) was added, and the reaction mixture stirred at room temperature for 16 hours. The reaction was monitored by LC-MS, quenched by the addition of saturated $NaHCO_3$, extracted into dichloromethane, dried over magnesium sulfate and concentrated. The crude was redissolved in dioxane (1 mL), and a solution of 4 *N* HCl in dioxane (2 mL) and water (0.2 mL) was added at 0^0 C (ice-bath). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, acetonitrile was added, concentrated and dried. Purification by Prep-LC and conversion to the hydrochloric salt afforded compounds **588** and **590** (Table 21) as white solids.

Table 21

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
588		343.1	344.1	2.99
590		534.2	535.2	2.79

Example 16A

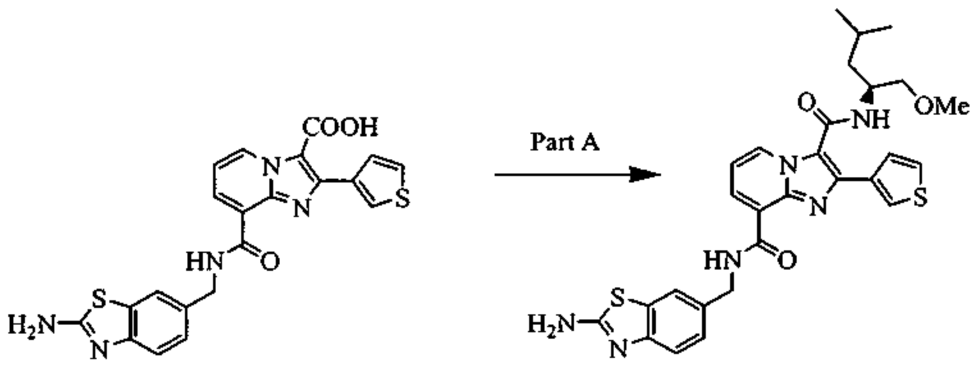


591 592

Part A:

A mixture of *N*-(*tert*-butoxycarbonyl)-L-leucinol (0.500 g, 2.3 mmol), silver oxide (2.67 g, 11.5 mmol) and iodomethane (1.43 mL, 23 mmol) in acetonitrile (20 mL) was stirred at room temperature for 72 hours. The reaction was monitored by LC-MS. The precipitates were removed by filtration, the filtrate concentrated and the crude purified by flash column chromatography (SiO_2, dichloromethane / ethyl acetate – 10:1) to afford compound **592** as the BOC protected amine. A mixture of trifluoroactic acid (1.8 mL) and water (0.2 mL) was added and the reaction mixture stirred at room temperature for 15 minutes. The volatiles were removed *in vacuo*, to afford compound **592** as a colorless oil. HPLC-MS t_R = 0.69 min ($UV_{254\ nm}$); mass calculated for formula C7H17NO 131.1, observed LCMS m/z 132.1 (M+H).

Example 16B

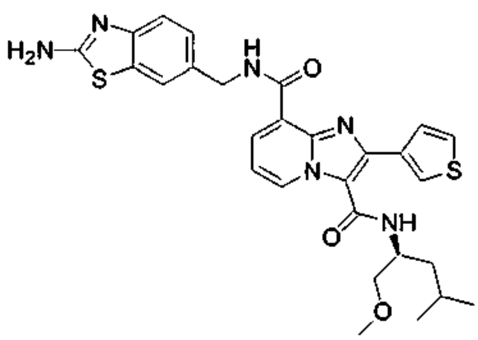


11 593

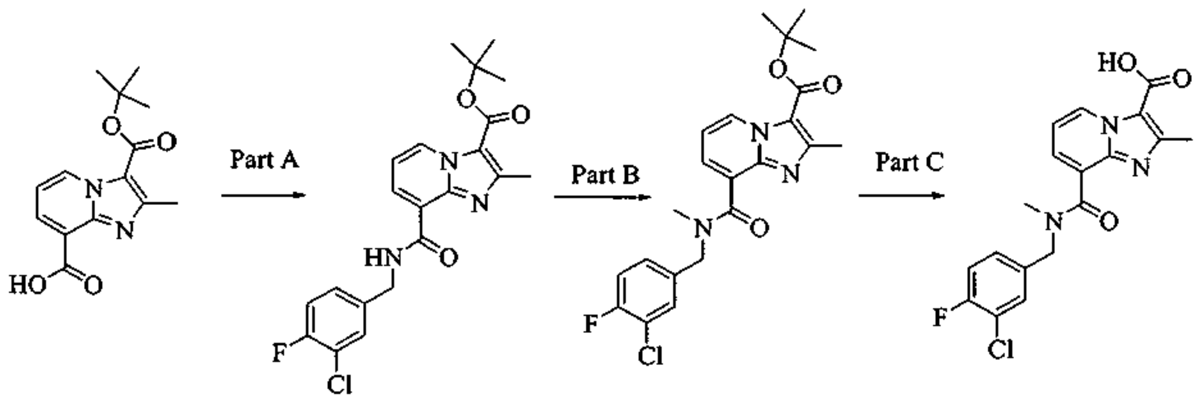
Compound **11** was prepared using procedures described in **Example1B.**

Part A:

Compound **593** was prepared from the coupling of compound **11** and compound **592** using procedures described in **Example 1B**, Part I.

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
593		562.2	563.2	4.26

Example 17



594 595 596 597

Part A:

2-methyl-imidazo[1,2-a]pyridine-3,8-dicarboxylic acid-3-tert-butyl ester **594** (0.138 g, 0.5 mmol) was dissolved in dichloromethane. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.093 g, 0.6 mmol;)was added followed by DIEA(1.5 mmol, 0.262 mL) and 3-chloro-4-fluoro benzyl amine (0.087 g, 0.55 mmol) was added. The reaction mixture stirred at room temperature for 10 hrs and LCMS analysis showed the completion of the reaction.

Reaction mixture diluted with water and extracted with EtOAc. The EtOAc layer separated, dried over anh.$MgSO_4$, filtered and evaporation of EtOAc gave crude 8-(3-Chloro-4-fluoro-benzylcarbomoyl)-2-methyl-imidazo[1,2-a]pyridine-3-carboxylic acid tert- butyl ester **595**. Column chromatography of this material by eluting with Hexan/EtOAc gave pure product, 75%; 0.310 g; M^++H 418.2)

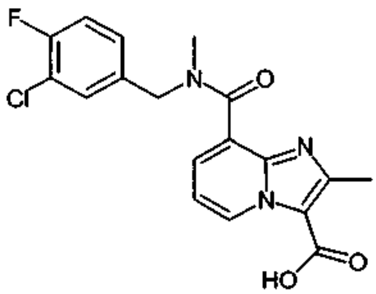
Part B:

8-(3-Chloro-4-fluoro-benzylcarbomoyl)-2-methyl[1,2-a]pyridine-3carboxylic acid-*tert*-butyl ester **595** (0.0417 g, 0.1 mmol) was dissolved in dry THF was added to the flask containing NaH (60%; 0.005 g) in THF.The reaction mixture cooled to 0^0 C. After 10 minutes the MeI (1.2 eq.0.017 mL) was added. The reaction mixture warmed to room temperature stirred at room temperature for 2 hours. LC MS analysis showed N-methylation was complete. 5mL of water was added to the solution and extracted in to EtOAC(50 mL). Organic layer dried with anh.$MgSO_4$, filtered, and evaporated to dryness to give the 8-(3-Chloro-4-fluoro-benzyl methylcarbomoyl)-2-

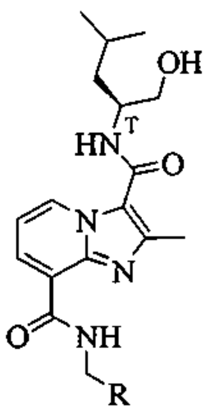
methyl[1,2-a]pyridine-3carboxylic acid-tert-butyl ester **596** in quantitative yield (0.043 g).

Part C:

8-(3-Chloro-4-fluoro-benzyl)methyl-carbamoyl)-2-methyl[1,2-a]pyridine-3-carboxylic acid *tert*-butyl ester **596** (0.040 g) was treated with 4N HCl in dioxane for 2 hours obtain free carboxylic acid **597**. The resulting solution was concentrated under vacuum to dryness and purified by prep.LC.

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
597		375.07	376.0	3.3

Example 18

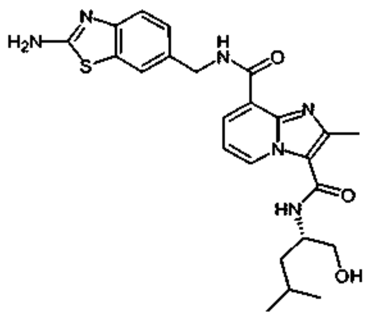
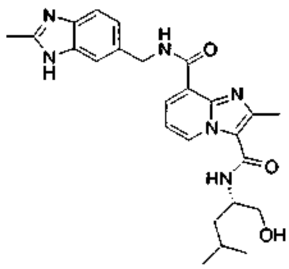
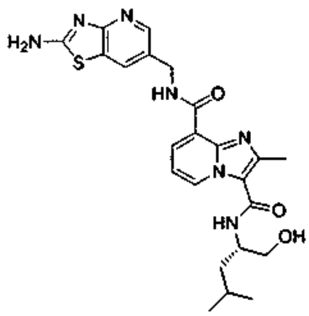


598-600

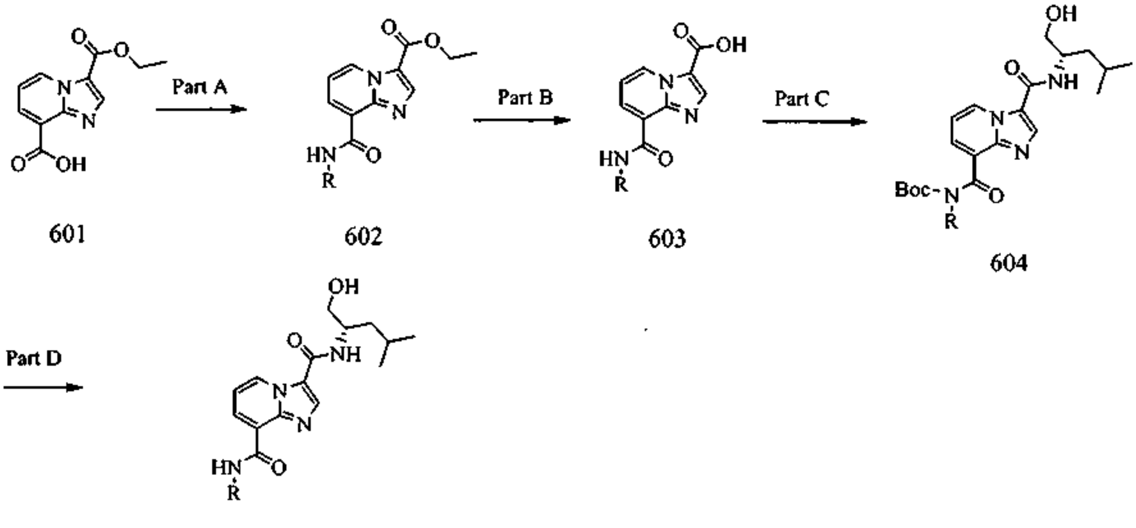
(wherein R is identified in Table 22)

The compounds in Table 22 are prepared using methods described in **Example 2C**

Table 22

compd #	Structure	EMW	MS m/z (M^{+}+H)
598		480.19	481.1
599		462.24	463.0
600		481.19	482.1

Example 19



605-629

(wherein R is identified in Table 23)

Part A:

Compound **602** was prepared using the peptide coupling condition described in **Example 1B**.

Part B:

Compound **603** was prepared using the hydrolysis conditions described in **Example 1B.**

Part C:

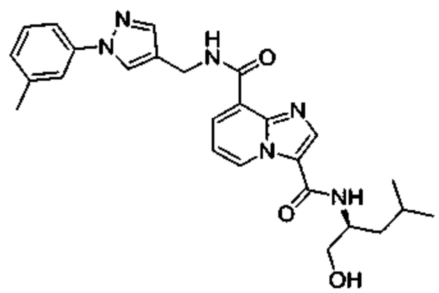
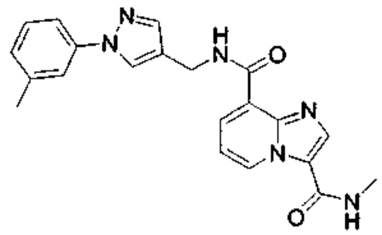
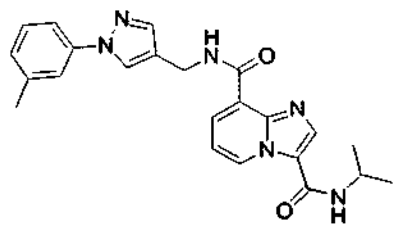
Compound **604** was prepared using the peptide coupling condition described in **Example 1B**

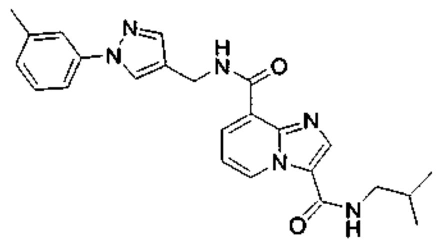
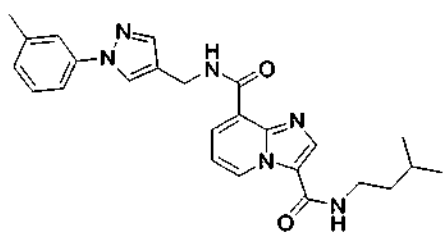
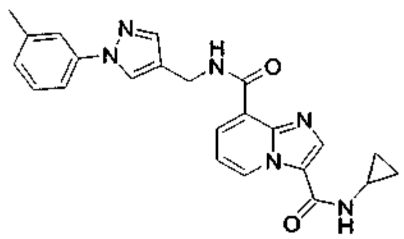
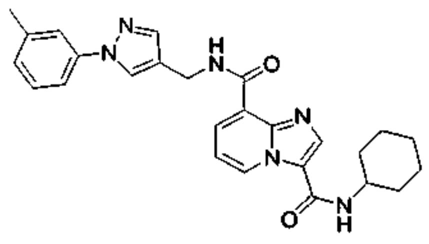
Part D:

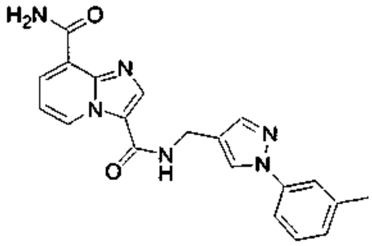
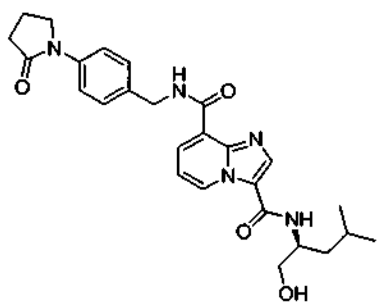
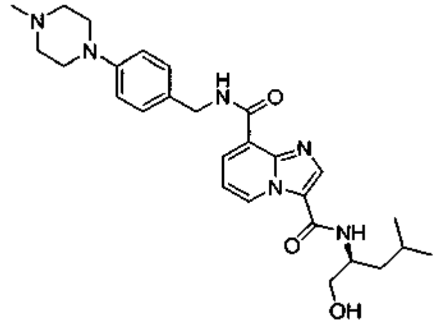
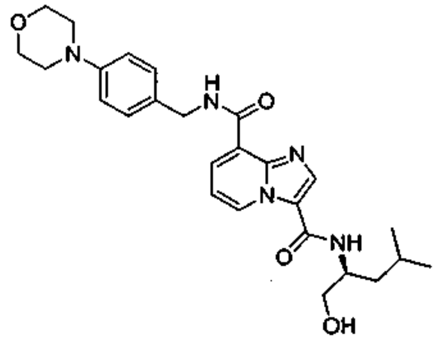
Compound **605** was prepared using the deprotecting condition described in **Example 1**B

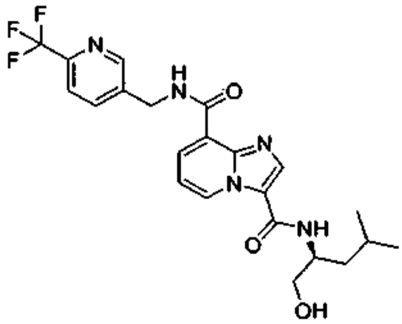
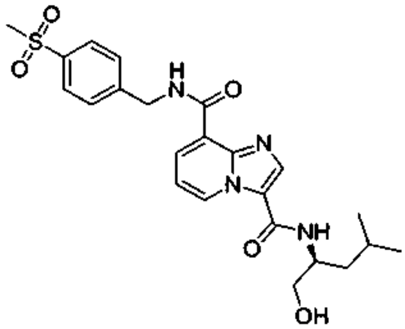
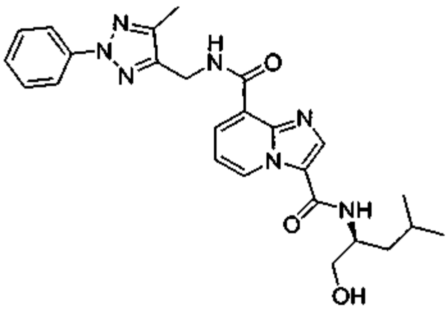
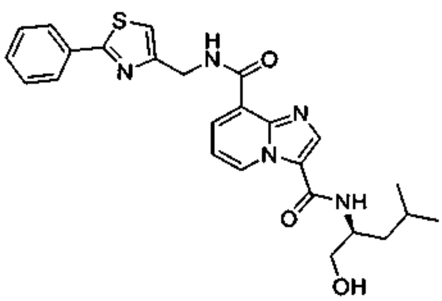
The compounds in Table 23 were synthesized using essentially similar procedures and conditions as described in **Example 19.**

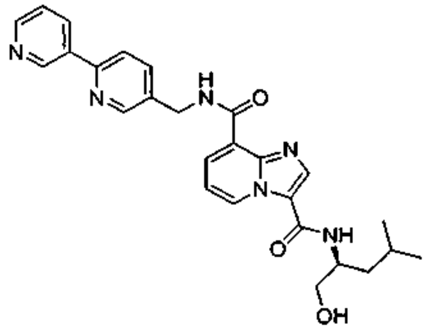
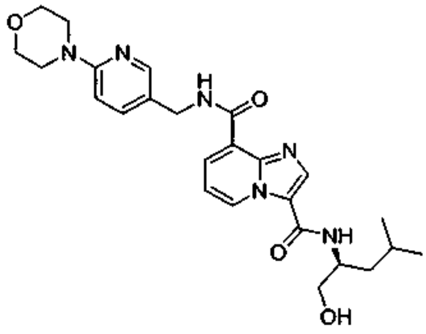
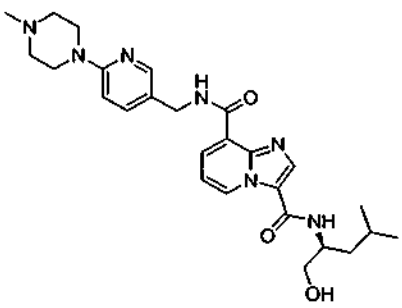
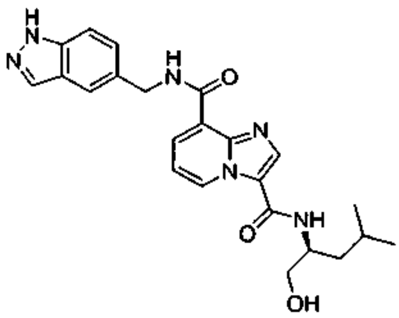
Table 23

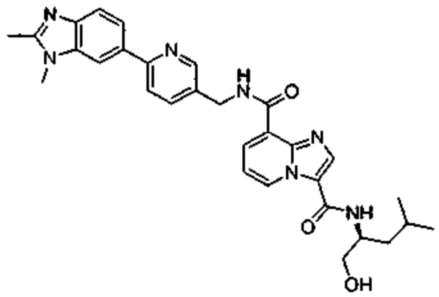
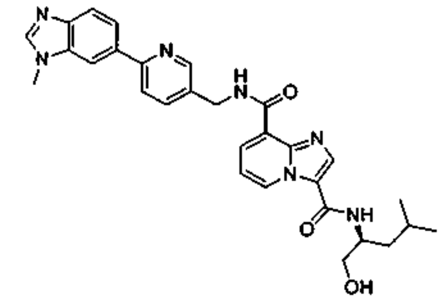
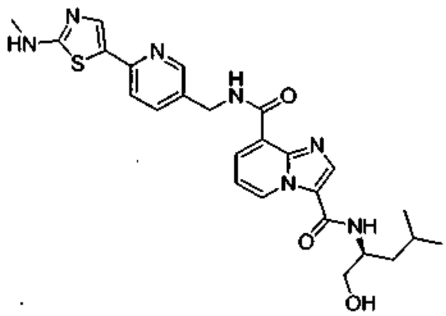
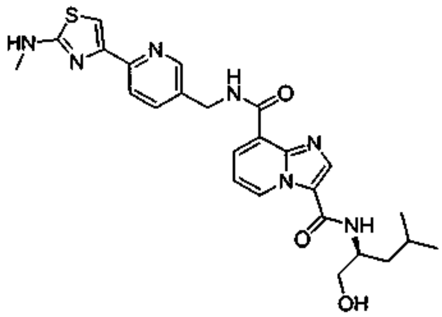
Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
605		474.2	475.1	1.84
606		388.2	389.2	1.58
607		416.2	417.1	1.84

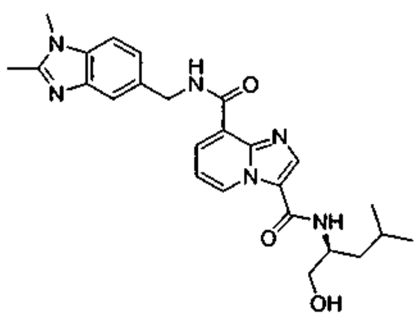
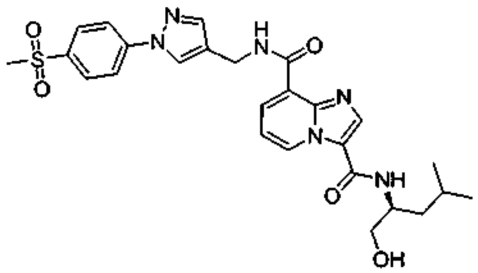
608		430.2	431.2	1.97
609		444.2	445.1	2.09
610		414.2	415.1	1.72
611		456.2	457.1	2.10

612		374.1	375.1	1.46
613		477.2	478.1	1.52
614		492.3	493.3	1.17
615		479.3	480.2	1.61

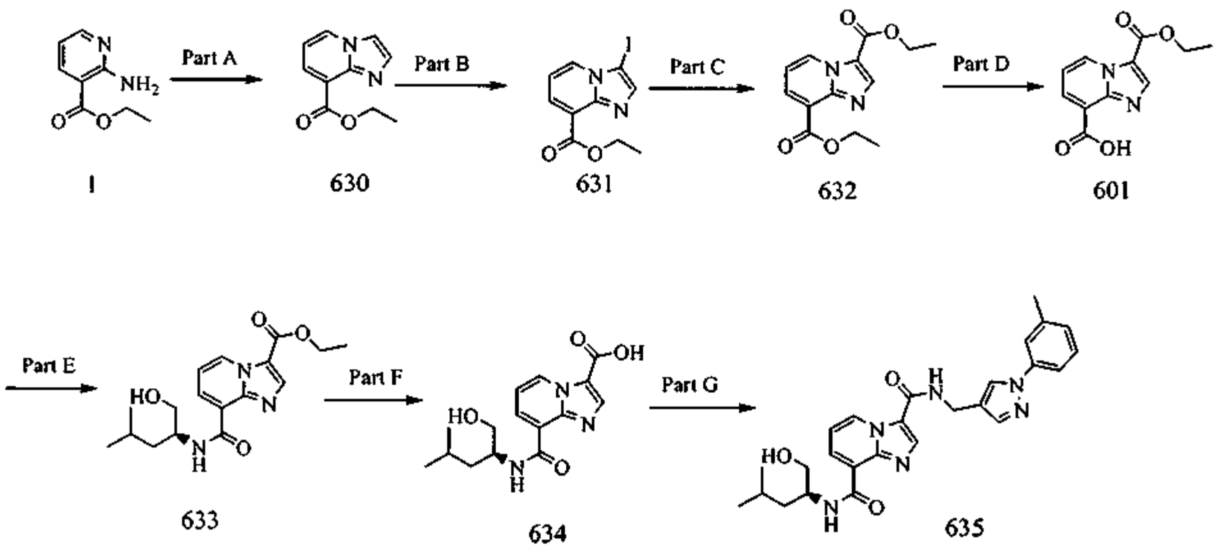
616		463.2	464.2	1.72
617		472.2	473.2	1.46
618		475.2	476.2	1.94
619		477.2	478.1	1.90

620		472.2	473.2	1.23
621		480.2	481.3	1.15
622		493.3	494.2	1.07
623		434.2	435.1	1.43

624		539.3	540.1	1.18
625		525.3	526.2	1.18
626		507.2	508.1	1.24
627		507.2	508.1	1.24

628		462.2	463.1	1.13
629		538.2	539	1.50

Example 20



Part A:

Compound **630** was prepared using the same conditions described in **Example 8** part C with chloroacetaldehyde. HPLC-MS t_R = 0.22 min ($UV_{254\ nm}$); mass calculated for formula C10H10N2O2 190.1, observed LCMS m/z 191.1 (M+H).

Part B:

Compound **630** (1.84 g, 9.7 mmol) was dissolved in EtOH (10 mL) and NIS (2.38 g, 10.6 mmol) was added at room temperature. The resulting mixture was allowed to stir for 1 hour and then concentrated. The residue was diluted with EtOAc (150 mL) and washed with $NaHCO_3$ (sat. aq., 50 mL x 3), brine and dried over Na_2SO_4. After concentration, the crude compound **631** was used in the next step directly without further purification. HPLC-MS t_R = 1.25 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_9IN_2O_2$ 316.0, observed LCMS m/z 317.0 (M+H).

Part C:

Under Argon, the flask was charged with compound **631** (crude, ~9.7 mmol), Pd(dppf)Cl2 (0.900 g, 1.1 mmol), and $Mo(CO)_6$ (5.28 g, 20 mmol). DIEA (2 mL, 12 mmol) and EtOH (20 mL) was added and the flask was sealed under Argon flow. The mixture was heated up to 80^0 C and stirred over night. After cooling to room temperature, the mixture was concentrated and diluted with EtOAc (250 mL) and washed with water, brine and dried over Na_2SO_4. After concentration, the residue was purified with column (silica gel, Hexane/EtOAc = 40/60) gave the product **632** (1.0 g) as white solid. HPLC-MS t_R = 1.22 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{14}N_2O_4$ 262.1, observed LCMS m/z 263.1 (M+H).

Part D:

Compound **601** was prepared using the hydrolysis conditions described in **Example 8** part E. HPLC-MS t_R = 0.77 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{10}N_2O_4$ 234.1, observed LCMS m/z 235.1 (M+H).

Part E:

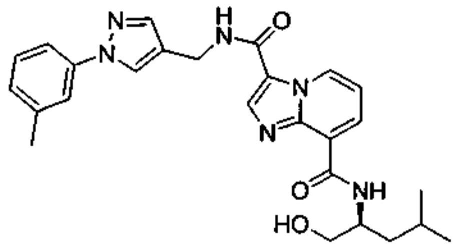
Compound **633** was prepared using the peptide coupling conditions described in **Example 1B**. HPLC-MS t_R = 1.81 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{23}N_3O_4$ 333.2, observed LCMS m/z 334.1 (M+H).

Part F:

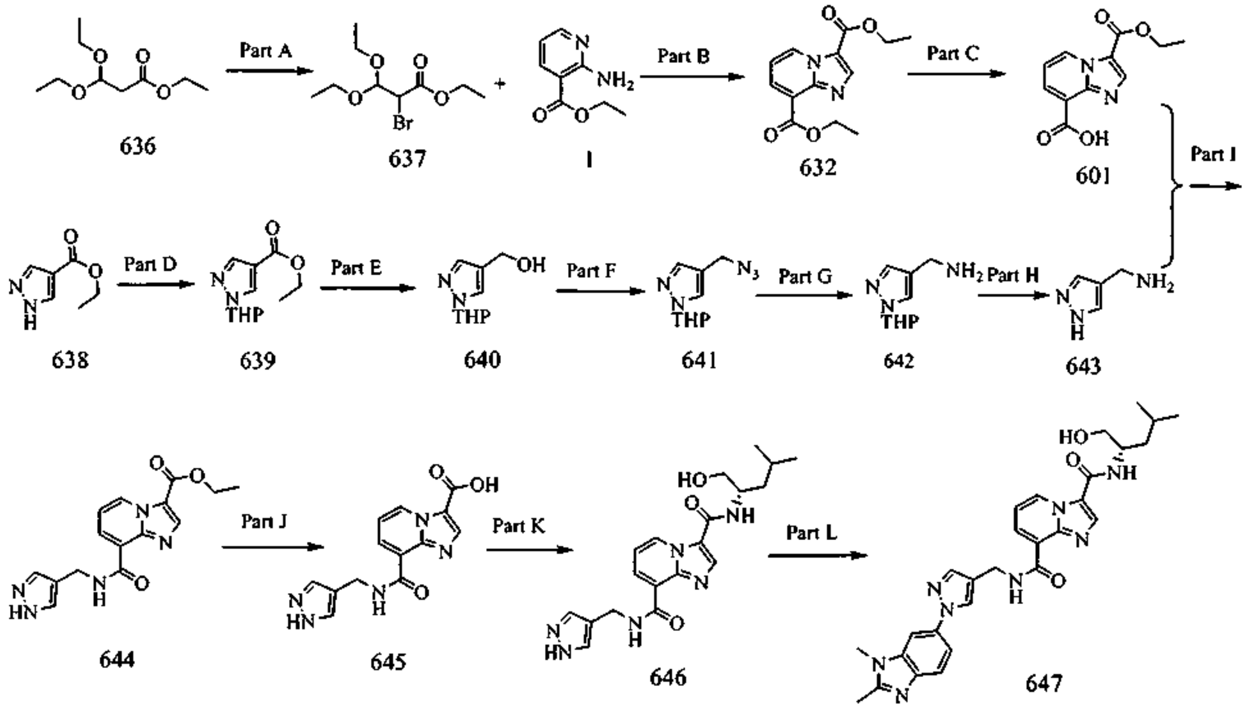
Compound **634** was prepared using the hydrolysis conditions described in **Example 8** part G. HPLC-MS t_R = 1.18 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{19}N_3O_4$ 305.1, observed LCMS m/z 306.1 (M+H).

Part G:

Compound **635** was prepared using the peptide coupling conditions described in **Example 1B**.

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
635		474.2	475.1	1.83

Example 21



Part A:

A few drops of bromine and pyridine (0.050 mL) were added to a well-stirred mixture of ethyl 3,3-diethoxylpropionate (15 g, 78.9 mmol), CCl_4 (50 mL) and dry precipitated Calcium carbonate (12 g, 120 mmol). After stirring for 15 min., the remained bromine (13.5 g, 84 mmol) was added dropwise during a period of 1 hour at 12-15^0 C. Carbon dioxide evolved regularly and the mixture thicked considerably. Stirring was continued for two hours at 12-15^0 C after complete addition of bromine. The mixture was then poured into ice-water and the excess calcium carbonate was removed by filtration through celite. The CCl_4 layer was removed and after washing with water, $NaHCO_3$ (sat. aq.), brine and dried over Na_2SO_4, did concentration to remove CCl_4. The crude product **637** was used in the next step directly without purification.

Part B:

Compound **632** was prepared using the same conditions described in **Example 8** part C. HPLC-MS t_R = 1.21 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{14}N_2O_4$ 262.1, observed LCMS m/z 263.1 (M+H).

Part C:

Compound **601** was prepared using the hydrolysis conditions described in **Example 8** part E. HPLC-MS t_R = 0.77 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{10}N_2O_4$ 234.1, observed LCMS m/z 235.1 (M+H).

Part D:

The mixture of pyrazole **638** (5.2 g, 30 mmol), DHP (11 mL, 120 mmol) and catalytic amount TFA (0.050 mL) was heated up to 60^{0}C and stirred for 6 hours. After cooling to room temperature, the excess amount of DHP was removed with concentration and the residue was purified with column gave the product **639** (5.5 g) as oil. HPLC-MS t_R = 1.52 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{16}N_2O_3$ 224.1, observed LCMS m/z 225.1 (M+H).

Part E:

To the solution of ester **639** (5.5 g, 24.5 mmol) in THF (100 mL), $LiAlH_4$ (1N in THF, 55 mL) was added slowly at room temperature and the resulting mixture was stirred for two hours. To the mixture, water (1.65 mL) was added carefully and stirred for 10 min. Then, 15% NaOH (1.65 mL) was added and stirred for another 10 min followed by the addition of water (5 mL) and stirred for another 30 min. The mixture was filtered through celite and washed with EtOAc. After concentration, the crude product **640** was used in the next step directly without further purification. HPLC-MS t_R = 1.18 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_{14}N_2O_2$ 182.1, observed LCMS m/z 183.1 (M+H).

Part F:

The mixture of alcohol **640** (6.7 g, crude, ~37 mmol), DBU (6.1 g, 40 mmol) and DPPA (11g, 40 mmol) in THF (100 mL) was stirred at room temperature overnight. After concentration, the residue was diluted with EtOAc (300 mL) and washed with water, brine dried over Na_2SO_4. After concentration, the residue was purified with column (silica gel, hexane/EtOAc = 20/80) gave the product **641** (6.2 g) as oil. HPLC-MS t_R = 1.42 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_{13}N_5O$ 207.1, observed LCMS m/z 208.2 (M+H).

Part G:

The compound **641** (6.2 g, 29.9 mmol) was dissolved in the mixture of dioxane (100 mL) and resin supported PPh_3 (~3 mmol/g, 15g, 45 mmol) was added. The resulting mixture was stirred at room temperature for 1 hour. Then, the mixture of dioxane/H_2O (4:1, 100 mL) was added and the mixture was stirred overnight. The resin was removed by filtration and concentration gave the crude product **642** which was used in the next step without further purification. HPLC-MS t_R = 0.23 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_{15}N_3O$ 181.1, observed LCMS m/z 182.1 (M+H).

Part H:

The crude compound **642** (~29.9 mmol) was dissolved in dioxane (50 mL). HCl (con. 20 mL) was added and the mixture was stirred at room temperature for 2 hours. After concentration, the residue was diluted with H_2O, extracted with ethyl ether. The aqueous was concentrated and dried under vacuum. The crude product **643** was used in the next step without further purification.

Part I:

Compound **644** was prepared using the peptide coupling conditions described in **Example 1B**. HPLC-MS t_R = 1.32 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{15}N_5O_3$ 313.1, observed LCMS m/z 314.2 (M+H).

Part J:

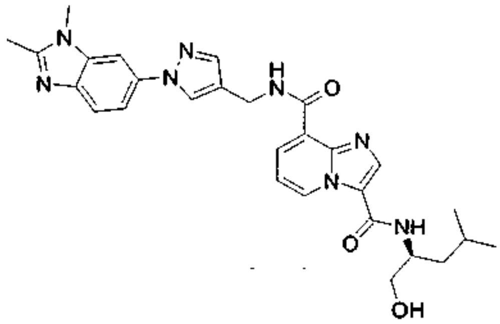
Compound **645** was prepared using the hydrolysis conditions described in **Example 8** part G. HPLC-MS t_R = 0.65 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{11}N_5O_3$ 285.1, observed LCMS m/z 286.1 (M+H).

Part K:

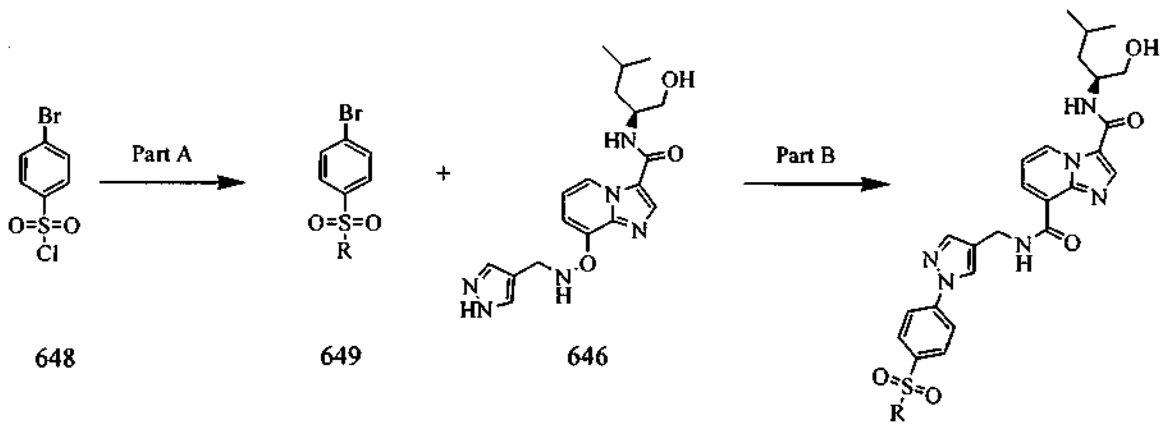
Compound **646** was prepared using the peptide coupling conditions described in **Example 1B** Part I. HPLC-MS t_R = 1.21 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{24}N_6O_3$ 384.2, observed LCMS m/z 385.1 (M+H).

Part L:

To the vial charged with compound **646** (0.039 g, 0.1 mmol), boronate (0.054 g, 0.2 mmol), $CuOAc_2$ (0.036 g, 0.2 mmol) and pyridine (0.016 g, 0.2 mmol), dioxane (2 mL) was added as solvent followed by the addition of 1 drop of water. The mixture was heated to 50^0 C and stirred overnight without cap. After cooling down to room temperature, the mixture was purified with HPLC gave the product **647**.

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
647		528.26	529.3	1.19

Example 22



648 649 646 650-652

(wherein R is as identified in Table 24)

Part A:

To a solution of compound **648** (1.00 g, 3.91 mmol) in dichloromethane (20 mL) was added diisopropylethylamine (0.75 mL, 4.30 mmol) at room temperature.

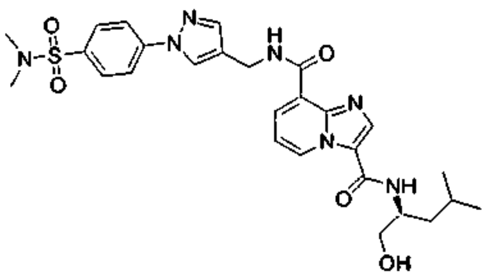
The reaction mixture was cooled to 0^0 C (ice-bath) and the corresponding amine (1.1 equivalents) added. The reaction mixture was allowed to warm to room temperature, stirred at ambient temperature for 16 hours, at which time LC-MS analysis indicated that the reaction was complete. The reaction mixture was concentrated under vacuum. Purification of by column chromatography ((SiO_2, 2% ethyl acetate / dichloromethane) afforded compound **649** as a white solid.

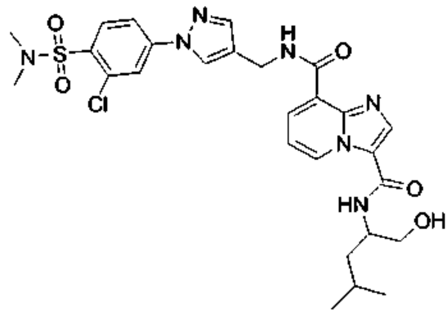
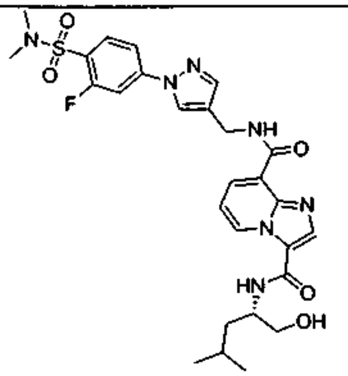
Part B:

A mixture of compound **646** (0.139 mmol), cesium carbonate (0.091 g, 0.278 mmol), the bromide (1.1 equivalents) and anhydrous dimethylacetamide (1.5 mL) were added to the reaction vessel. The reaction vessel was flushed with Argon. Added copper (I) iodide (0.278 mmol) and 1,10-phenanthroline (0.051 g, 0.278 mmol). Flushed the reaction vessel again with argon and the mixture was stirred in a sealed tube for 20 hours at 140^0 C. LC-MS analysis of the reaction indicates that the reaction is complete. The mixture was then cooled to room temperature and filtered. The filtrate was concentrated. Purification by Prep-LC and conversion to a hydrochloride salt afforded to compound **650-652**.

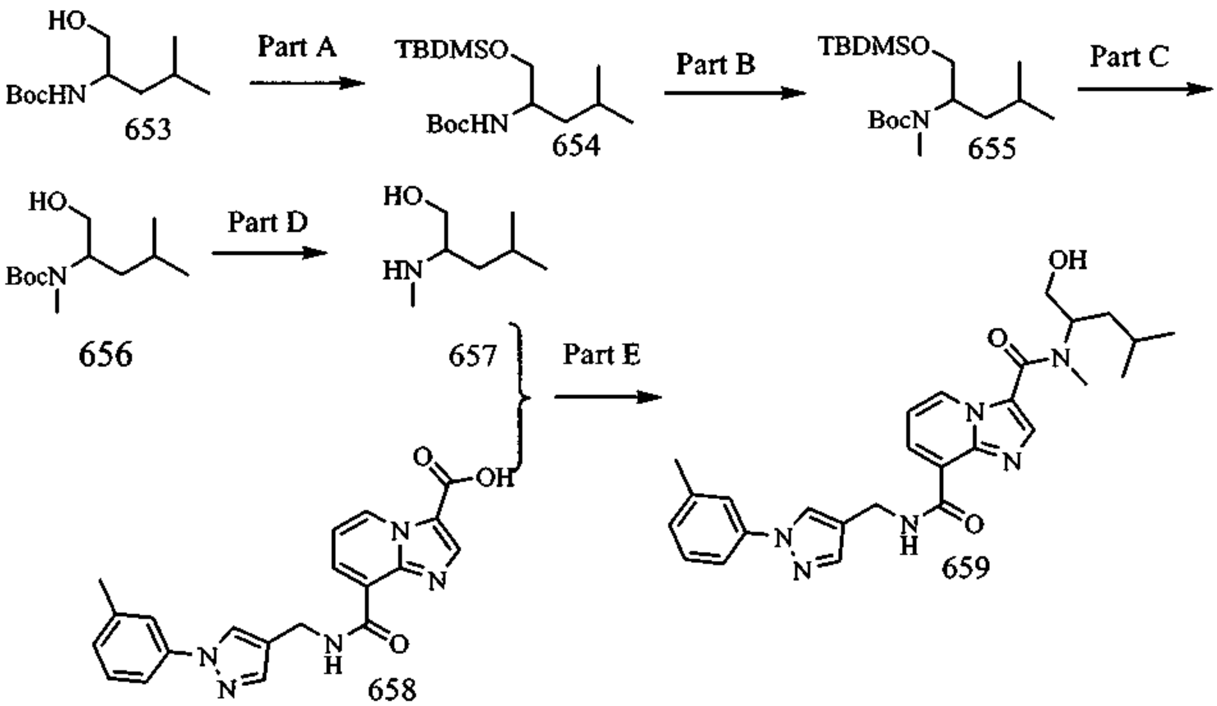
The compounds In Table 24 were synthesized using this procedure.

Table 24

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
650		567.23		

651		601.19	602.2	1.796
652		578.23	579.2	5.063

Example 23



Compound **658** was synthesized using essentially the same procedure as described in **Example 19**.

Part A:

The N-boc-L-lucinol compound **653** (2.2 g, 95%, 10 mmol) was dissolved in DCM (50 mL) and cooled to 10^0C. The TBDMCl (1.5 g, 10 mmol), and imidazole (1.36 g, 20 mmol) were added. The mixture was allowed to warm to room temperature and stirred overnight. Then, the mixture was diluted with EtOAc (100 mL) and washed with water, brine and dried over Na_2SO_4. After concentration, the residue was purified with column (silica gel, hexane/EtOAc = 95/5) gave the product **655** (3.25 g) as oil.

Part B:

To the solution of compound **654** (3.25 g, 10 mmol) in THF (50 mL), NaH (0.600 g, 60% in oil, 15 mmol) was added carefully. The mixture was stirred at room temperature for 10 min, then MeI (20 mmol) was added. The resulting mixture was stirred overnight, then cooled to 0 oC with ice-water bath and H_2O was added carefully to quench the reaction. The aqueous was extracted with EtOAc and the organics was dried over Na_2SO_4. After concentration, the crude product **655** was used in the next step directly without further purification. HPLC

Part C:

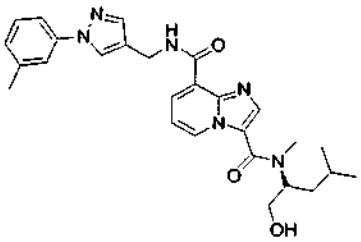
The crude compound **655** (3.19 g) was dissolved in THF (50 mL) and treated with Bu_4NF (12 mL, 1N in THF). The mixture was stirred at room temperature overnight and then concentrated. The residue was diluted with EtOAc (200 mL) and washed with water (50 mL x 2), brine and dried over Na_2SO_4. After concentration, the crude product was purified with column (silica gel, hexane/EtOAc = 50/50) gave product **656** (2.09 g) as oil.

Part D:

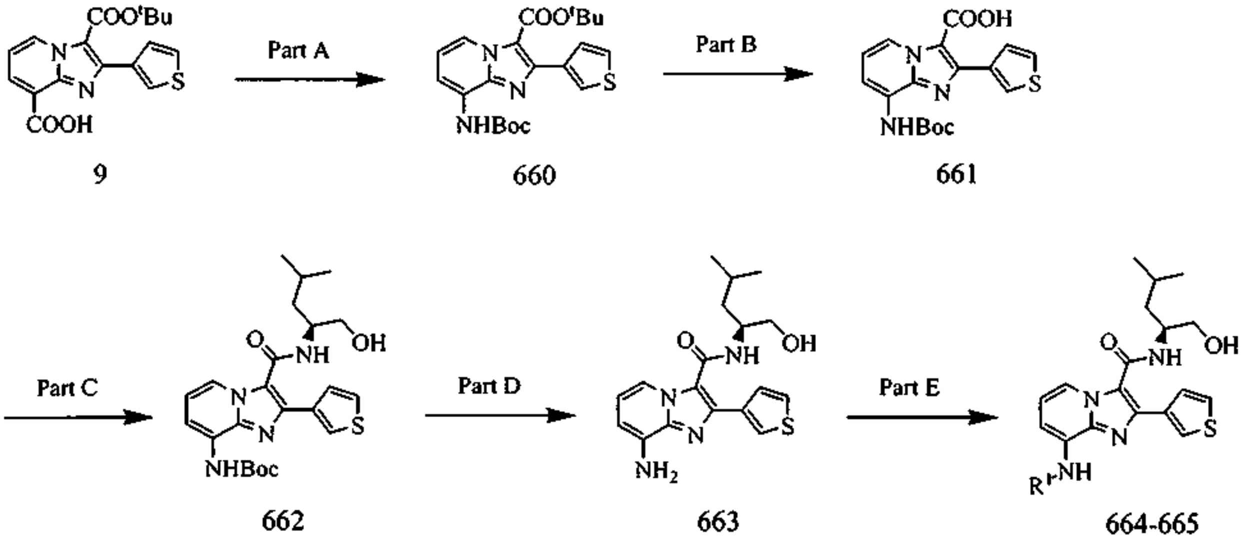
The compound **656** (2.09 g, 9.0 mmol) was dissolved in dioxane (5 mL) and treated with HCl (6N, 10 mL). The mixture was stirred at room temperature for 1 hour, and then extracted with ethyl ether (40 mL). The aqueous was concentrated under vacuum and dried with lyphlization gave the product **657** (1.11g) as white solid.

Part E:

Compound **659** was prepared using the peptide coupling conditions described in **Example 1B.**

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
659		488.3	489.2	1.86

Example 24



(wherein R^1 is identified in Table 25)

Compound **9** was prepared from procedures described in **Example 1B**.

Part A:

A mixture of compound **9** (0.266 g, 0.77 mmol), diphenylphosphorylazide (0.334 mL, 1.54 mmol) and triethylamine (0.323 mL, 2.31 mmol) in *t*-butanol (10 mL) was heated at reflux for 16 hours. The reaction mixture was cooled to room temperature and monitored by LC-MS. The volatiles were removed *in vacuo*, and the crude purified by flash column chromatography to afford compound **660** as a white solid. HPLC-MS t_R = 2.68 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{25}N_3O_4S$ 415.2, observed LCMS m/z 416.1 (M+H).

Part B:

Compound **661** was prepared from compound **660** using procedures described in Example 1B, Part F.

Part C:

Compound **662** was prepared from compound **661** using procedures described in Example 1B, Part G. HPLC-MS t_R = 2.19 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{30}N_4O_4S$ 458.2, observed LCMS m/z 459.1 (M+H).

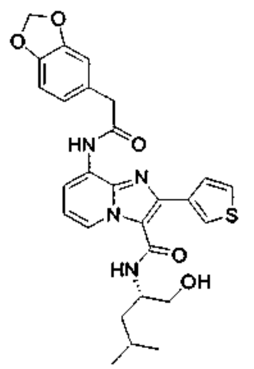
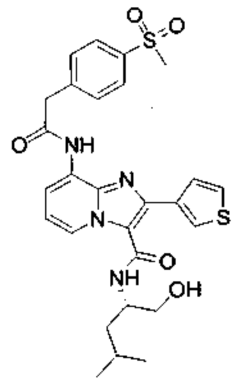
Part D:

Compound **663** was prepared from compound **662** using procedures described in **Example 1B**, Part H. HPLC-MS t_R = 1.27 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{22}N_4O_2S$ 358.1, observed LCMS m/z 359.1 (M+H).

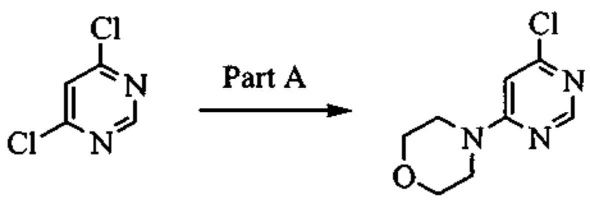
Part E:

Compounds **664-665** (Table 25) were prepared from compound 307 using procedures described in **Example 1B**, Part I.

Table 25

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
664		520.2	521.2	4.77
665		554.2	555.2	4.14

Example 25A

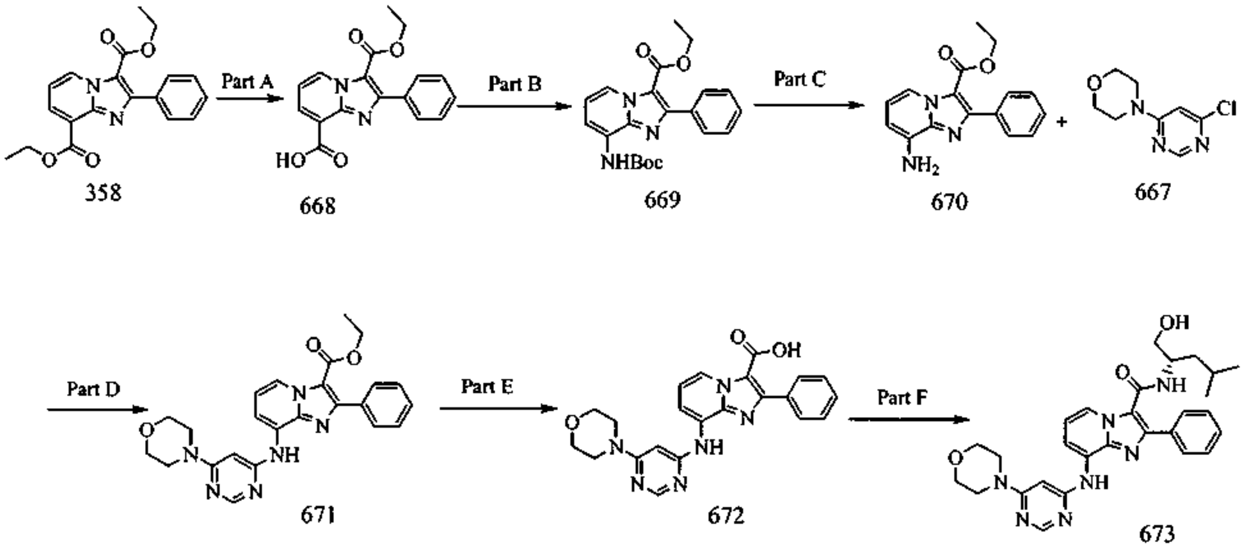


666 667

Part A:

To the solution of compound **666** (0.300 g, 2.0 mmol) in dioxane (5 mL), DIEA (0.356 mL, 2.0 mmol) was added followed by the addition of morpholine (0.174 mL, 2.0 mmol). The mixture was stirred at room temperature over night and concentrated. The residue was purified with column (silica gel, DCM/EtOAc = 50/50) to give the product **667** (0.320 g) as white solid. HPLC-MS t_R = 1.12 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_{10}ClN_3O$ 199.1, observed LCMS m/z 200.1 (M+H).

Example 25B



Compound **358** was synthesized in **Example 8**.

Part A:

Compound **668** was prepared using the hydrolysis conditions described in **Example 8** part E. HPLC-MS t_R = 0.67 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{11}N_3O_2$ 253.1, observed LCMS m/z 254.1 (M+H).

Part B:

The monoacid **668** (0.212 g, 0.68 mmol) was dissolved in t-butyl alcohol (20 mL), TEA (0.096 mL, 0.68 mmol) and DPPA (0.187 g, 0.68 mmol) was added. The mixture was heated up to refluxed and stirred over night. After cooled to room temperature, the solvent was removed with concentration. The residue was purified with column (silica gel, Hexane/EtOAc = 80/20) gave the product **669** (0.221 g) as oil. HPLC-MS t_R = 2.73 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{23}N_3O_4$ 381.2, observed LCMS m/z 382.1 (M+H).

Part C:

Compound **670** was prepared using the same deprotecting conditions described in **Example 8**. HPLC-MS t_R = 1.72 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{15}N_3O_2$ 281.1, observed LCMS m/z 282.1 (M+H).

Part D:

Under Argon, the vial was charged with 4-(6—chloropyrimidin-4-yl)-morpholine **667** (0.060 g, 0.3 mmol), compound **670** (0.168 mg, 0.6 mmol), Pd_2dba_3 (0.016 g, 0.017 mmol), 1,3-Bis(2,6-di-i-propylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (0.016 g, 0.35 mmol) and NaO^tBu (0.096 g, 1.0 mmol). Dioxane (2 mL) was added as solvent and the vial was sealed under Argon flow. The mixture was heated up to 80^0 C and stirred over night. After cooling to room temperature, the mixture was diluted with EtOAc (50 mL) and washed with NH_4Cl (sat. aq.), brine and dried over Na_2SO_4. After concentration, the residue was purified with column (silica gel, Hexane/EtOAc = 60/40) gave the product **671** (0.069 g) as oil. HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{24}N_6O_3$ 444.2, observed LCMS m/z 445.1 (M+H).

Part E:

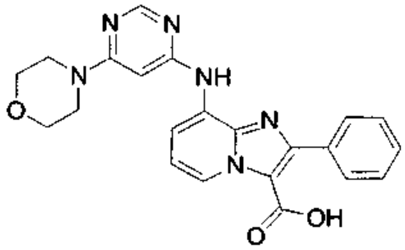
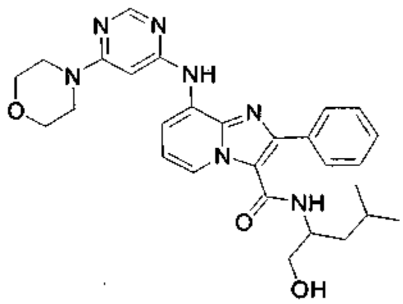
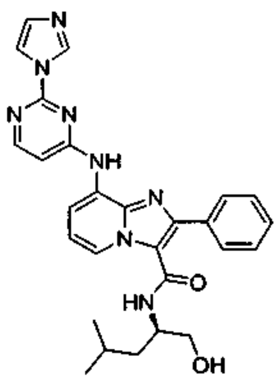
Compound **672** was prepared using the hydrolysis conditions described in **Example 8** part G. HPLC-MS t_R = 1.18 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{20}N_6O_3$ 416.2, observed LCMS m/z 417.1 (M+H).

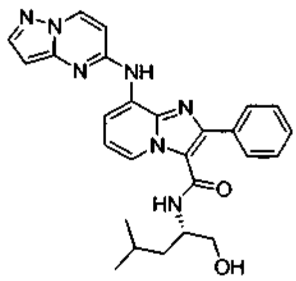
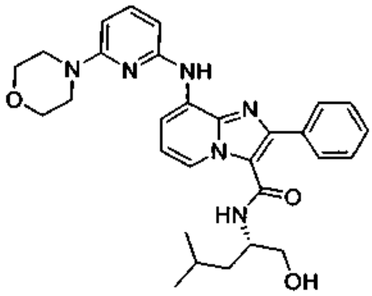
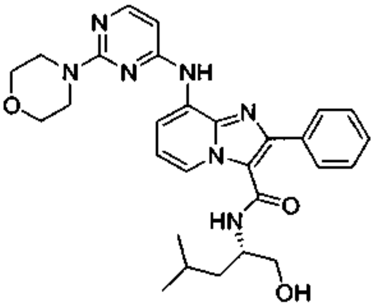
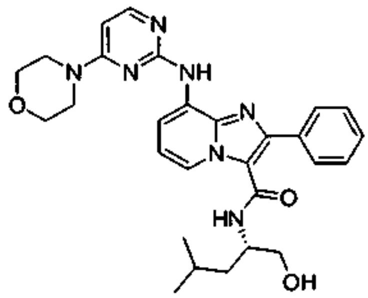
Part F:

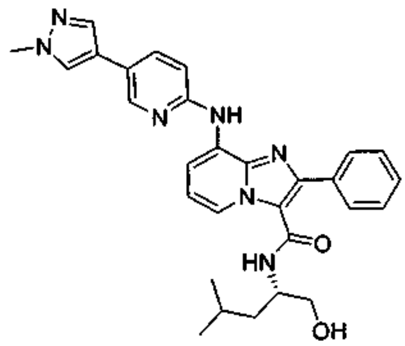
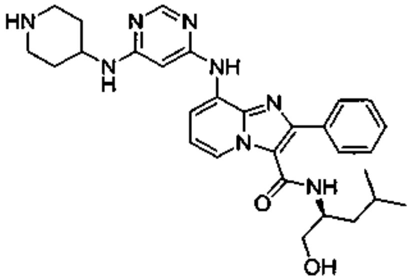
Compound **673** was prepared using the peptide coupling conditions described in **Example 1B,** Part I. HPLC-MS t_R = 1.43 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{32}N_6O_3$ 500.3, observed LCMS m/z 501.1 (M+H).

The compounds In Table 26 were synthesized using the same procedure described in **Example 25B**.

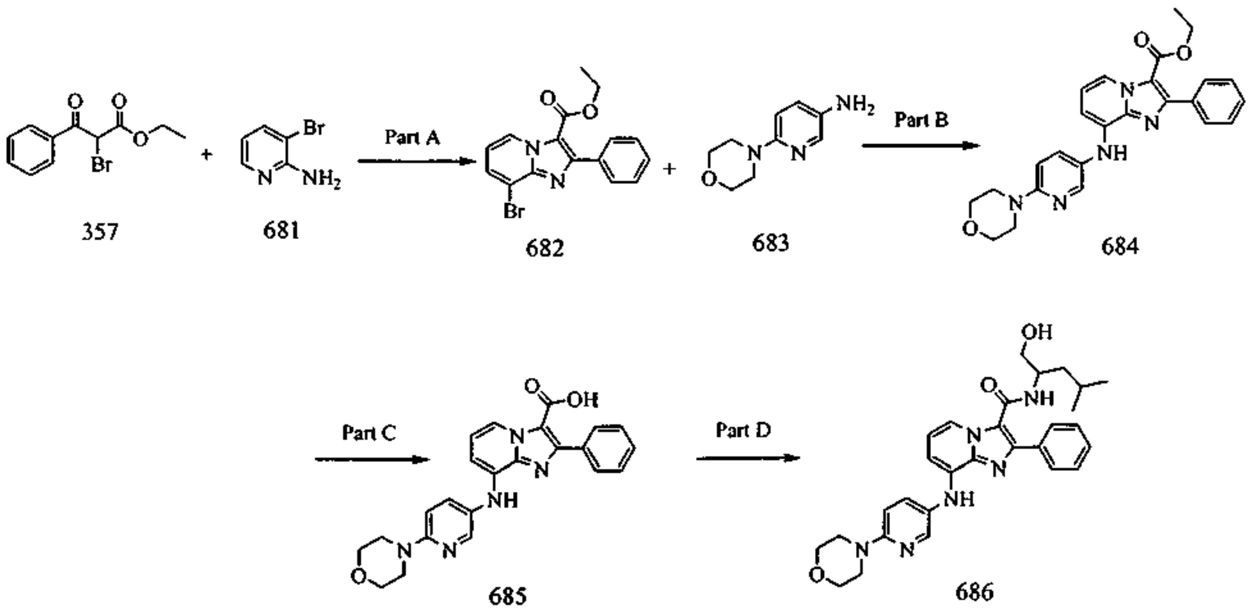
Table 26

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
672		416.2	417.1	1.18
673				
674		496.2	497.2	1.38

675		469.2	470.2	1.83
676		514.3	515.2	2.04
677		515.3	516.3	1.35
678		515.3	516.3	1.34

679		509.3	510.1	2.24
680		528.3	529.2	0.95

Example 26



Part A:

Compound **682** was prepared using the conditions described in **Example 8** part C. HPLC-MS t_R = 2.11 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{13}BrN_2O_2$ 344.0, observed LCMS m/z 345.0 (M+H).

Part B:

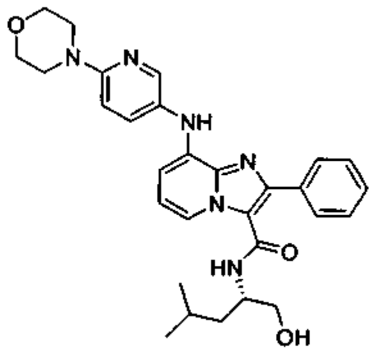
Compound **684** was prepared using the amination conditions described in **Example 22** part D. HPLC-MS t_R = 1.84 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{25}N_5O_3$ 443.2, observed LCMS m/z 444.2 (M+H).

Part C:

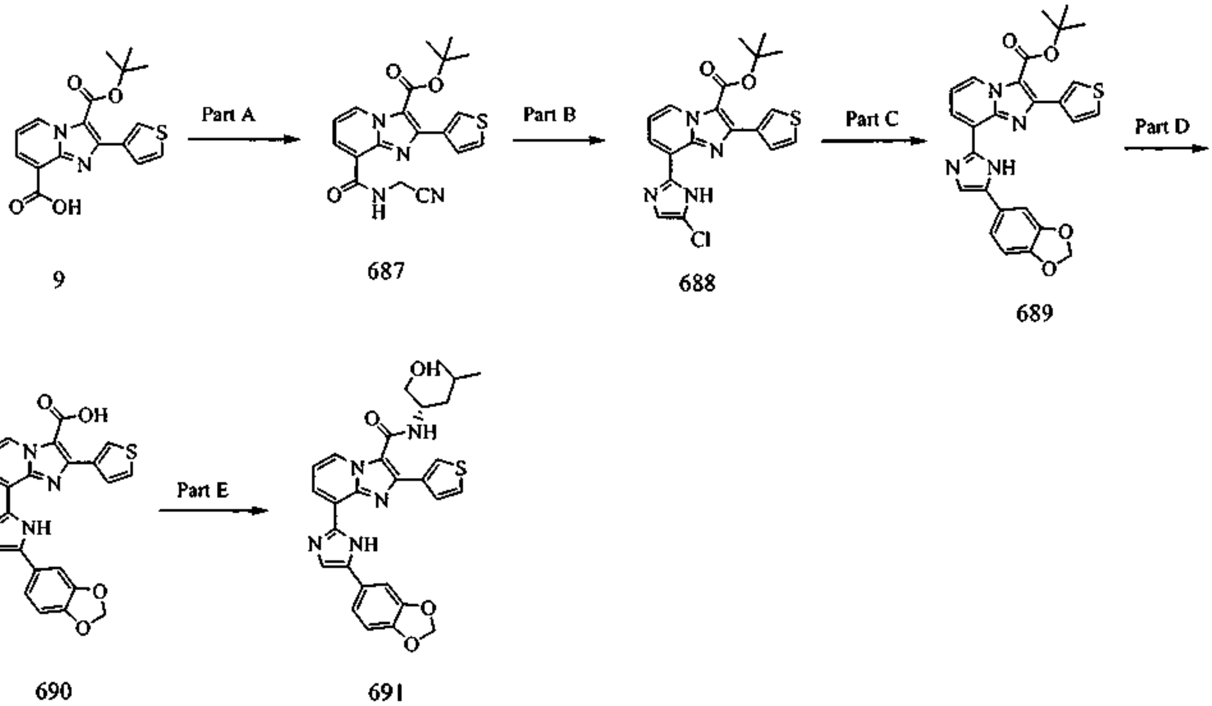
Compound **685** was prepared using the hydrolysis conditions described in **Example 22** part G. HPLC-MS t_R = 1.20 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{19}N_5O_3$ 415.2, observed LCMS m/z 416.2 (M+H).

Part C:

Compound **686** was prepared using the peptide coupling conditions described in **Example 1B.**

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
686		514.3	515.2	1.55

Example 27



Part A:

Compound **687** was prepared using the peptide coupling conditions described in **Example 1B** Part G. HPLC-MS t_R = 2.89 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{18}N_4O_3S$ 382.1, observed LCMS m/z 383.0 (M+H).

Part B:

The compound **687** (0.038 g, 0.1 mmol) was dissolved in CAN (5 mL), PPh_3 (0.066 g, 0.25 mmol) and CCl_4 (0.024 mL, 0.25 mmol) were added. The mixture was heated to 40^0 C and stirred overnight. After concentration, the residue was took up with NaOH (0.5N, 4 mL) and stirred for another 10 min. The mixture was extracted with EtOAc (20 mL x 3), and the organics was dried over Na_2SO_4. After concentration, the crude product was purified with column (silica gel, Hexane/EtOAc = 70/30) gave the product **688** (0.031 g) as yellowish solid. HPLC-MS t_R = 2.47 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{17}ClN_4O_2S$ 400.1, observed LCMS m/z 401.0 (M+H).

Part C:

Under Ar, the chloroimidazole compound **688** (0.020 g, 0.05 mmol) in toluene (2.0 ml) was added to the flask which was charged with Pd_2dba_3 (0.008 g, 0.01 mmol), 2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl (0.019 g, 0.04 mmol), K_3PO_4 (0.212 g, 1.0 mmol), and boronic acid (0.017 g, 0.1 mmol). The mixture was thoroughly degassed by alternately connected the flask to vacuum and Argon. The resulting solution was heated upto 100^0 C and stirred overnight and diluted by EtOAc after cooled to room temperature. The solid was removed by filter through Celite and washed with some EtOAc. Concentration to remove the solvent and the resulting residue was purified with column (silica gel, Hexane/EtOAc = 50/50) gave the product **689** as oil. HPLC-MS t_R = 2.23 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{22}N_4O_4S$ 486.1, observed LCMS m/z 487.0 (M+H).

Part D:

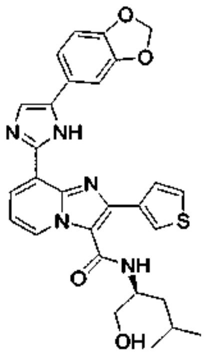
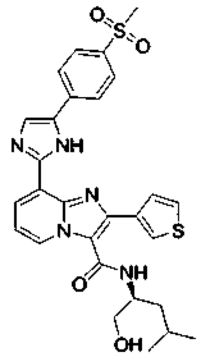
Compound **689** (0.010 g, 0.02 mmol) was treated with HCl (con. 2 mL) and stirred at room temperature for 10 min. After concentration, the crude product **690** was used in the next step directly. HPLC-MS t_R = 1.52 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{22}N_4O_4S$ 430.0, observed LCMS m/z 431.0 (M+H).

Part E:

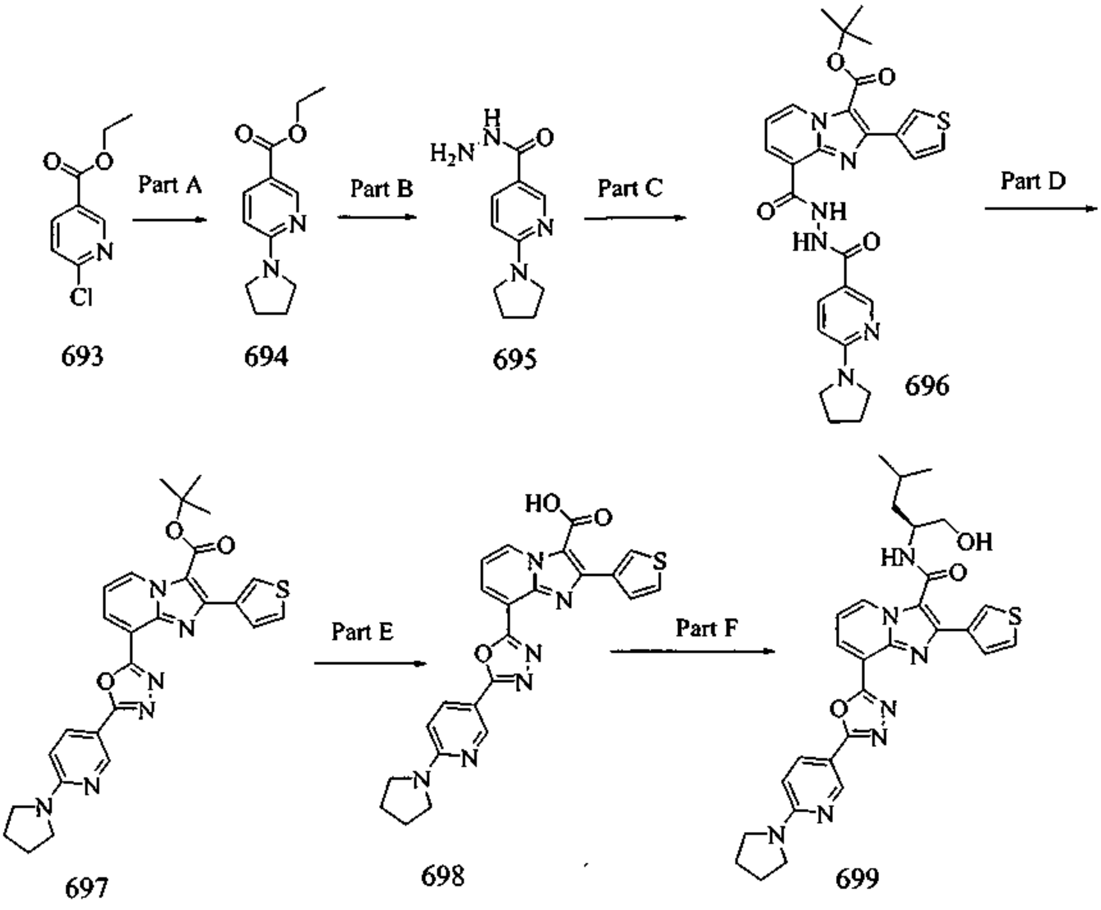
Compound **691** was prepared using the peptide coupling conditions described in **Example 1B** Part I.

The compounds in Table 27 were synthesized using the same procedure described in **Example 27**

Table 27

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
691		529.2	530.0	1.73
692		545.2	546.1	1.77

Example-28



693 694 695 696 697 698 699

Part A:

Ethyl-6-chloronicotinate **693** (5 mmol; 0.900 g) was dissolved in 5 mL of Pyrrolidine and refluxed for 14 hours. The Pyrrolidine was removed under vaccum and resulting gummy material diluted with Ethyl acetate and washed with water, brine and dried over anhydrous $MgSO_4$ and filtered and concentrated. Purification by silica column resulted in title compound (40%).

Part B:

6-pyrrolidin-1-yl-nicotinic acid ethyl ester **694** obtained in the above step was dissolved in Ethanol (25 mL) and hydrazine hydrate (5 mL,) was added and the reaction mixture refluxed for 4 hours. Concentration of ethanol afforded the title compound, hydrazide **695** as crystalline compound (100%).

Part C:

2- Thiphene-3-yl-imidazo[1,2-a]pyridine-3,8-dicarboxylic acid-3-t-butyl ester (0.5 mmol ;0.172 g) dissolved in dichloromethane (5 mL). To this (1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide (0.093 g ;1.2 eq; 0.6 mmol) was added. Followed by Diisopropyl ethyl amine (3 equivalents, 0.315 mL) was added and the solution stirred at room temperature for 15 minutes.

The activated acid was added with 0.55 mmol (0.115 g) solution of 6-pyrrolidin-1-yl-nicotinic acid hydrazide **695** (pre dissolved in to NMP; 0.5 mL). The solution was shaken at room temperature for 4 hours. LCMS analysis showed the completion of the reaction.

The reaction vessel added with water and extracted with EtOAc (60 mL). The EtOAc extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered, and EOAc evaporated under vacuum. Purification by column chromatography (SiO_2,Hexane- ethyl acetate) afforded title compound **696**.

Part D:

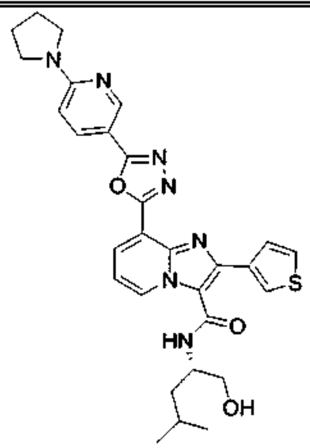
8-[N'-(6-Pyrrolidin-1-yl-pyridine-3-carbonyl) hydrazinocarbonyl]-2-thiophen-3yl-imidazo[1,2-a]pyridine-3carboxylic acid t-butyl ester **696** was dissolved in dichloromethane-carbon tetrachloride (1:1) and triphenyl phosphine on resin (3mmol/g, 3 g) was added and the reaction was refluxed for 8 hours. The reaction cooled to room temperature, filtered off the resin. The filtrate was evaporated under vacuum. The resulting material was used in the next step with out purification.

Part E:

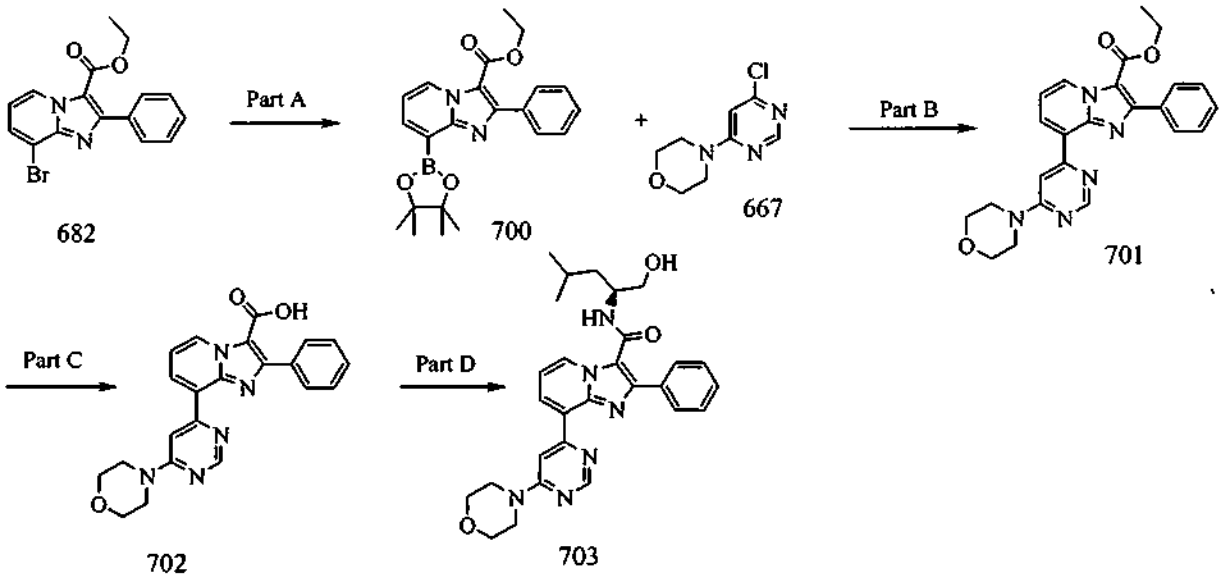
8-[5-(6-pyrrolidin-1-yl-)[1,3,4-]oxadizol-2yl-] -2-thiophen-3yl-imidazo[1,2-a]pyridine-3-carboxylic acid- tert-butyl ester **697** is dissolved in 4N HCl in dioxane and stirred for 2 hours. The dioxane/HCl was evaporated under vacuum to give title compound, free carboxylic acid. The crude product is dissolved in Acetonitrile-water and freeze dried, lyophilized to get a product in powder form, which used in the next step with out purification. Mass calculated formula: C23H18N6O3S; M.Wt=458.11; M+H=459.21]

Part F:

8-[5-(6-pyrrolidin-1-yl-)[1,3,4-]oxadizol-2yl-] -2-thiophen-3yl-imidazo[1,2-a]pyridine-3-carboxylic acid **698** thus obtained was dissolved in NMP (2 mL), and HATU (1.2 eq), DIEA (3 equivalents) were added in sequence. L-leucinol (1.2 equivalents) was added and the reaction mixture stirred at room temperature for 3 hours. The reaction mixture was diluted with Ethyl acetate and water. The ethyl acetate layer washed with water, brine and dried over anhydrous magnesium sulfate. Filtered, and EtOAc removed under vacuum to get the title compound **699**. This was purified by mass triggered Preparative HPLC to get 90% pure product.

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
699		557.2	558.2	3.77

Example 29



Part A:

Compound **682** was prepared using the conditions described in **Example 26**. HPLC-MS t_R = 2.11 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{13}BrN_2O_2$ 344.0, observed LCMS m/z 345.0 (M+H).

Part B:

To a 25 ml round bottom flask charged with bis(pinacolato)diboron (0.307 g, 1.2 mmol), (0.294 g, 3.0 mmol) of KOAc and (0.027 g, 0.03 mmol) of $PdCl_2$(dppf) was added a solution of compound **682** (0.375 g, 1.0 mmol) in DMSO (6 ml). The mixture was thoroughly degassed by alternately connected the flask to vacuum and Argon. This resulting mixture was then heated at 80^0 C overnight, diluted by EtOAc (40 ml) and filtered through celite. After concentration, the residue was purified with column (silica gel, Hexane/EtOAc = 60/40) to give the product **700** (0.301 g) as oil. HPLC-MS t_R = 1.88 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{25}BN_2O_4$ 392.2, observed LCMS m/z 393.1 (M+H).

Part C:

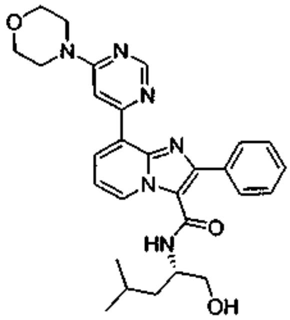
Under Ar, the bornate compound **700** (0.050 g, 0.13 mmol) in dioxane (2.0 ml) was added to the flask which was charged with Pd(dppf)Cl_2 (0.008 g), K_3PO_4 (1.790 g, 0.4 mmol), and chloropyrimidine **667** (0.026 g, 0.13 mmol). The mixture was thoroughly degassed by alternately connected the flask to vacuum and Argon. The resulting solution was heated upto 80^0 C and stirred overnight and diluted by EtOAc after cooled to room temperature. The solid was removed by filter through Celite and washed with some EtOAc. Concentration to remove the solvent and the resulting residue was purified with column (silica gel, Hexane/EtOAc = 50/50) gave the product **701** as oil. HPLC-MS t_R = 1.89 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{23}N_5O_3$ 429.2, observed LCMS m/z 430.1 (M+H).

Part D:

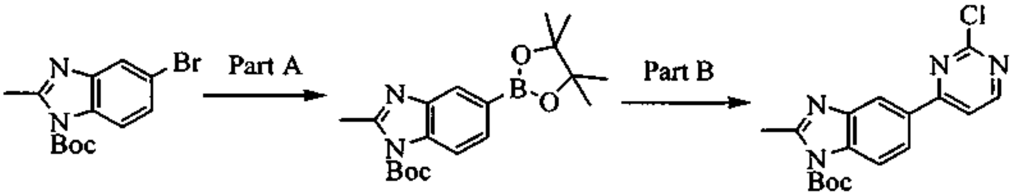
Compound **702** was prepared using the hydrolysis conditions described in **Example 8** Part G. HPLC-MS t_R = 1.14 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{19}N_5O_3$ 401.1, observed LCMS m/z 402.1 (M+H).

Part E:

The compound **703** (0.040 g, 0.1 mmol) was dissolved in DMF (2 mL), TIEA (0.018 mL, 0.1 mmol) and HATU (0.038 g, 0.1 mmol) were added at room temperature followed by the addition of L-lucinol (0.011 g, 0.1 mmol). The mixture was stirred over night and purified with HPLC.

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
703		500.3	501.1	1.43

Example 30A



704 705 706

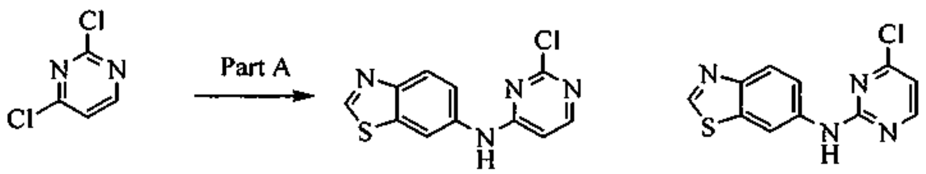
Part A:

Compound **705** was prepared using the conditions described in **Example 29** Part A. HPLC-MS t_R = 2.33 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{27}BN_2O_4$ 358.2, observed LCMS m/z 359.2 (M+H).

Part B:

Compound **706** was prepared using the conditions described in **Example 29** Part B. HPLC-MS t_R = 2.07 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{17}ClN_4O_2$ 344.1, observed LCMS m/z 345.1 (M+H).

Example 30B

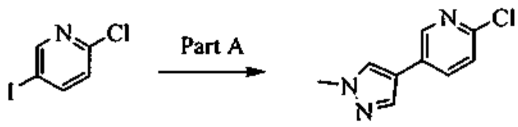


707 708 709

Part A:

Under Argon, the vial was charged with 2, 4-dichloropyrimidine **707** (0.149 g, 1.0 mmol), 6-aminobenzothiazole (0.150 g, 1.0 mmol), Pd_2dba_3 (0.090 g, 0.1 mmol), 1,3-Bis(2,6-di-i-propylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (0.095 g, 0.2 mmol) and NaO^tBu (0.096 g, 1.0 mmol). Dioxane (2 mL) was added as solvent and the vial was sealed under Argon flow. The mixture was heated up to 80^0 C and stirred over night. After cooling to room temperature, the mixture was diluted with EtOAc (50 mL) and washed with NH_4Cl (sat. aq.), brine and dried over Na_2SO_4. After concentration, the residue was purified with column (silica gel, Hexane/EtOAc = 60/40) gave the product **708** and **709** as oil. **708**: HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula C11H7ClN4S 262.0, observed LCMS m/z 263.0 (M+H). **709**: HPLC-MS t_R = 1.62 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_7ClN_4S$ 262.0, observed LCMS m/z 263.0 (M+H).

Example 30C

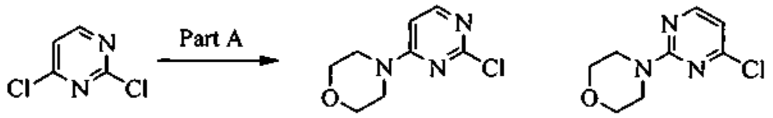


710 711

Part A:

Compound **711** was prepared using the conditions described in **Example 29** part D. HPLC-MS t_R = 1.26 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_8ClN_3$ 193.0, observed LCMS m/z 194.0 (M+H).

Example 30D

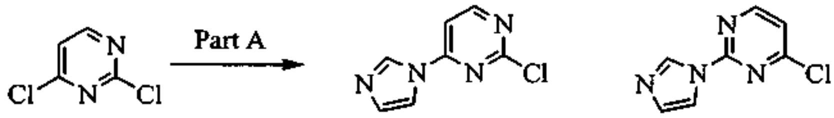


707 712 713

Part A

Compound **712** and **713** were prepared using the same procedure and condition described in **Example 29** part C.

Example 30E

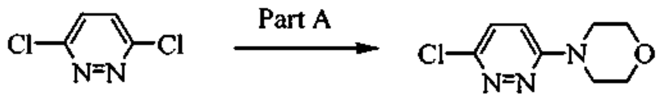


707 714 715

Part A:

Compound **714** and **715** were synthesized from Compound **707** according to the procedures of Borowski et. al. (*J. Med. Chem.* 2000, *43*, 1901 and the references therein.)

Example 30F

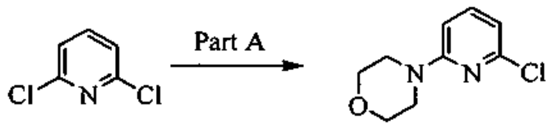


716 717

Part A:

Compound **716** was prepared using the same procedure and condition described in **Example 29** part C. HPLC-MS t_R = 0.96 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_{10}ClN_3O$ 199.1, observed LCMS m/z 200.1 (M+H).

Example 30G

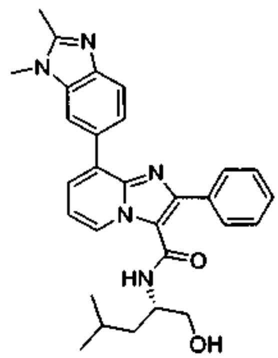
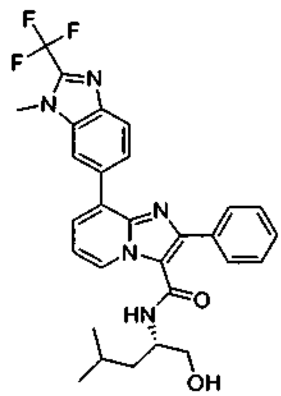


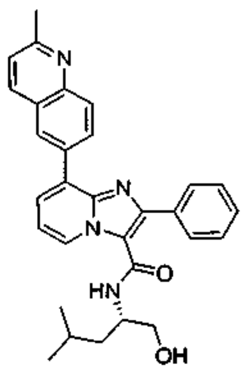
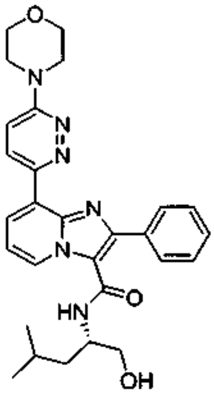
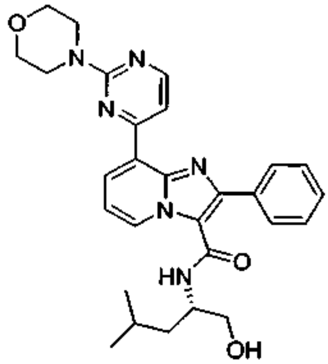
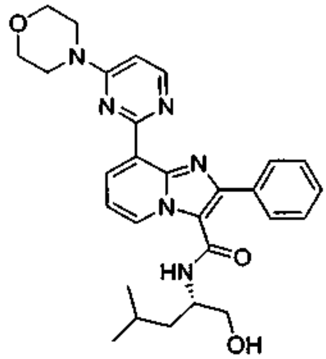
718 719

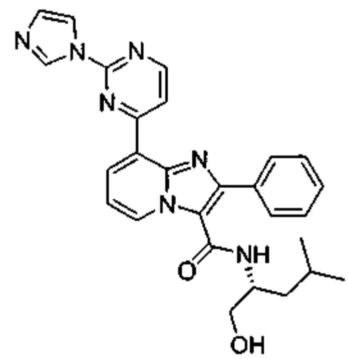
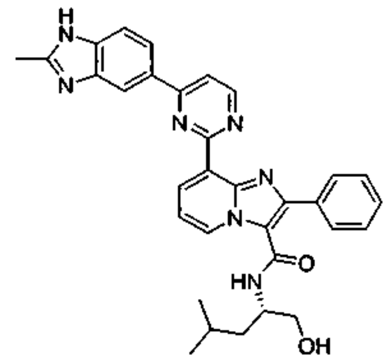
Part A:

Compound **719** was prepared using the same procedure and condition described in **Example 29** part C. HPLC-MS t_R = 1.69 min ($UV_{254\ nm}$); mass calculated for formula C9H11ClN2O 198.1, observed LCMS m/z 199.1 (M+H).

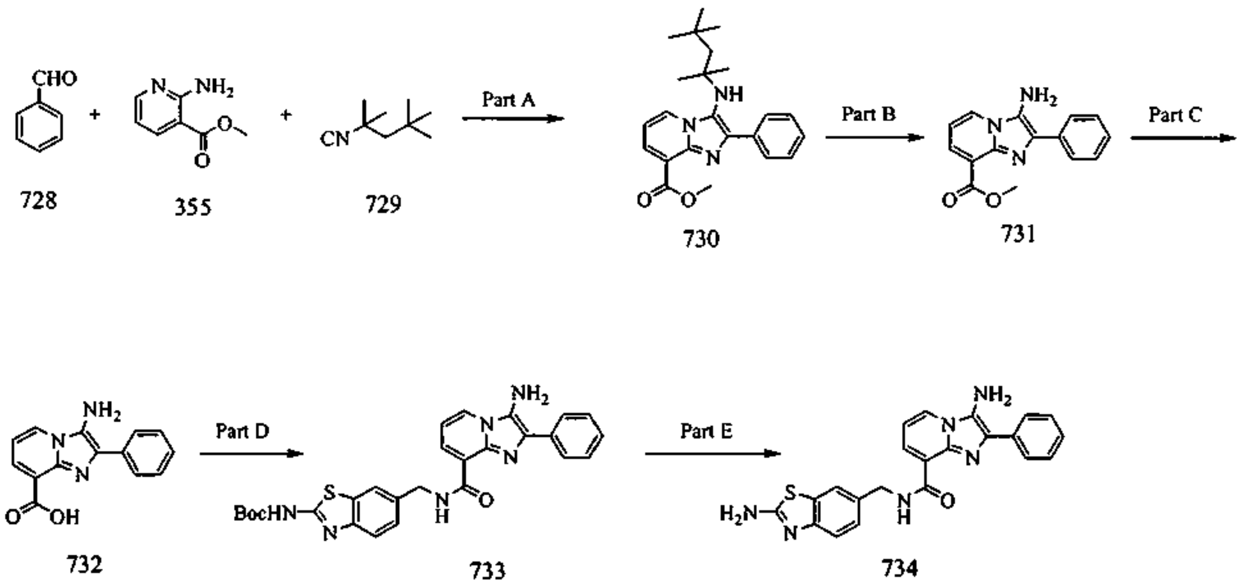
The compounds in Table 28 were prepared using the same procedure described in **Example 29.**

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
720		481.2	482.2	1.22
721		535.2	536.2	2.06

722		478.2	479.2	1.41
723		500.3	501.1	1.48
724		500.3	501.1	1.98
725		500.3	501.1	1.31

726		481.2	482.2	1.54
727		545.3	546.2	1.49

Example 31



Part A

The mixture of benzaldehyde **728** (1.06 g, 10 mmol), 2-aminopyridine **355** (1.52 g, 10 mmol), and 1,1,3,3-tetramethylbutyl isocyanide (1.94 mL, 90%, 10 mmol) in MeOH/DCM (1:3, 40 mL) was added $Sc(OTf)_3$ (0.492 g, 1.0 mmol). The reaction mixture was heated up to 70^0 C and stirred for 3 days. After cooled down to room temperature, the solvent was removed by concentration and the residue was purified with column (silica gel, Hexane/EtOAc = 70:30) gave the product **730** as yellow solid (2.1 g). HPLC-MS t_R = 1.51 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{29}N_3O_2$ 379.2, observed LCMS m/z 380.2 (M+H).

Part B

The compound **730** (0.400 g) was dissolved in the mixture of DCM (5 mL) and TFA (5 mL) and stirred for 10 min. Then the solvent was removed with concentration and the resulting residue was treated aq. $NaHCO_3$ (40 mL). The aqueous was extracted with EtOAc (50 mL x 3) and the organics was washed with brine and dried over Na_2SO_4. After concentration, the crude product **731** was used in the next step directly. HPLC-MS t_R = 0.77 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{13}N_3O_2$ 267.1, observed LCMS m/z 268.1 (M+H).

Part C:

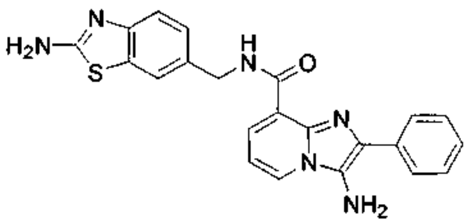
Compound **732** was prepared using the hydrolysis conditions described in **Example 8**. HPLC-MS t_R = 0.67 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{11}N_3O_2$ 253.1, observed LCMS m/z 254.1 (M+H).

Part D:

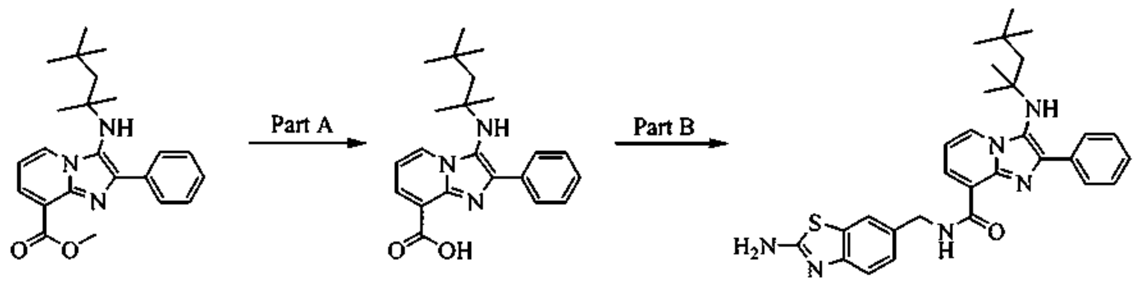
Compound **733** was prepared using the peptide coupling conditions described in **Example 8.** HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{26}N_6O_3S$ 514.2, observed LCMS m/z 515.0 (M+H).

Part E:

Compound **738** was prepared using the same deprotecting conditions described in **Example 8**.

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
734		414.1	415.1	1.10

Example 32



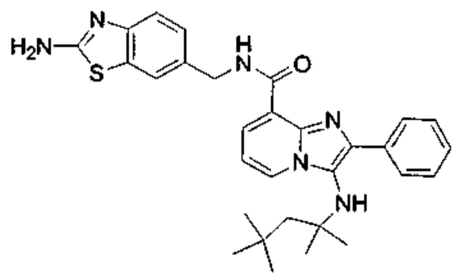
730 735 736

Part A:

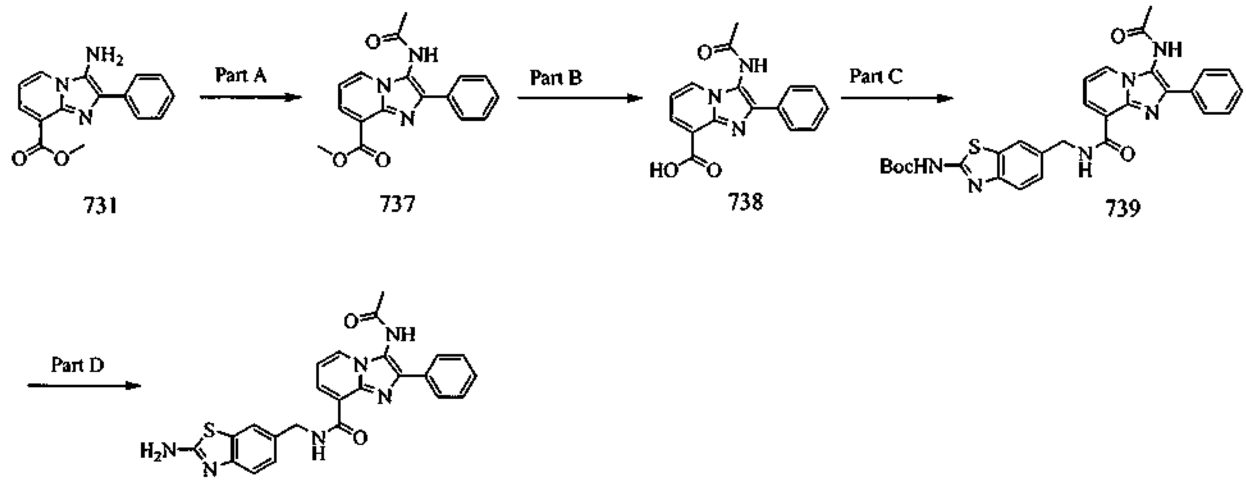
Compound **735** was prepared using the hydrolysis conditions described in **Example 8**. HPLC-MS t_R = 1.64 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{27}N_3O_2$ 365.2, observed LCMS m/z 366.3 (M+H).

Part B:

Compound **736** was prepared using the peptide coupling conditions described in **Example 8** with 2-amino-6-aminomethyl-benzothiazole

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
736		526.2	527.2	1.64

Example 33



731 737 738 739 740

Part A:

To the solution of **731** (0.027 g, 0.1 mmol) in DCM (5 mL), DIEA (0.100 mL, 0.6 mmol) was added followed by the addition of acetyl chloride (0.012 g, 0.15 mmol). The mixture was stirred at room temperature over night and diluted with EtOAc (50 mL). The organic was washed with water, brine and dried over Na_2SO_4. After concentration, the resulting residue was purified with column (silica gel, hexane/EtOAc = 60/40) gave the product **737** as oil (0.023 g). HPLC-MS t_R = 0.84 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{15}N_3O_3$ 309.11, observed LCMS m/z 310.1 (M+H).

Part B:

Compound **738** was prepared using the hydrolysis conditions described in **Example 8.** HPLC-MS t_R = 0.69 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{13}N_3O_3$ 295.01, observed LCMS m/z 296.0 (M+H).

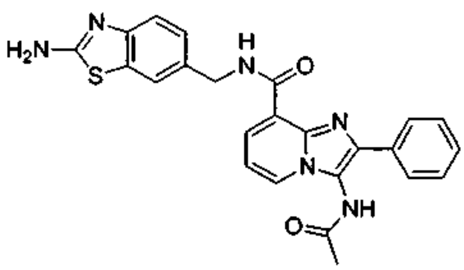
Part C:

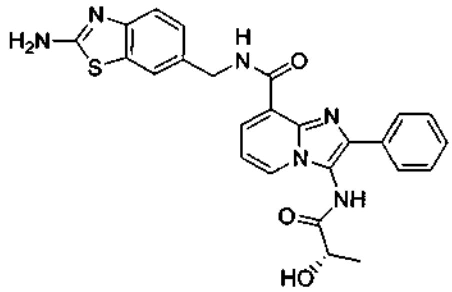
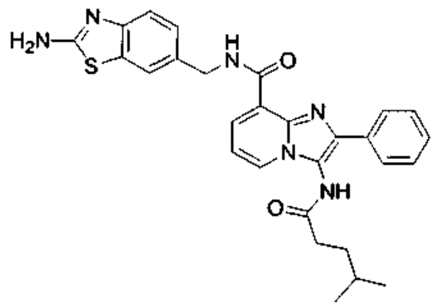
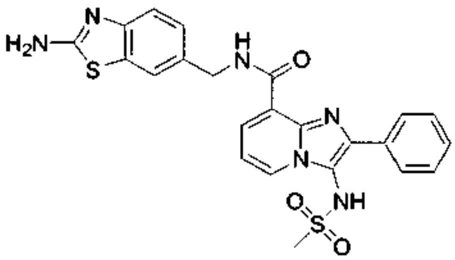
Compound **739** was prepared using the peptide coupling conditions described in **Example 8.** HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{28}N_6O_4S$ 556.19, observed LCMS m/z 557.0 (M+H).

Part D:

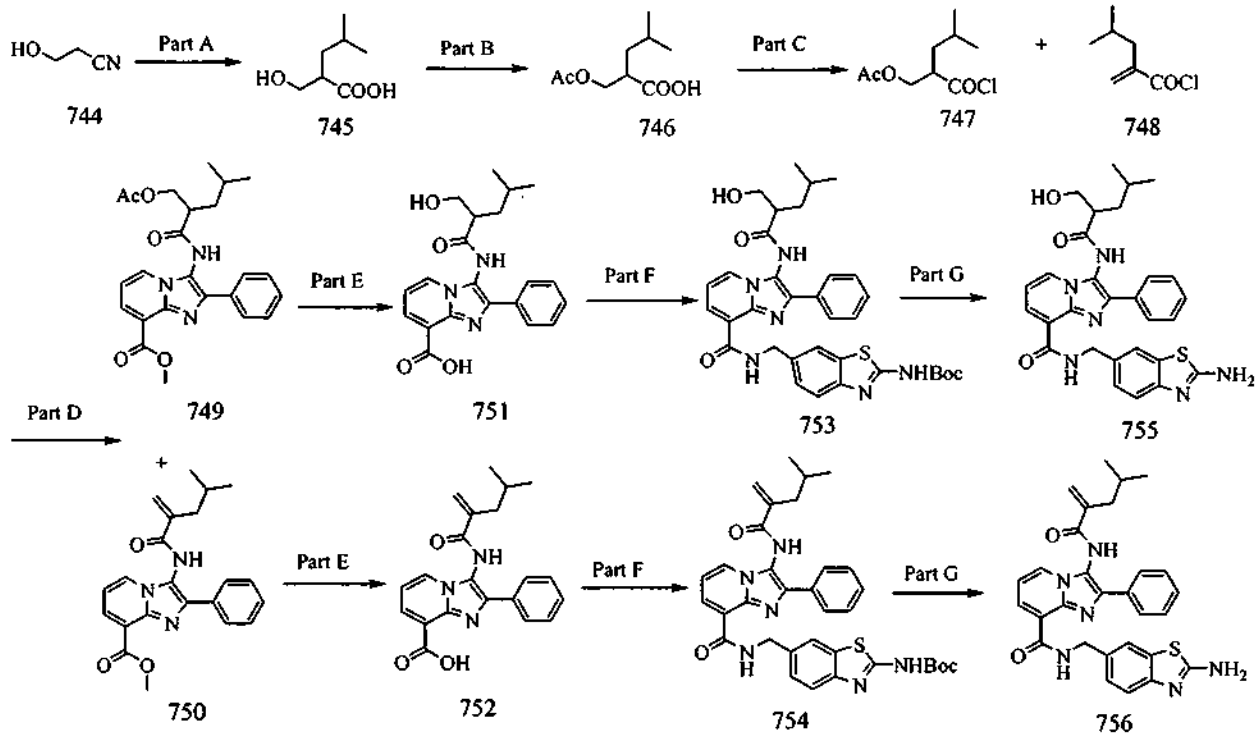
Compound **740** was prepared using the same deprotecting conditions described in **Example 8**. HPLC-MS t_R = 1.12 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{20}N_6O_2S$ 456.1, observed LCMS m/z 457.0.1 (M+H).

The compounds in Table 29 were prepared using the same procedure in **Example 33**.

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
740		456.13	457.0	2.74

741		486.1	487.0	1.13
742		512.2	513.1	1.58
743		492.1	493	1.18

Example 34



Part A:

Compound **745** was synthesized from Compound **744** according to the procedures of Jung Dae Park et. al. (*J. Med. Chem.* 2002, *45*, 911 and the references therein.).

Part B:

To the mixture of compound **745** (0.146 g, 1.0 mmol) and DIEA (0.8 mL, 4.5 mmol) in DCM (10 mL), acetyl chloride (0.235 g, 3.0 mmol) was added. The resulting mixture was stirred at room temperature overnight and diluted with EtOAc (50 mL). The organic was washed with H_2O, $NaHCO_3$ (10% aq. 10 mL x 3). The combined aqueous was treated with HCl (1N) to adjust pH to ~5 and extracted with EtOAc. The organics was washed with brine and dried over Na_2SO_4. After concentration, the crude product **746** was used in the next step directly without further purification.

Part C:

To the solution of compound **746** (0.125 g, 0.66 mmol) in dry DCM (3 mL), Oxalyl chloride (0.3 mL) was added dropwise at room temperature. The resulting mixture was stirred for 3 hours, and then the excess amount of oxalyl chloride and

DCM was removed under vacuum. The mixture of **747**, and **748** were used in the next step directly without purification.

Part D:

Compound **749**, and **750** were prepared using the same peptide coupling conditions described in **Example 33**, part A and separated by column. **749**: HPLC-MS t_R = 1.43 min ($UV_{254\ nm}$); mass calculated for formula C24H27N3O5 437.2, observed LCMS m/z 438.1 (M+H). **750**: HPLC-MS t_R = 1.46 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{23}N_3O_3$ 377.2, observed LCMS m/z 378.1 (M+H).

Part E:

Compound **751** was prepared using the hydrolysis conditions described in **Example 8**. HPLC-MS t_R = 1.20 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{23}N_3O_4$ 381.2, observed LCMS m/z 382.1 (M+H).

Compound **752** was prepared using the hydrolysis conditions described in **Example 8**. HPLC-MS t_R = 1.46 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{21}N_3O_3$ 363.2, observed LCMS m/z 364.2 (M+H).

Part F:

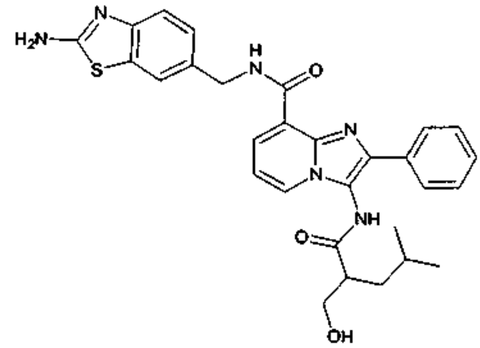
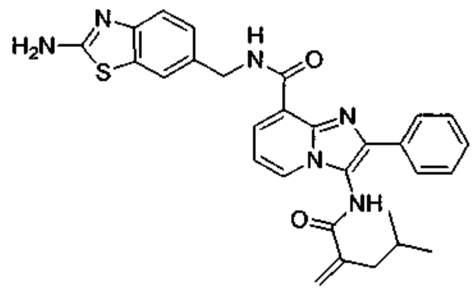
Compound **753** was prepared using the peptide coupling conditions described in Example 1. HPLC-MS t_R = 2.03 min ($UV_{254\ nm}$); mass calculated for formula $C_{34}H_{38}N_6O_5S$ 642.3, observed LCMS m/z 643.2 (M+H).

Compound **754** was prepared using the peptide coupling conditions described in **Example 8**. HPLC-MS t_R = 2.25 min ($UV_{254\ nm}$); mass calculated for formula $C_{34}H_{36}N_6O_4S$ 624.3, observed LCMS m/z 625.2 (M+H).

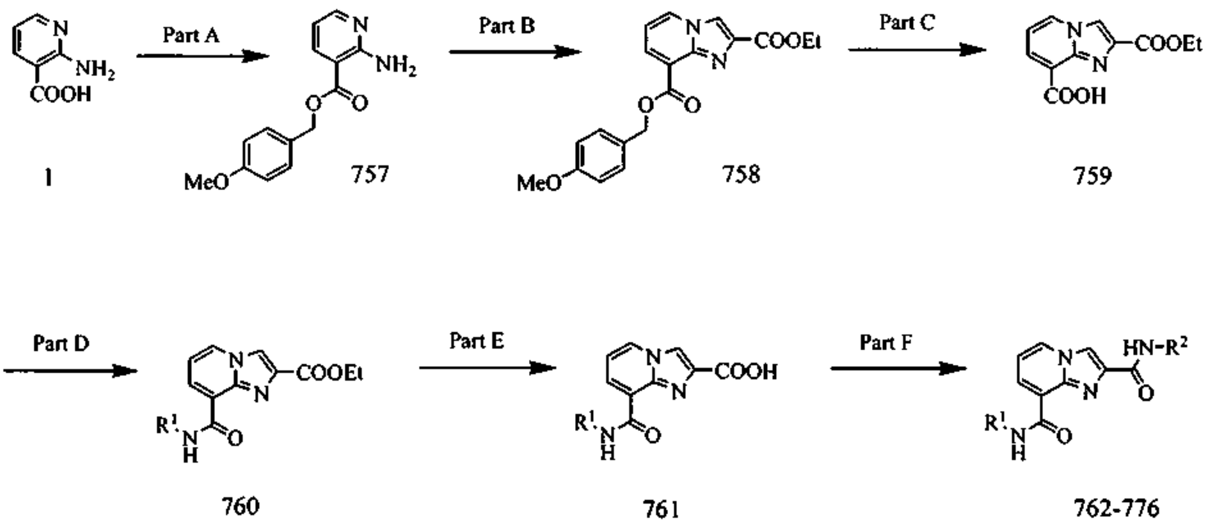
Part G:

Compound **755** was prepared using the same deprotecting conditions described in **Example 8**. HPLC-MS t_R = 1.40 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{30}N_6O_3S$ 542.2, observed LCMS m/z 543.1 (M+H).

Compound **756** was prepared using the same deprotecting conditions described in **Example 8**. HPLC-MS t_R = 1.66 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{28}N_6O_2S$ 524.2, observed LCMS m/z 525.1 (M+H).

Compd #	Structure	EMW	MS m/z (M^++H)	Ret. Time (min)
755		542.2	543.1	1.40
756		524.20	525.1	1.66

Example 35



(wherein R^1 and R^2 are identified in Table 30)

Part A:

To a solution of 2-aminonicotinic acid **1** (15.0 g, 109 mmol) in DCM (250 mL) was added thionyl chloride (22 g, 163 mmol). The resulting mixture was heated at reflux for 16 hours. The solution was cooled to room temperature then concentrated by reduced pressure. The resulting solid was re-dissolved in chloroform (150 mL), and then a pre-mixed solution of 4-methoxybenzyl alcohol (22.5 g, 163 mmol) and diisopropylethylamine (9.46 mL, 54.3 mmol) in chloroform (50 mL) was added to the acid chloride solution. The mixture was heated at reflux for 16 hours. The volatiles were removed *in vacuo*, ethyl acetate was added and the organic solution washed with saturated $NaHCO_3$ (x1), brine (x1), dried over magnesium sulfate and concentrated. The isolated crude product was purified by flash column chromatography (SiO_2, dichloromethane / ethyl acetate – 9:1) to afford compound **757** as a slightly yellow solid.

Part B:

To a solution of compound **757** (2.7 g, 11 mmol) in DMF (5 mL) was added ethyl-bromopyruvate (4.1 g, 21 mmol) and cesium carbonate (6.8 g. 21 mmol). The reaction mixture was heated at 80^0 C for 16 hours. The precipitates were removed by filtration, and the filtrate concentrated and then purified by flash column chromatography (SiO_2, ethyl acetate / hexanes – 7:3) to afford compound **758** as a white solid.

Part C:

To compound **758** (1.0 g) was added a mixture of trifluoroacetic acid (4.5 mL) and water (0.5 mL) and the reaction mixture was stirred at room temperature for 30 minutes. The solution was quenched with a mixture of acetonitrile (5 mL) and water (5 mL), and then concentrated to dryness to afford compound **759** as a white solid.

Part D:

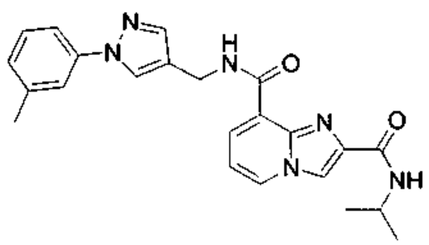
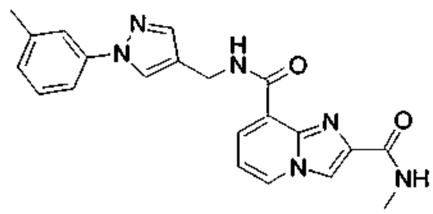
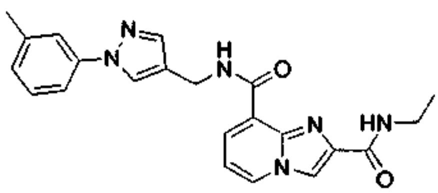
Compounds **760** were prepared using the coupling procedures described in **Example 1B**, Part G.

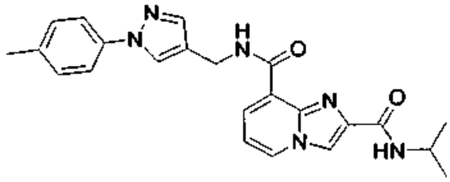
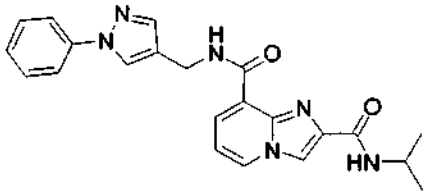
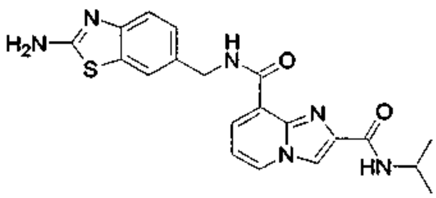
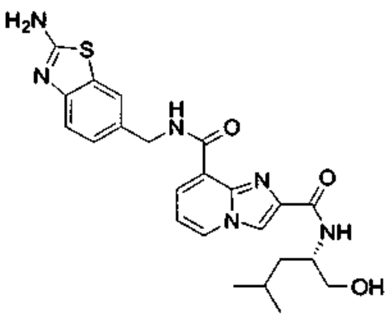
Part E:

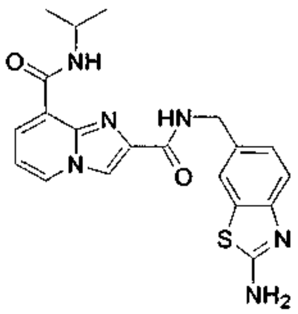
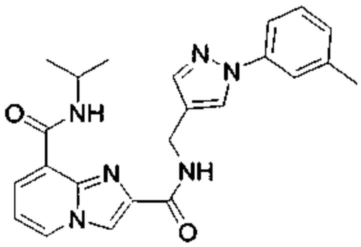
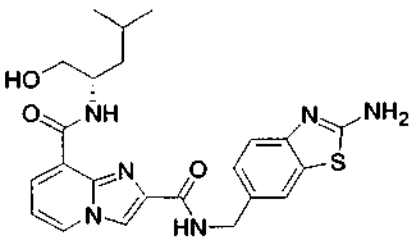
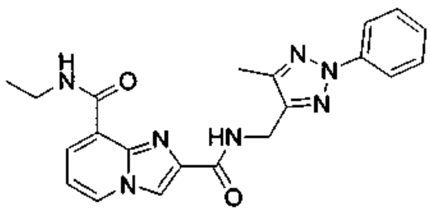
Compounds **761** were prepared using the saponification procedures described in **Example 1B,** Part D.

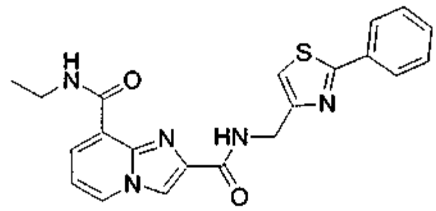
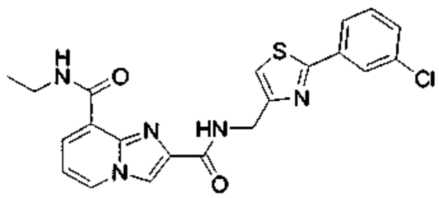
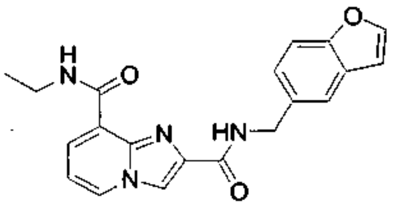
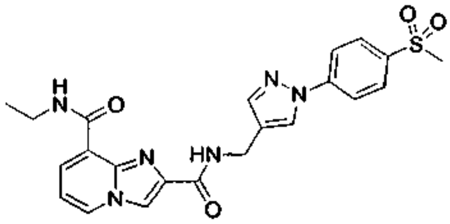
Part F:

Compounds **762-776** (Table 30) were prepared using the coupling procedures described in **Example 1B**, Part E.

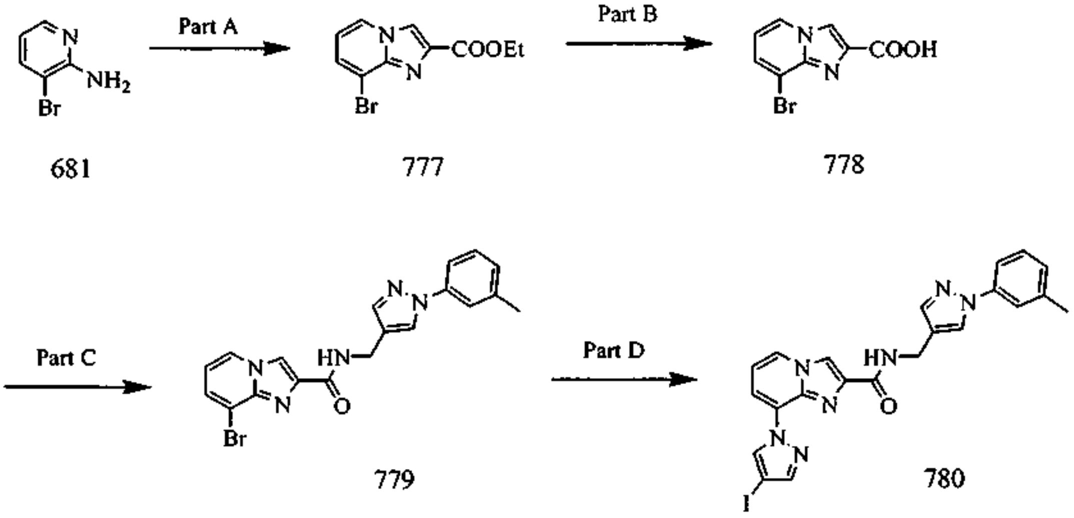
Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
762		416.2	417.2	4.57
763		388.2	389.2	4.02
764		402.2	403.2	4.33

765		416.2	417.2	4.65
766		402.2	403.2	4.29
767		408.1	409.1	2.58
768		466.2	467.2	2.82

769		408.1	409.1	2.64
770		416.2	417.1	4.09
771		466.2	467.0	2.81
772		402.2	403.2	4.18

773		403.2	404.2	4.39
774		405.1	406.1	4.43
775		439.1	440.1	4.93
776		362.1	363.1	4.05

Example 36



Part A:

Compound **777** was prepared from the coupling of 2-amino-3-brmopyridine **681** and ethyl bromopyruvate using procedures described in **Example 7A**, Part A. HPLC-MS t_R = 1.25 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_9BrN_2O_2$ 268.0, observed LCMS m/z 269.0 (M+H).

Part B:

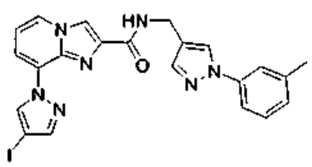
Compound **778** was prepared from compound **777** using the saponification procedures described in **Example 1B**, Part D. HPLC-MS t_R = 0.51 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_5BrN_2O_2$ 240.0, observed LCMS m/z 241.0 (M+H).

Part C:

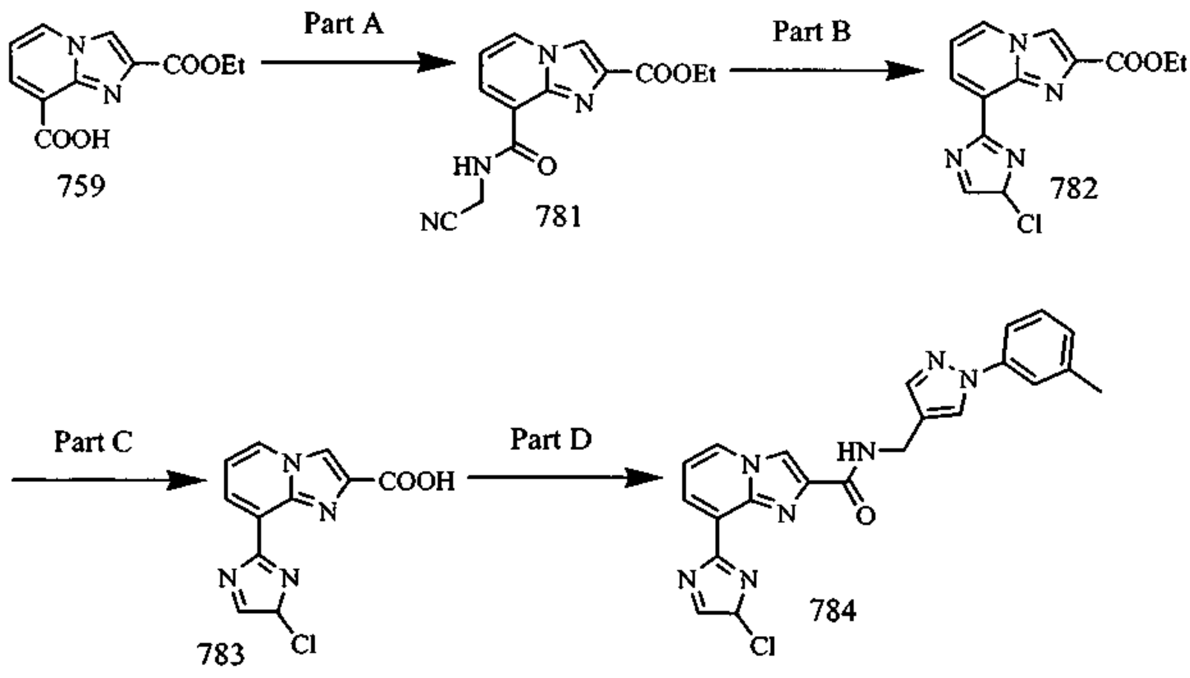
Compound **779** was prepared from compound **778** using the coupling procedures described in **Example 1B**, Part G. HPLC-MS t_R = 1.74min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{16}BrN_5O$ 409.1, observed LCMS m/z 410.0 (M+H).

Part D:

4-Iodopyrazole (0.120 g, 0.61 mmol) was added to a solution of NMP (2 mL) containing sodium hydride (60 %, 25 mg, 0.61 mmol) and then stirred at room temperature for 30 minutes. A solution of compound **779** (0.025 g, 0.061 mmol) in NMP (2 mL) was added and the reaction mixture heated at 110^0 C for 120 hours. The reaction was monitored by LC-MS. Once the reaction was complete, the volatiles were removed *in vacuo*, and the isolated crude purified by Prep.LC to give **780**.

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
780		523.1	524.1	5.53

Example 37



Compound **759** was prepared using procedures described in **Example 35.**

Part A:

Compound **781** was prepared from the coupling of compound **759** and aminoacetonitrile using procedures described in **Example 1B**, Part G. HPLC-MS t_R = 1.08 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{12}N_4O_3$ 272.1, observed LCMS m/z 273.0 (M+H).

Part B:

A mixture of compound **781** (0.022 g, 0.08 mmol), triphenylphosphine (0.053 g, 0.2 mmol), and carbon tetrachloride (0.020 mL, 0.2 mmol) in acetonitrile (5 mL) was heated at 45^0 C for 16 hours. The reaction mixture was cooled to room temperature, concentrated, and dried to afford compound **782** which was taken forward directly to the next step. HPLC-MS t_R = 1.53 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{11}ClN_4O_2$ 290.1, observed LCMS m/z 291.1 (M+H).

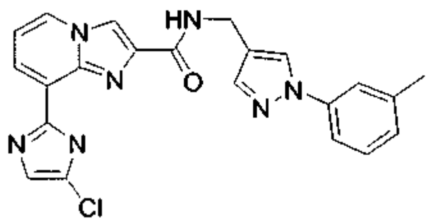
Part C:

Compound **783** was prepared from compound **781** using procedures described in **Example 1B**, Part D. HPLC-MS t_R = 1.00 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_7ClN_4O_2$ 262.0, observed LCMS m/z 263.0 (M+H).

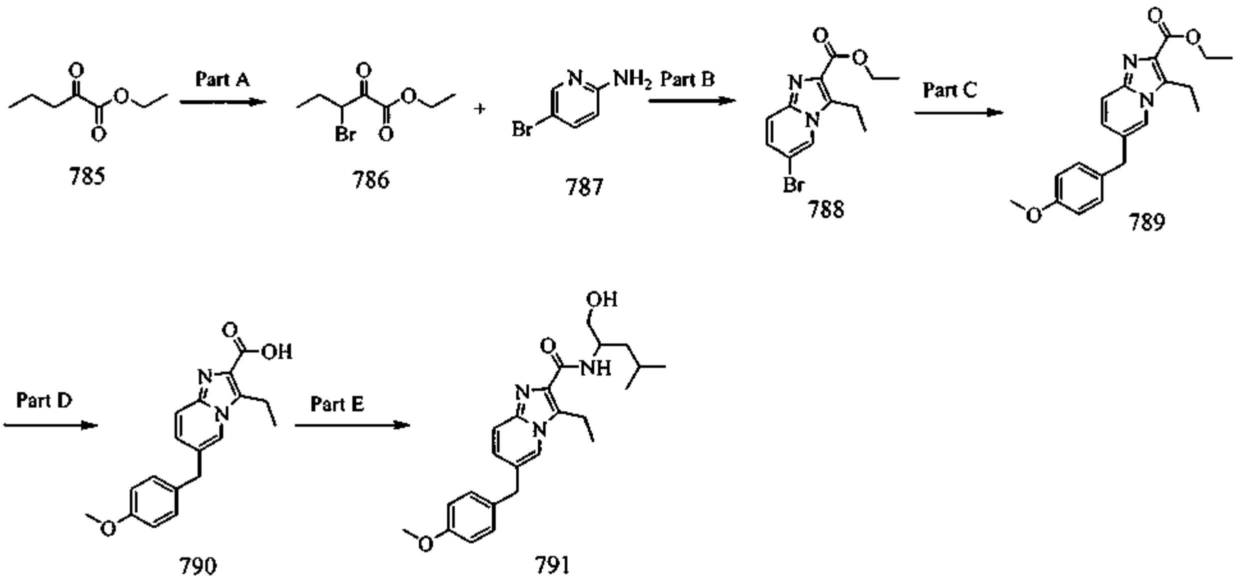
Part D:

Compound **784** was prepared from compound **783** using the coupling procedures described in **Example 1B**, Part G.

The following ligand was synthesized using this procedure:

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
784		431.1	432.1	5.53

Example 38



Part A:

Compound **786** was prepared using the bromonation conditions described in **Example 8** Part B.

Part B:

Compound **787** was prepared using the cyclization conditions described in **Example 8** Part C. HPLC-MS t_R = 1.54 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{13}BrN_2O_2$ 296.0, observed LCMS m/z 297.0 (M+H).

Part C:

Under Ar, the bromine compound **788** (0.060 g, 0.2 mmol) in dioxane (2.0 ml) was added to the flask which was charged with Pd(dppf)Cl_2 (0.018 g, 0.02 mmol) followed by the addition of 4-methoxybenzylzinc chloride (0.089 g, 0.4 mmol). The mixture was thoroughly degassed by alternately connected the flask to vacuum and Argon. The resulting solution was heated upto 80^0 C and stirred overnight and diluted by EtOAc after cooled to room temperature. The solid was removed by filter through Celite and washed with some EtOAc. Concentration to remove the solvent and the resulting residue was purified with column (silica gel, Hexane/EtOAc = 40/60) gave the product **789** as oil. HPLC-MS t_R = 1.48 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{22}N_2O_3$ 338.2, observed LCMS m/z 339.1 (M+H).

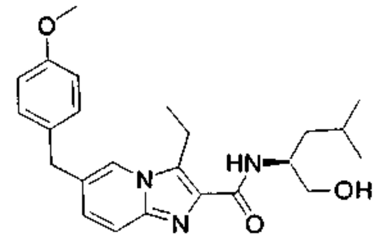
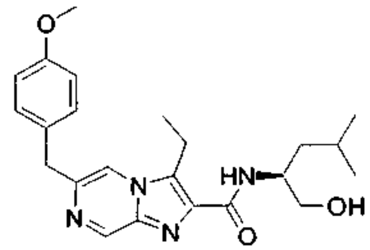
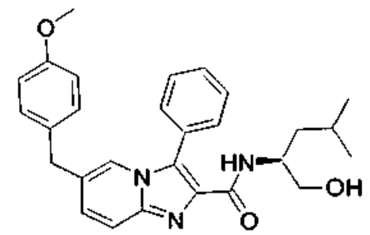
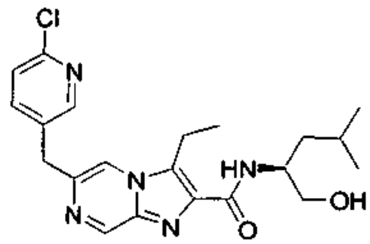
Part D:

Compound **790** was prepared using the hydrolysis conditions described in **Example 8** Part G. HPLC-MS t_R = 1.18 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{18}N_2O_3$ 310.1, observed LCMS m/z 311.0 (M+H).

Part E:

Compound **791** was prepared using the peptide coupling conditions described in **Example 1B**. HPLC-MS t_R = 1.84 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{31}N_3O_3$ 409.2, observed LCMS m/z 410.2 (M+H).

The compounds in Table 31 were synthesized using the same procedure:

Compd #	Structure	EMW	MS m/z (M^{+}+H)	Ret. Time (min)
791		409.24	410.2	
792		410.2	411.1	1.83
793		457.2	458.2	1.96
794		415.2	416.0	1.71

Biological assays:

DELFIA (Dissociation Enhanced Lanthanide Fluorescence Immuno-assay)

Before initiation of kinase reactions, compounds were pre-incubated with the enzyme for 10 minutes. Pre-incubation reactions contained 50 mM HEPES pH 7.3, 10 mM $MgCl_2$, 1 mM DTT, 75 mM NaCl, 1 mM EDTA, 1 mM EGTA, 0.01% CHAPS, 2 nM JNK1, 6 ug/mL biotinylated GST-ATF2, 0.1 mg/ml BSA, 5% DMSO and 0-100 μM compound in a total volume of 40 μL. After a 10 minute room temperature pre-incubation, 10 μL of 35 μM ATP was added to start the reaction (final concentration of ATP = 7 uM). Reactions were incubated at room temperature for 30 minutes. A small aliquot (10 uL) was taken and quenched by adding into 190 uL of DELFIA Assay buffer containing 100 mM EDTA. The amount of phosphate transferred to biotinylated GST-ATF2 was measured using the Dissociation Enhanced Lanthanide Fluorescence Immuno-assay (DELFIA) from Perkin Elmer according to manufacturers protocol. Briefly, biotinylated GST-ATF2 was captured on streptavidin coated plates for 1 hour, washed twice, then incubated for 1 hour with a 1:1000 dilution of rabbit-anti-phospho-ATF2 antibody and a 1:3500 dilution of Europium-labeled anti-rabbit secondary antibody. Free antibody was removed with six washes, Europium was dissociated from the antibody, and Europium fluorescence was measured using an excitation wavelength of 340 nM and an emission wavelength of 615 nM. JNK2 and JNK3 kinase reactions were carried out similarly, with the exception that the final concentration of ATP was 4 uM and 2 uM, respectively.

Cell Assay

Jurkat IL2 assay

One hundred microliters of cultured Jurkat cells (1,000,000/milliliter) in the following medium: RPMI 1640, 10% fetal bovine serum supplemented with glutamine, penicillin and streptomycin was added to a 96 well plate containing adherent anti-CD3 antibody (T-Cell Activation Plate, BD Biosciences # 354725). An additional plate without attached antibody was also cultured with and without soluble anti-CD28 antibody and cells as additional anti-CD3 controls. Fifty microliters of medium containing serially diluted compound (0.4% DMSO) was added to compound wells, and 50 microliters of medium + 0.4% DMSO was added to control wells in place of compound. Fifty microliters of medium containing anti-CD28 antibody, 1.6 micromolar, was next added to all wells except anti-CD28 controls. The cells, in a final volume of 200 microliters, were incubated in a cell culture cabinet (4% carbon dioxide) for 2 days at 37C. After incubation 100 microliters of supernatant (cells are adherent) was removed from wells and IL2 production was quantified by ELISA, (Pierce Endogen Kit # EH2IL25). IL2 production was quantified on a Spectra Max Plus (Molecular Devices, Inc.) plate reader. Cell viability was determined by addition of 100 microliters of Promega CellTiter-Glo kit # G7571, followed by quantitation of fluorescence with a Victor^2 V 1420 fluorescence reader. IL2 inhibition and cell viability data were analyzed with GraphPad Prism software, (GraphPad Software, Inc.).

Compound Numbers: 13-16, 21-24, 27, 30, 33-40, 42-48, 51-74, 80, 84-94, 99, 101, 111, 112-131, 139-158, 162-172, 175, 177-181, 184, 186, 190, 191, 193-195, 200-235, 237-246, 271-307, 321-324, 326, 327, 354, 404-410, 444-453, 456, 457, 460-466, 468, 469, 471-489, 494-506, 542-545, 573, 574, 576, 578, 584, 588, 590, 593, 598-600, 605-611, 613-615, 619, 620, 622-629, 635, 647, 650-652, 664, 665, 672, 673-680, 686, 691, 692, 699, 703, 720-727, 734, 736, 740-743, 755, 756, 762-776, 780, 784, and 791-794 had a JNK1 IC_{50} within the range of 6 to 100,000 nM.

Compound Numbers: 14, 16, 17, 22, 46, 47, 48, 56, 69, 93, 94, 111-115, 117, 118, 130, 131, 139, 140, 150, 154, -158, 204-206, 209, 213, 215-220, 224, 238, 242, 274, 277, 279, 280, 283, 285, 291, 292, 296, 298, 299, 300, 301, 305, 306, 307, 323, 324, 326, 327, 405, 445, 451, 452, 453, 456, 457, 460-466, 471, 472, 477, 478, 479, 480, 481, 483, 484, 485, 489, 490, 491, 502, 542, 543, 544, 545, 593, 598, 599, 605, 623-629, 647, 650, 651, 652, and 664 had a JNK1 IC_{50} within the range of 6 to 100 nM.

Compound Numbers: 14, 16, 112, 114, 139, 156, 216, 218, 219, 277, 296, 300, 306, 307, 463, 478, 479, 483, 485, 491, 502, 598, 629, 647, 650, 651, and 652 had a JNK1 IC_{50} within the range of 6 to 20 nM.

Compound Numbers: 14, 16, 112, 114, 139, 156, 216, 218, 219, 277, 296, 300, 306, 307, 463, 478, 479, 483, 485, 491, 502, 598, 629, 647, 650, 651, and 652 had a JNK1 IC_{50} within the range of 6 to 20 nM.

Compound Numbers: 112, 478, 479, 502, 629, 651, and 652 had a JNK1 IC_{50} within the range of 6 to 10 nM.

Compound Numbers: 14, 16, 17, 112, 114, 115, 130, 155, 216, 218, 219, 296, 299, 300, 301, 306, 307, 323, 327, 451, 456, 463, 478, 479, 483, 542, 544, 599 and 605 had a JNK2 IC_{50} within the range of 4.0 to 46.0 nM.

Compound Numbers: 22, 42, 93, 111, 113, 205, 206, 215, and 452 had a JNK2 IC_{50} within the range of 52.0 to 94.0 nM.

Compound Numbers: 15, 23, 48, 56, 62 and 291 had a JNK2 IC_{50} within the range of 107.0 to 173.0 nM.

Compound Numbers: 13, 38, 178, 181, and 230 had a JNK2 IC_{50} within the range of 201.0 to 666.0 nM.

Compound Numbers: 170, 350, and 351 had a JNK2 IC_{50} within the range of 1070 to 11,500 nM.

Compound Numbers: 14, 16, 17, 22, 112, 114, 115, 130, 155, 215, 216, 218, 219, 296, 299, 300, 301, 306, 307, 323, 451, 456, 463, 478, 479, 483, 542, 544, 599, and 605 had a JNK3 IC_{50} within the range of 9.0 to 50.0 nM.

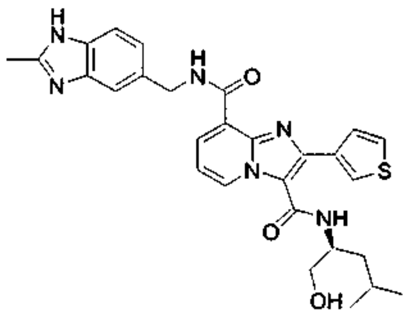
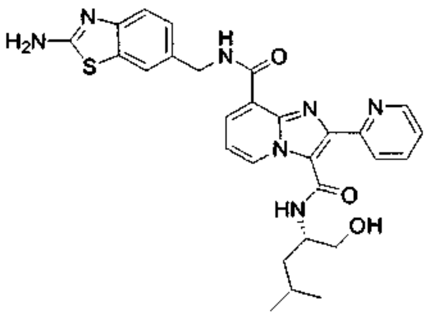
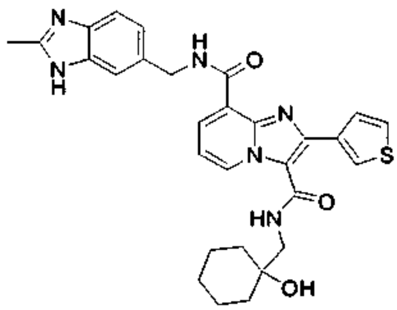
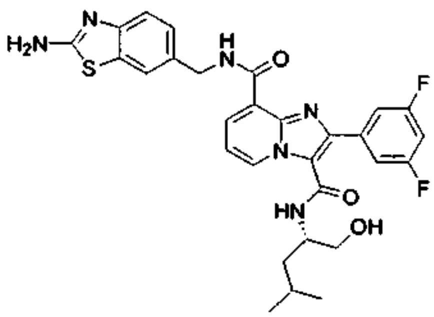
Compound Numbers: 13, 38, 62, 93, 111, 113, 205, 206, 291, 327, and 452 had a JNK3 IC_{50} within the range of 54.0 to 98.0 nM.

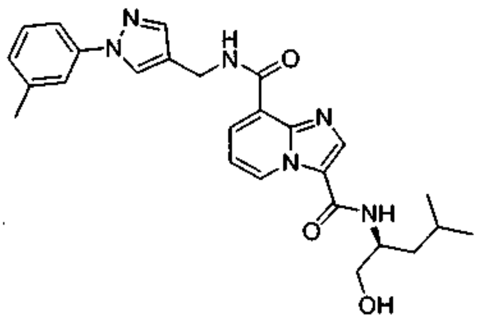
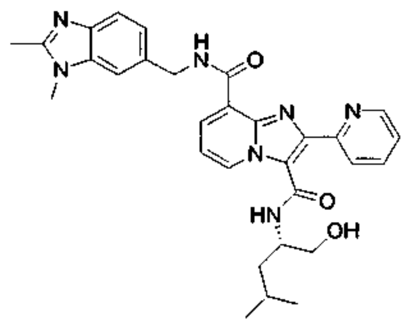
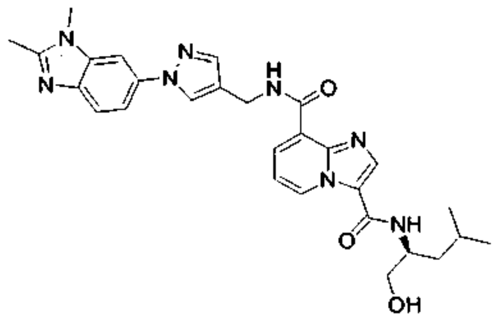
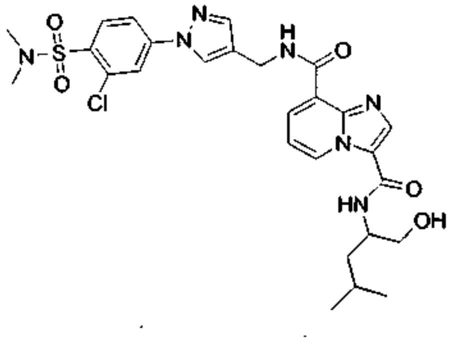
Compound Numbers: 15, 23, 42, 56, 170, and 181 had a JNK3 IC_{50} within the range of 118.0 to 174.0 nM.

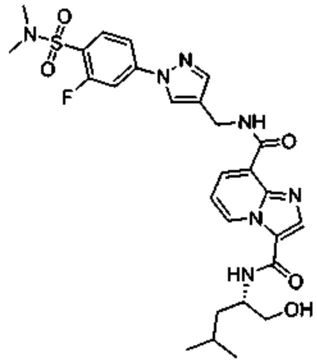
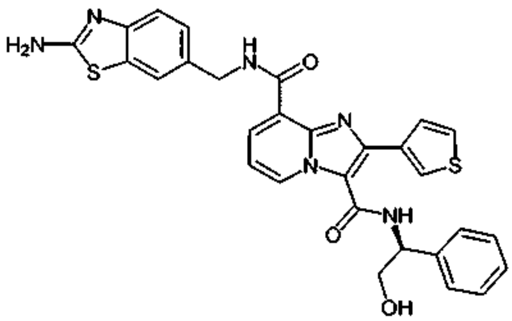
Compound Numbers: 48, 178, and 230 had a JNK3 IC_{50} within the range of 209.0 to 479.0 nM.

Compound Number 350 had a JNK3 IC_{50} of 16,100 nM, and compound Number 3561 had a JNK3 IC_{50} of 10,000 nM.

JNK1 Data (in nM) for Compound Numbers 16, 112, 118, 478, 483, 544, 605, 647, 651, and 652 are given in the table below.

Compd #	Compound	JNK 1 IC_{50} nM
112		8
478		10
118		23
544		23

605		21
483		11
647		16
651		10

652		11
16		19

The compounds of this invention inhibit the activity of ERK1 and ERK2 Thus, this invention further provides a method of inhibiting ERK in mammals, especially humans, by the administration of an effective amount (e.g., a therapeutically effective amount) of one or more (e.g., one) compounds of this invention. The administration of the compounds of this invention to patients, to inhibit ERK1 and/or ERK2, is useful in the treatment of cancer.

In any of the methods of treating cancer described herein, unless stated otherwise, the methods can optionally include the administration of an effective amount of one or more (e.g., 1, 2 or 3, or 1 or 2, or 1) chemotherapeutic agents. The chemotherapeutic agents can be administered currently or sequentially with the compounds of this invention.

The methods of treating cancer described herein include methods wherein a combination of drugs (i.e., compounds, or pharmaceutically active ingredients, or pharmaceutical compositions) are used (i.e., the methods of treating cancer of this invention include combination therapies). Those skilled in the art will appreciate that the drugs are generally administered individually as a pharmaceutical composition. The use of a pharmaceutical composition comprising more than one drug is within the scope of this invention.

In any of the methods of treating cancer described herein, unless stated otherwise, the methods can optionally include the administration of an effective amount of radiation therapy. For radiation therapy, γ-radiation is preferred.

Examples of cancers which may be treated by the methods of this invention include, but are not limited to: (A) lung cancer (e.g., lung adenocarcinoma and non small cell lung cancer), (B) pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), (C) colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), (D) myeloid leukemias (for example, acute myelogenous leukemia (AML), CML, and CMML), (E) thyroid cancer, (F) myelodysplastic syndrome (MDS), (G) bladder carcinoma, (H) epidermal carcinoma, (I) melanoma, (J) breast cancer, (K) prostate cancer, (L) head and neck cancers (e.g., squamous cell cancer of the head and neck), (M) ovarian cancer, (N) brain cancers (e.g., gliomas, such as glioma blastoma multiforme), (O) cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas), (P) sarcomas, (Q) tetracarcinomas, (R) nuroblastomas, (S) kidney carcinomas, (T) hepatomas, (U) non-Hodgkin's lymphoma, (V) multiple myeloma, and (W) anaplastic thyroid carcinoma.

Chemotherapeutic agents (antineoplastic agent) include but are not limited to: microtubule affecting agents, alkylating agents, antimetabolites, natural products and their derivatives, hormones and steroids (including synthetic analogs), and synthetics.

Examples of alkylating agents (including nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes) include: Uracil mustard, Chlormethine, Cyclophosphamide (Cytoxan®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-melamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

Examples of antimetabolites (including folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors) include: Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, and Gemcitabine.

Examples of natural products and their derivatives (including vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins) include: Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Paclitaxel (paclitaxel is a microtubule affecting agent and is commercially available as Taxol®), Paclitaxel derivatives (e.g. taxotere), Mithramycin, Deoxyco-formycin, Mitomycin-C, L-Asparaginase, Interferons (especially IFN-a), Etoposide, and Teniposide.

Examples of hormones and steroids (including synthetic analogs) include: 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Tamoxifen, Methylprednisolone, Methyl-testosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, and Zoladex.

Examples of synthetics (including inorganic complexes such as platinum coordination complexes): Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, and Hexamethylmelamine.

Examples of other chemotherapeutics include: Navelbene, CPT-11, Anastrazole, Letrazole, Capecitabinbe, Reloxafine, and Droloxafine.

A microtubule affecting agent (e.g., paclitaxel, a paclitaxel derivative or a paclitaxel-like compound), as used herein, is a compound that interferes with cellular mitosis, i.e., having an anti-mitotic effect, by affecting microtubule formation and/or action. Such agents can be, for instance, microtubule stabilizing agents or agents which disrupt microtubule formation.

Microtubule affecting agents, useful in the methods of this invention, are well known to those skilled in the art and include, but are not limited to: Allocolchicine (NSC 406042), Halichondrin B (NSC 609395), Colchicine (NSC 757), Colchicine derivatives (e.g., NSC 33410), Dolastatin 10 (NSC 376128), Maytansine (NSC 153858), Rhizoxin (NSC 332598), Paclitaxel (Taxol®, NSC 125973), Paclitaxel derivatives (e.g., Taxotere, NSC 608832), Thiocolchicine (NSC 361792), Trityl Cysteine (NSC 83265), Vinblastine Sulfate (NSC 49842), Vincristine Sulfate (NSC 67574), Epothilone A, Epothilone, Discodermolide (see Service, (1996) Science, 274:2009), Estramustine, Nocodazole, MAP4, and the like. Examples of such agents are described in, for example, Bulinski (1997) J. Cell Sci. 110:3055-3064, Panda (1997) Proc. Natl. Acad. Sci. USA 94:10560-10564, Muhlradt (1997) Cancer Res. 57:3344-3346, Nicolaou (1997) Nature 387:268-272, Vasquez (1997) Mol. Biol. Cell. 8:973-985, and Panda (1996) J. Biol. Chem. 271:29807-29812.

Chemotherapeutic agents with paclitaxel-like activity include, but are not limited to, paclitaxel and paclitaxel derivatives (paclitaxel-like compounds) and analogues.

Paclitaxel and its derivatives (e.g. Taxol and Taxotere) are available commercially. In addition, methods of making paclitaxel and paclitaxel derivatives and analogues are well known to those of skill in the art (see, e.g., U.S. Patent Nos: 5,569,729; 5,565,478; 5,530,020; 5,527,924; 5,508,447; 5,489,589; 5,488,116; 5,484,809; 5,478,854; 5,478,736; 5,475,120; 5,468,769; 5,461,169; 5,440,057; 5,422,364; 5,411,984; 5,405,972; and 5,296,506).

More specifically, the term "paclitaxel" as used herein refers to the drug commercially available as Taxol® (NSC number: 125973). Taxol® inhibits eukaryotic cell replication by enhancing polymerization of tubulin moieties into stabilized microtubule bundles that are unable to reorganize into the proper structures for mitosis. Of the many available chemotherapeutic drugs, paclitaxel has generated interest because of its efficacy in clinical trials against drug-refractory tumors, including ovarian and mammary gland tumors (Hawkins (1992) Oncology, 6: 17-23, Horwitz (1992) Trends Pharmacol. Sci. 13: 134-146, Rowinsky (1990) J. Natl. Canc. Inst. 82: 1247-1259).

Additional microtubule affecting agents can be assessed using one of many such assays known in the art, e.g., a semiautomated assay which measures the tubulin-polymerizing activity of paclitaxel analogs in combination with a cellular assay to measure the potential of these compounds to block cells in mitosis (see Lopes (1997) Cancer Chemother. Pharmacol. 41:37-47).

Generally, activity of a test compound is determined by contacting a cell with that compound and determining whether or not the cell cycle is disrupted, in particular, through the inhibition of a mitotic event. Such inhibition may be mediated by disruption of the mitotic apparatus, e.g., disruption of normal spindle formation. Cells in which mitosis is interrupted may be characterized by altered morphology (e.g., microtubule compaction, increased chromosome number, etc.).

Compounds with possible tubulin polymerization activity can be screened in vitro. For example, the compounds are screened against cultured WR21 cells (derived from line 69-2 wap-ras mice) for inhibition of proliferation and/or for altered cellular morphology, in particular for microtubule compaction. In vivo screening of positive-testing compounds can then be performed using nude mice bearing the WR21 tumor cells. Detailed protocols for this screening method are described by Porter (1995) Lab. Anim. Sci., 45(2):145-150.

Other methods of screening compounds for desired activity are well known to those of skill in the art. Typically such assays involve assays for inhibition of microtubule assembly and/or disassembly. Assays for microtubule assembly are described, for example, by Gaskin et al. (1974) J. Molec. Biol., 89: 737-758. U.S. Patent No. 5,569,720 also provides in vitro and in vivo assays for compounds with paclitaxel-like activity.

Thus, in the methods of this invention wherein at least one chemotherapeutic agent is used, examples of said chemotherapeutic agents include those selected from the group consisting of: microtubule affecting agents, alkylating agents, antimetabolites, natural products and their derivatives, hormones and steroids (including synthetic analogs), and synthetics.

In the methods of this invention wherein at least one chemotherapeutic agent is used, examples of said chemotherapeutic agents also include: (1) taxanes, (2) platinum coordinator compounds, (3) epidermal growth factor (EGF) inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) vascular endolithial growth factor (VEGF) inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, (13) folate antagonists, (14) ribonucleotide reductase inhibitors, (15) anthracyclines, (16) biologics; (17) inhibitors of angiogenesis and/or suppressors of tumor necrosis factor alpha (TNF-alpha) such as thalidomide (or related imid), (18) Bcr/abl kinase inhibitors, (19) MEK1 and/or MEK 2 inhibitors that are small molecules, (20) IGF-1 and IGF-2 inhibitors that are small molecules, (21) small molecule inhibitors of RAF and BRAF kinases, (22) small molecule inhibitors of cell cycle dependent kinases such as CDK1, CDK2, CDK4 and CDK6, (23) alkylating agents, and (24) farnesyl protein transferase inhibitors (also know as FPT inhibitors or FTI (i.e., farnesyl transfer inhibitors)).

In the methods of this invention wherein at least one chemotherapeutic agent is used, examples of such chemotherapeutic agents include:

(1) taxanes such as paclitaxel (TAXOL®) and/or docetaxel (Taxotere®);

(2) platinum coordinator compounds, such as, for example, carboplatin, cisplatin and oxaliplatin (e.g. Eloxatin);

(3) EGF inhibitors that are antibodies, such as: HER2 antibodies (such as, for example trastuzumab (Herceptin®), Genentech, Inc.), Cetuximab (Erbitux, IMC-C225, ImClone Systems), EMD 72000 (Merck KGaA), anti-EFGR monoclonal antibody ABX (Abgenix), TheraCIM-h-R3 (Center of Molecular Immunology), monoclonal antibody 425 (Merck KGaA), monoclonal antibody ICR-62 (ICR, Sutton, England); Herzyme (Elan Pharmaceutical Technologies and Ribozyme Pharmaceuticals), PKI 166 (Novartis), EKB 569 (Wyeth-Ayerst), GW 572016 (GlaxoSmithKline), CI 1033 (Pfizer Global Research and Development), trastuzmab-maytansinoid conjugate (Genentech, Inc.), mitumomab (Imclone Systems and Merck KGaA) and Melvax II (Imclone Systems and Merck KgaA);

(4) EGF inhibitors that are small molecules, such as, Tarceva (TM) (OSI-774, OSI Pharmaceuticals, Inc.), and Iressa (ZD 1839, Astra Zeneca);

(5) VEGF inhibitors that are antibodies such as: bevacizumab (Genentech, Inc.), and IMC-1C11 (ImClone Systems), DC 101 (a KDR VEGF Receptor 2 from ImClone Systems);

(6) VEGF kinase inhibitors that are small molecules such as SU 5416 (from Sugen, Inc), SU 6688 (from Sugen, Inc.), Bay 43-9006 (a dual VEGF and bRAF inhibitor from Bayer Pharmaceuticals and Onyx Pharmaceuticals);

(7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), such as tamoxifen, idoxifene, raloxifene, trans-2,3-dihydroraloxifene, levormeloxifene, droloxifene, MDL 103,323, and acolbifene (Schering Corp.);

(8) anti-tumor nucleoside derivatives such as 5-fluorouracil, gemcitabine, capecitabine, cytarabine (Ara-C), fludarabine (F-Ara-A), decitabine, and chlorodeoxyadenosine (Cda, 2-Cda);

(9) epothilones such as BMS-247550 (Bristol-Myers Squibb), and EPO906 (Novartis Pharmaceuticals);

(10) topoisomerase inhibitors such as topotecan (Glaxo SmithKline), and Camptosar (Pharmacia);

(11) vinca alkaloids, such as, navelbine (Anvar and Fabre, France), vincristine and vinblastine;

(12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, such as, LM-609 (see, Clinical Cancer Research, Vol. 6, page 3056-3061, August 2000, the disclosure of which is incorporated herein by reference thereto);

(13) folate antagonists, such as Methotrexate (MTX), and Premetrexed (Alimta);

(14) ribonucleotide reductase inhibitors, such as Hydroxyurea (HU);

(15) anthracyclines, such as Daunorubicin, Doxorubicin (Adriamycin), and Idarubicin;

(16) biologics, such as interferon (e.g., Intron-A and Roferon), pegylated interferon (e.g., Peg-Intron and Pegasys), and Rituximab (Rituxan, antibody used for the treatment of non-Hodgkin's lymphoma);

(17) thalidomide (or related imid);

(18) Bcr/abl kinase inhibitors, such as, for example Gleevec (STI-571), AMN-17, ONO12380, SU11248 (Sunitinib) and BMS-354825

(19) MEK1 and/or MEK2 inhibitors, such as PD0325901 and Arry-142886 (AZD6244);

(20) IGF-1 and IGF-2 inhibitors that are small molecules, such as, for example, NVP-AEW541;

(21) small molecule inhibitors of RAF and BRAF kinases, such as, for example, BAY 43-9006 (Sorafenib);

(22) small molecule inhibitors of cell cycle dependent kinases such as CDK1, CDK2, CDK4 and CDK6, such as, for example, CYC202, BMS387032, and Flavopiridol;

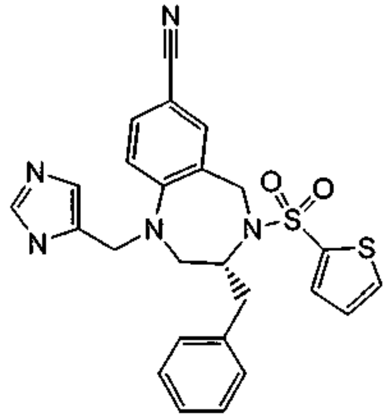
(23) alkylating agents, such as, for example, Temodar® brand of temozolomide;

(24) farnesyl protein transferase inhibitors, such as, for example:

(a) Sarasar® brand of lonifarnib (i.e., 4-[2-[4-(3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-*b*]byridin-11-yl)-1-piperidinyl)-2-oxoethyl]-1-piperidinecarboxamide, see for example, U.S. 5,874,442 issued February 23, 1999, and U.S. 6,632,455 issued October 14, 2003 the disclosures of each being incorporated herein by reference thereto),

(b) Zarnestra® brand of tipifarnib (i.e., (R)-6-amino[(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1- methyl-2(1H)-quinolinone, see for example, WO 97/16443 published May 9, 1997 and U.S. 5,968,952 issued October 19, 1999, the disclosures of each being incorporated herein by reference thereto), and

(c) Bristol-Myers Squibb 214662:



(see WO97/30992 published August 28, 1997, U.S. 6,011,029 issued January 4, 2000, and U.S. 6,455,523, the disclosures of each being incorporated herein by reference thereto).

The Bcr/abl kinase inhibitors, EGF receptor inhibitors, and HER-2 antibodies (EGF receptor inhibitors that are antibodies) described above are also known as signal transduction inhibitors. Therefore, chemotherapeutic agents, as used herein, include signal transduction inhibitors.

Typical signal transduction inhibitors, that are chemotherapeutic agents, include but are not limited to: (i) Bcr/abl kinase inhibitors such as, for example, STI 571 (Gleevec), (ii) Epidermal growth factor (EGF) receptor inhibitor such as, for example, Kinase inhibitors (Iressa, OSI-774) and antibodies (Imclone: C225 [Goldstein et al. (1995), Clin Cancer Res. 1:1311-1318], and Abgenix: ABX-EGF) and (iii) HER-2/neu receptor inhibitors such as, for example, Herceptin® (trastuzumab).

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA), the Physician's Desk Reference, 56th Edition, 2002 (published by Medical Economics company, Inc. Montvale, NJ 07645-1742), and the Physician's Desk Reference, 57th Edition, 2003 (published by Thompson PDR, Montvale, NJ 07645-1742); the disclosures of which is incorporated herein by reference thereto.

For example, the compound of formula 1.0 (e.g., a pharmaceutical composition comprising the compound of formula 1.0); can be administered orally (e.g., as a capsule), and the chemotherapeutic agents can be administered intravenously, usually as an IV solution. The use of a pharmaceutical composition comprising more than one drug is within the scope of this invention.

The compound of formula 1.0 and the chemotherapeutic agents are administered in therapeutically effective dosages to obtain clinically acceptable results, e.g., reduction or elimination of symptoms or of the tumor. Thus, the compound of formula 1.0 and chemotherapeutic agents can be administered concurrently or consecutively in a treatment protocol. The administration of the chemotherapeutic agents can be made according to treatment protocols already known in the art.

In general when more than one chemotherapeutic agent is used in the methods of this invention, the chemotherapeutic agents are administered on the same day either concurrently or consecutively in their standard dosage form. For example, the chemotherapeutic agents are usually administered intravenously, preferably by an IV drip using IV solutions well known in the art (e.g., isotonic saline (0.9% NaCl) or dextrose solution (e.g., 5% dextrose)).

When two or more chemotherapeutic agents are used, the chemotherapeutic agents are generally administered on the same day; however, those skilled in the art will appreciate that the chemotherapeutic agents can be administered on different days and in different weeks. The skilled clinician can administer the chemotherapeutic agents according to their recommended dosage schedule from the manufacturer of the agent and can adjust the schedule according to the needs of the patient, e.g., based on the patient's response to the treatment. For example, when gemcitabine is used in combination with a platinum coordinator compound, such as, for example, cisplatin, to treat lung cancer, both the gemcitabine and the cisplatin are given on the same day on day one of the treatment cycle, and then gemcitabine is given alone on day 8 and given alone again on day 15

The compounds of this invention and chemotherapeutic agents can be administered in a treatment protocol that usually lasts one to seven weeks, and is repeated typically from 6 to 12 times. Generally the treatment protocol can last one to four weeks. Treatment protocols of one to three weeks can also be used. A treatment protocol of one to two weeks can also be used. During this treatment protocol or cycle the compounds of this invention can be administered daily while the chemotherapeutic agents can be administered one or more times a week. Generally, a compound of this invention can be administered daily (i.e., once per day), and in one embodiment twice per day, and the chemotherapeutic agent is administered once a week or once every three weeks. For example, the taxanes (e.g., Paclitaxel (e.g., Taxol®) or Docetaxel (e.g.,Taxotere®)) can be administered once a week or once every three weeks.

However, those skilled in the art will appreciate that treatment protocols can be varied according to the needs of the patient. Thus, the combination of compounds (drugs) used in the methods of this invention can be administered in variations of the protocols described above. For example, the compounds of this invention can be administered discontinuously rather than continuously during the treatment cycle. Thus, for example, during the treatment cycle the compounds of this invention can be administered daily for a week and then discontinued for a week, with this administration repeating during the treatment cycle. Or the compounds of this invention can be administered daily for two weeks and discontinued for a week, with this administration repeating during the treatment cycle. Thus, the compounds of this invention can be administered daily for one or more weeks during the cycle and discontinued for one or more weeks during the cycle, with this pattern of administration repeating during the treatment cycle. This discontinuous treatment can also be based upon numbers of days rather than a full week. For example, daily dosing for 1 to 6 days, no dosing for 1 to 6 days with this pattern repeating during the treatment protocol. The number of days (or weeks) wherein the compounds of this invention are not dosed do not have to equal the number of days (or weeks) wherein the compounds of this invention are dosed. Usually, if a discontinuous dosing protocol is used, the number of days or weeks that the compounds of this invention are dosed is at least equal or greater than the number of days or weeks that the compounds of this invention are not dosed.

The chemotherapeutic agent could be given by bolus or continuous infusion. The chemotherapeutic agent could be given daily to once every week, or once every two weeks, or once every three weeks, or once every four weeks during the treatment cycle. If administered daily during a treatment cycle, this daily dosing can be discontinuous over the number of weeks of the treatment cycle. For example, dosed for a week (or a number of days), no dosing for a week (or a number of days, with the pattern repeating during the treatment cycle.

The compounds of this invention can be administered orally, preferably as a solid dosage form, and in one embodiment as a capsule, and while the total therapeutically effective daily dose can be administered in one to four, or one to two divided doses per day, generally, the therapeutically effective dose is given once or twice a day, and in one embodiment twice a day. The compounds of this invention can be administered in an amount of about 50 to about 400 mg once per day, and can be administered in an amount of about 50 to about 300 mg once per day. The compounds of this invention are generally administered in an amount of about 50 to about 350 mg twice a day, usually 50 mg to about 200 mg twice a day, and in one embodiment about 75 mg to about 125 mg administered twice a day, and in another embodiment about 100 mg administered twice a day.

If the patient is responding, or is stable, after completion of the therapy cycle, the therapy cycle can be repeated according to the judgment of the skilled clinician. Upon completion of the therapy cycles, the patient can be continued on the compounds of this invention at the same dose that was administered in the treatment protocol, or, if the dose was less than 200mg twice a day, the dose can be raised to 200 mg twice a day. This maintenance dose can be continued until the patient progresses or can no longer tolerate the dose (in which case the dose can be reduced and the patient can be continued on the reduced dose).

The chemotherapeutic agents, used with the compounds of this invention, are administered in their normally prescribed dosages during the treatment cycle (i.e., the chemotherapeutic agents are administered according to the standard of practice for the administration of these drugs). For example: (a) about 30 to about 300 mg/m^2 for the taxanes; (b) about 30 to about 100 mg/m^2 for Cisplatin; (c) AUC of about 2 to about 8 for Carboplatin; (d) about 2 to about 4 mg/m^2 for EGF inhibitors that are antibodies; (e) about 50 to about 500 mg/m^2 for EGF inhibitors that are small molecules; (f) about 1 to about 10 mg/m^2 for VEGF kinase inhibitors that are antibodies; (g) about 50 to about 2400 mg/m^2 for VEGF inhibitors that are small molecules; (h) about 1 to about 20 mg for SERMs; (i) about 500 to about 1250 mg/m^2 for the anti-tumor nucleosides 5-Fluorouracil, Gemcitabine and Capecitabine; (j) for the anti-tumor nucleoside Cytarabine (Ara-C) 100-200mg/m^2/day for 7 to 10 days every 3 to 4 weeks, and high doses for refractory leukemia and lymphoma, i.e., 1 to 3 gm/m^2 for one hour every 12 hours for 4-8 doses every 3 to four weeks; (k) for the anti-tumor nucleoside Fludarabine (F-ara-A) 10-25mg/m^2/day every 3 to 4 weeks; (l) for the anti-tumor nucleoside Decitabine 30 to 75 mg/m^2 for three days every 6 weeks for a maximum of 8 cycles; (m) for the anti-tumor nucleoside Chlorodeoxyadenosine

(CdA, 2-CdA) 0.05-0.1 mg/kg/day as continuous infusion for up to 7 days every 3 to 4 weeks; (n) about 1 to about 100 mg/m^2 for epothilones; (o) about 1 to about 350 mg/m^2 for topoisomerase inhibitors; (p) about 1 to about 50 mg/m^2 for vinca alkaloids; (q) for the folate antagonist Methotrexate (MTX) 20-60 mg/m^2 by oral, IV or IM every 3 to 4 weeks, the intermediate dose regimen is 80-250 mg/m^2 IV over 60 minutes every 3 to 4 weeks, and the high dose regimen is 250-1000mg/m^2 IV given with leucovorin every 3 to 4 weeks; (r) for the folate antagonist Premetrexed (Alimta) 300-600 mg/m^2 (10 minutes IV infusion day 1) every 3 weeks; (s) for the ribonucleotide reductase inhibitor Hydroxyurea (HU) 20-50 mg/kg/day (as needed to bring blood cell counts down); (t) the platinum coordinator compound Oxaliplatin (Eloxatin) 50-100 mg/m^2 every 3 to 4 weeks (preferably used for solid tumors such as non-small cell lung cancer, colorectal cancer and ovarian cancer); (u) for the anthracycline daunorubicin 10-50 mg/m^2/day IV for 3-5 days every 3 to 4 weeks; (v) for the anthracycline Doxorubicin (Adriamycin) 50-100 mg/m^2 IV continuous infusion over 1-4 days every 3 to 4 weeks, or 10-40 mg/m^2 IV weekly; (w) for the anthracycline Idarubicin 10-30 mg/m^2 daily for 1-3 days as a slow IV infusion over 10-20 minutes every 3 to 4 weeks; (x) for the biologic interferon (Intron-A, Roferon) 5 to 20 million IU three times per week; (y) for the biologic pegylated interferon (Peg-intron, Pegasys) 3 to 4 micrograms/kg/day chronic sub cutaneous (until relapse or loss of activity); (z) for the biologic Rituximab (Rituxan) (antibody used for non-Hodgkin's lymphoma) 200-400mg/m^2 IV weekly over 4-8 weeks for 6 months; (aa) for the alkylating agent temozolomide 75 mg/m^2 to 250mg/m^2, for example, 150 mg/m^2, or for example, 200 mg/m^2, such as 200mg/m^2 for 5 days; and (bb) for the MEK1 and/or MEK2 inhibitor PD0325901, 15 mg to 30 mg, for example, 15 mg daily for 21 days every 4 weeks.

Gleevec can be used orally in an amount of about 200 to about 800 mg/day.

Thalidomide (and related imids) can be used orally in amounts of about 200 to about 800 mg/day, and can be contiuously dosed or used until releapse or toxicity. See for example Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analoqs in human multiple myeloma cells;therapeutic implications", Blood, 99(12):4525-30, June 15, 2002, the disclosure of which is incorporated herein by reference thereto.

The FPT inhibitor Sarasar® (brand of lonifarnib) can be administered orally (e.g., capsule) in amounts of about 50 to about 200 mg given twice a day, or in amounts of about 75 to about 125 mg given twice a day, or in amounts of about 100 to about 200 mg given twice a day, or in an amount of about 100 mg given twice a day.

Paclitaxel (e.g., Taxol®), for example, can be administered once per week in an amount of about 50 to about 100 mg/m^2 and in another example about 60 to about 80 mg/m^2. In another example Paclitaxel (e.g., Taxol®) can be administered once every three weeks in an amount of about 150 to about 250 mg/m^2 and in another example about 175 to about 225 mg/m^2.

In another example, Docetaxel (e.g., Taxotere®) can be administered once per week in an amount of about 10 to about 45 mg/m^2. In another example Docetaxel (e.g., Taxotere®) can be administered once every three weeks in an amount of about 50 to about 100 mg/m^2.

In another example Cisplatin can be administered once per week in an amount of about 20 to about 40 mg/m^2. In another example Cisplatin can be administered once every three weeks in an amount of about 60 to about 100 mg/m^2.

In another example Carboplatin can be administered once per week in an amount to provide an AUC of about 2 to about 3. In another example Carboplatin can be administered once every three weeks in an amount to provide an AUC of about 5 to about 8.

In another embodiment this invention is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0.

Another embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 and an effective amount of a chemotherapeutic agent.

Another embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 and an effective amount of a chemotherapeutic agent, wherein the chemotherapeutic agent is selected from the group consisting of: paclitaxel, docetaxel, carboplatin, cisplatin, gemcitabine, tamoxifen, Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, navelbine, IMC-1C11, SU5416 and SU6688.

Another embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 and an effective amount of a chemotherapeutic agent, wherein the chemotherapeutic agent is selected from the group consisting of: paclitaxel, docetaxel, carboplatin, cisplatin, navelbine, gemcitabine, and Herceptin.

Another embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 and an effective amount of a chemotherapeutic agent, wherein the chemotherapeutic agent is selected from the group consisting of: Cyclophasphamide, 5-Fluorouracil, Temozolomide, Vincristine, Cisplatin, Carboplatin, and Gemcitabine.

Another embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 and an effective amount of a chemotherapeutic agent, wherein the chemotherapeutic agent is selected from the group consisting of: Gemcitabine, Cisplatin and Carboplatin.

This invention also provides a method of treating cancer in a patient in need of such treatment, said treatment comprising administering to said patient a therapeutically effective amount at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and therapeutically effective amounts of at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) chemotherapeutic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) epidermal growth factor (EGF) inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) vascular endolithial growth factor (VEGF) inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, (13) folate antagonists, (14) ribonucleotide reductase inhibitors, (15) anthracyclines, (16) biologics; (17) inhibitors of angiogenesis and/or suppressors of tumor necrosis factor alpha (TNF-alpha) such as thalidomide (or related imid), (18) Bcr/abl kinase inhibitors, (19) MEK1 and/or MEK 2 inhibitors that are small molecules, (20) IGF-1 and IGF-2 inhibitors that are small molecules, (21) small molecule inhibitors of RAF and BRAF kinases, (22) small molecule inhibitors of cell cycle dependent kinases such as CDK1, CDK2, CDK4 and CDK6, (23) alkylating agents, and (24) farnesyl protein transferase inhibitors (also know as FPT inhibitors or FTI (i.e., farnesyl transfer inhibitors)).

This invention also provides a method of treating cancer in a patient in need of such treatment, said treatment comprising administering to said patient a therapeutically effective amount at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and therapeutically effective amounts of at least two (e.g., 2 or 3, or 2, and usually 2) different antineoplastic agents selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) epidermal growth factor (EGF) inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) vascular endolithial growth factor (VEGF) inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, (13) folate antagonists, (14) ribonucleotide reductase inhibitors, (15) anthracyclines, (16) biologics; (17) inhibitors of angiogenesis and/or suppressors of tumor necrosis factor alpha (TNF-alpha) such as thalidomide (or related imid), (18) Bcr/abl kinase inhibitors, (19) MEK1 and/or MEK 2 inhibitors that are small molecules, (20) IGF-1 and IGF-2 inhibitors that are small molecules, (21) small molecule inhibitors of RAF and BRAF kinases, (22) small molecule inhibitors of cell cycle dependent kinases such as CDK1, CDK2, CDK4 and CDK6, (23) alkylating agents, and (24) farnesyl protein transferase inhibitors (also know as FPT inhibitors or FTI (i.e., farnesyl transfer inhibitors)).

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and an antineoplastic agent selected from the group consisting of: (1) EGF inhibitors that are antibodies, (2) EGF inhibitors that are small molecules, (3) VEGF inhibitors that are antibodies, and (4) VEGF inhibitors that are small molecules. Radiation therapy can also be used in conjunction with this above combination therapy, i.e., the above method using a combination of compounds of the invention and antineoplastic agent can also comprise the administration of a therapeutically effect amount of radiation.

This invention also provides a method of treating leukemias (e.g., acute myeloid leukemia (AML), and chronic myeloid leukemia (CML)) in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and: (1) Gleevec and interferon to treat CML; (2) Gleevec and pegylated interferon to treat CML; (3) Gleevec to treat CML; (4) an anti-tumor nucleoside derivative (e.g., Ara-C) to treat AML; or (5) an anti-tumor nucleoside derivative (e.g., Ara-C) in combination with an anthracycline to treat AML.

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering therapeutically effective amounts at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 and: (1) a biologic (e.g., Rituxan); (2) a biologic (e.g., Rituxan) and an anti-tumor nucleoside derivative (e.g., Fludarabine); or (3) Genasense (antisense to BCL-2).

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 and: (1) a proteosome inhibitor (e.g., PS-341 from Millenium); or (2) Thalidomide (or related imid).

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) EGF inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) VEGF inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators, (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, and (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) EGF inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) VEGF inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators, (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, and (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, (3) anti-tumor nucleoside derivatives, (4) topoisomerase inhibitors, and (5) vinca alkaloids.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, (b) carboplatin, and (c) paclitaxel.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, (b) cisplatin, and (c) gemcitabine.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, (b) carboplatin, and (c) gemcitabine.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, (b) Carboplatin, and (c) Docetaxel.

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) an antineoplastic agent selected from the group consisting of: (1) EGF inhibitors that are antibodies, (2) EGF inhibitors that are small molecules, (3) VEGF inhibitors that are antibodies, (4) VEGF kinase inhibitors that are small molecules.

This invention also provides a method of treating squamous cell cancer of the head and neck, in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent selected from the group consisting of: (1) taxanes, and (2) platinum coordinator compounds.

This invention also provides a method of treating squamous cell cancer of the head and neck, in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent selected from the group consisting of: (1) taxanes, (2) platinum coordinator compounds, and (3) anti-tumor nucleoside derivatives (e.g., 5-Fluorouracil).

This invention also provides a method of treating CML in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, (b) Gleevec, and (c) interferon (e.g., Intron-A).

This invention also provides a method of treating CML in a patient in need of such treatment comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, (b) Gleevec; and (c) pegylated interferon (e.g., Peg-Intron, and Pegasys).

This invention also provides a method of treating CML in a patient in need of such treatment comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 (for example, as described in any one of Embodiment Nos. 1 to 161) and (b) Gleevec.

This invention also provides a method of treating CMML in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0.

This invention also provides a method of treating AML in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) an anti-tumor nucleoside derivative (e.g., Cytarabine (i.e., Ara-C)).

This invention also provides a method of treating AML in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, (b) an anti-tumor nucleoside derivative (e.g., Cytarabine (i.e., Ara-C)), and (c) an anthracycline.

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) Rituximab (Rituxan).

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, (b) Rituximab (Rituxan), and (c) an anti-tumor nucleoside derivative (e.g., Fludarabine (i.e., F-ara-A).

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) Genasense (antisense to BCL-2).

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) a proteosome inhibitor (e.g., PS-341 (Millenium)).

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment, said method comprising administering to said patient therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) Thalidomide or related imid.

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment, said method comprising administering therapeutically effective amounts of: (a) at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, and (b) Thalidomide.

This invention is also directed to the methods of treating cancer described herein, particularly those described above, wherein in addition to the administration of the compound of formula 1.0 and antineoplastic agents, radiation therapy is also administered prior to, during, or after the treatment cycle.

This invention also provides a method for treating cancer (e.g., lung cancer, prostate cancer and myeloid leukemias) in a patient in need of such treatment, said method comprising administering to said patient (1) an effective amount of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0, in combination with (2) at least one (e.g., 1, 2 or 3, or 1 or 2, or 2, or 1) antineoplastic agent, microtubule affecting agent and/or radiation therapy.

This invention also provides a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) compound of formula 1.0 in combination with an effective amount of at least one (e.g., 1, 2 or 3, or 1 or 2, or 1, and usually 1) signal transduction inhibitor.

Thus, in one example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Paclitaxel (e.g., Taxol® is administered once per week in an amount of about 50 to about 100 mg/m^2, and in another example about 60 to about 80 mg/m^2, and (3) Carboplatin is administered once per week in an amount to provide an AUC of about 2 to about 3.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and yet in another example about 100 mg administered twice a day, (2) Paclitaxel (e.g., Taxol® is administered once per week in an amount of about 50 to about 100 mg/m^2, and in another example about 60 to about 80 mg/m^2, and (3) Cisplatin is administered once per week in an amount of about 20 to about 40 mg/m^2.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Docetaxel (e.g., Taxotere®) is administered once per week in an amount of about 10 to about 45 mg/m^2, and (3) Carboplatin is administered once per week in an amount to provide an AUC of about 2 to about 3.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Docetaxel (e.g., Taxotere®) is administered once per week in an amount of about 10 to about 45 mg/m^2, and (3) Cisplatin is administered once per week in an amount of about 20 to about 40 mg/m^2.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Paclitaxel (e.g., Taxol® is administered once every three weeks in an amount of about 150 to about 250 mg/m^2, and in another example about 175 to about 225 mg/m^2, and in yet another example 175 mg/m^2, and (3) Carboplatin is administered once every three weeks in an amount to provide an AUC of about 5 to about 8, and in another example 6.

In another example of treating non small cell lung cancer: (1) the compound of formula 1.0 is administered in an amount of 100 mg administered twice a day, (2) Paclitaxel (e.g., Taxol® is administered once every three weeks in an amount of 175 mg/m^2, and (3) Carboplatin is administered once every three weeks in an amount to provide an AUC of 6.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Paclitaxel (e.g., Taxol® is administered once every three weeks in an amount of about

150 to about 250 mg/m^2, and in another example about 175 to about 225 mg/m^2, and (3) Cisplatin is administered once every three weeks in an amount of about 60 to about 100 mg/m^2.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Docetaxel (e.g., Taxotere® is administered once every three weeks in an amount of about 50 to about 100 mg/m^2, and (3) Carboplatin is administered once every three weeks in an amount to provide an AUC of about 5 to about 8.

In another example (e.g., treating non small cell lung cancer): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Docetaxel (e.g., Taxotere® is administered once every three weeks in an amount of about 50 to about 100 mg/m^2, and (3) Cisplatin is administered once every three weeks in an amount of about 60 to about 100 mg/m^2.

In another example for treating non small cell lung cancer using the compounds of formula 1.0, Docetaxel and Carboplatin: (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, (2) Docetaxel (e.g., Taxotere® is administered once every three weeks in an amount of about 75 mg/m^2, and (3) Carboplatin is administered once every three weeks in an amount to provide an AUC of about 6.

In another example of the treatments of non-small cell lung cancer described above the Docetaxel (e.g., Taxotere® and Cisplatin, the Docetaxel (e.g., Taxotere® and Carboplatin, the Paclitaxel (e.g., Taxol® and Carboplatin, or the Paclitaxel (e.g., Taxol® and Cisplatin are administered on the same day.

In another example (e.g., CML): (1) the compound of formula 1.0 is administered in an amount of about 100 mg to about 200 mg administered twice a day, (2) Gleevec is administered in an amount of about 400 to about 800 mg/day orally, and (3) interferon (Intron-A) is administered in an amount of about 5 to about 20 million IU three times per week.

In another example (e.g., CML): (1) the compound of formula 1.0 is administered in an amount of about 100 mg to about 200 mg administered twice a day, (2) Gleevec is administered in an amount of about 400 to about 800 mg/day orally, and (3) pegylated interferon (Peg-Intron or Pegasys) is administered in an amount of about 3 to about 6 micrograms/kg/day.

In another example (e.g., non-Hodgkin's lymphoma): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, and (2) Genasense (antisense to BCL-2) is administered as a continuous IV infusion at a dose of about 2 to about 5 mg/kg/day (e.g., 3 mg/kg/day) for 5 to 7 days every 3 to 4 weeks.

In another example (e.g., multiple myeloma): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, and (2) the proteosome inhibitor (e.g., PS-341 – Millenium) is administered in an amount of about 1.5mg/m^2 twice weekly for two consecutive weeks with a one week rest period.

In another example (e.g., multiple myeloma): (1) the compound of formula 1.0 is administered in an amount of about 50 mg to about 200 mg twice a day, and in another example about 75 mg to about 125 mg administered twice a day, and in yet another example about 100 mg administered twice a day, and (2) the Thalidomide (or related imid) is administered orally in an amount of about 200 to about 800 mg/day, with dosing being continuous until relapse or toxicity.

In one embodiment of the methods of treating cancer of this invention, the chemotherapeutic agents are selected from the group consisting of: paclitaxel, docetaxel, carboplatin, cisplatin, gemcitabine, tamoxifen, Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, navelbine, IMC-1C11, SU5416 and SU6688.

In another embodiment of the methods of treating cancer of this invention, the chemotherapeutic agents are selected from the group consisting of: paclitaxel, docetaxel, carboplatin, cisplatin, navelbine, gemcitabine, and Herceptin.

Thus, one embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0, a taxane, and a platinum coordination compound.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0, a taxane, and a platinum coordination compound, wherein said compound of formula 1.0 is administered every day, said taxane is administered once per week per cycle, and said platinum coordinator compound is administered once per week per cycle. In another embodiment the treatment is for one to four weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0, a taxane, and a platinum coordination compound, wherein said compound of formula 1.0 is administered every day, said taxane is administered once every three weeks per cycle, and said platinum coordinator compound is administered once every three weeks per cycle. In another embodiment the treatment is for one to three weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0, paclitaxel, and carboplatin. In another embodiment, said compound of formula 1.0 is administered every day, said paclitaxel is administered once per week per cycle, and said carboplatin is administered once per week per cycle. In another embodiment the treatment is for one to four weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0, paclitaxel, and carboplatin. In another embodiment, said compound of formula 1.0 is administered every day, said paclitaxel is administered once every three weeks per cycle, and said carboplatin is administered once every three weeks per cycle. In another embodiment the treatment is for one to three weeks per cycle.

Another embodiment of this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering daily a therapeutically effective amount of the compound of formula 1.0, administering a therapeutically effective amount of carboplatin once a week per cycle, and administering a therapeutically effective amount of paclitaxel once a week per cycle, wherein the treatment is given for one to four weeks per cycle. In another embodiment said compound of formula 1.0 is administered twice per day. In another embodiment said carboplatin and said paclitaxel are administered on the same day, and in another embodiment said carboplatin and said paclitaxel are administered consecutively, and in another embodiment said carboplatin is administered after said paclitaxel.

Another embodiment of this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering daily a therapeutically effective amount of a compound of formula 1.0, administering a therapeutically effective amount of carboplatin once every three weeks per cycle, and administering a therapeutically effective amount of paclitaxel once every three weeks per cycle, wherein the treatment is given for one to three weeks. In another embodiment compound of formula 1.0 is administered twice per day. In another embodiment said carboplatin and said paclitaxel are administered on the same day, and in another embodiment said carboplatin and said paclitaxel are administered consecutively, and in another embodiment said carboplatin is administered after said paclitaxel.

Another embodiment of this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering about 50 to about 200 mg of a compound of formula 1.0 twice a day, administering carboplatin once per week per cycle in an amount to provide an AUC of about 2 to about 8 (and in another embodiment about 2 to about 3), and administering once per week per cycle about 60 to about 300 mg/m^2 (and in another embodiment about 50 to 100mg/m^2, and in yet another embodiment about 60 to about 80 mg/m^2) of paclitaxel, wherein the treatment is given for one to four weeks per cycle. In another embodiment said compound of formula 1.0 is administered in amount of about 75 to about 125 mg twice a day, and in another embodiment about 100 mg twice a day. In another embodiment said carboplatin and said paclitaxel are administered on the same day, and in another embodiment said carboplatin and said paclitaxel are administered consecutively, and in another embodiment said carboplatin is administered after said paclitaxel.

In another embodiment, this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering about 50 to about 200 mg of a compound of formula 1.0 twice a day, administering carboplatin once every three weeks per cycle in an amount to provide an AUC of about 2 to about 8 (in another embodiment about 5 to about 8, and in another embodiment 6), and administering once every three weeks per cycle about 150 to about 250 mg/m^2 (and in another embodiment about 175 to about 225 mg/m^2, and in another embodiment 175 mg/m^2) of paclitaxel, wherein the treatment is given for one to three weeks. In another embodiment said compound of formula 1.0 is administered in an amount of about 75 to about 125 mg twice a day, and in another embodiment about 100 mg twice a day. In another embodiment said carboplatin and said paclitaxel are administered on the same day, and in another embodiment said carboplatin and said paclitaxel are administered consecutively, and in another embodiment said carboplatin is administered after said paclitaxel.

Other embodiments of this invention are directed to methods of treating cancer as described in the above embodiments (i.e., the embodiments directed to treating cancer and to treating non small cell lung cancer with a taxane and platinum coordinator compound) except that in place of paclitaxel and carboplatin the taxanes and platinum coordinator compounds used together in the methods are: (1) docetaxel (Taxotere®) and cisplatin; (2) paclitaxel and cisplatin; and (3) docetaxel and carboplatin. In another embodiment of the methods of this invention cisplatin is used in amounts of about 30 to about 100 mg/m^2. In the another embodiment of the methods of this invention docetaxel is used in amounts of about 30 to about 100 mg/m^2.

In another embodiment this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0, a taxane, and an EGF inhibitor that is an antibody. In another embodiment the taxane used is paclitaxel, and the EGF inhibitor is a HER2 antibody (in one embodiment Herceptin) or Cetuximab, and in another embodiment Herceptin is used. The length of treatment, and the amounts and administration of said compound of formula 1.0 and the taxane are as described in the embodiments above. The EGF inhibitor that is an antibody is administered once a week per cycle, and in another embodiment is administered on the same day as the taxane, and in another embodiment is administered consecutively with the taxane. For example, Herceptin is administered in a loading dose of about 3 to about 5 mg/m^2 (in another embodiment about 4 mg/m^2), and then is administered in a maintenance dose of about 2 mg/m^2 once per week per cycle for the remainder of the treatment cycle (usually the cycle is 1 to 4 weeks). In one embodiment the cancer treated is breast cancer.

In another embodiment this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of: (1) a compound of formula 1.0, (2) a taxane, and (3) an antineoplastic agent selected from the group consisting of: (a) an EGF inhibitor that is a small molecule, (b) a VEGF inhibitor that is an antibody, and (c) a VEGF kinase inhibitor that is a small molecule. In another embodiment, the taxane paclitaxel or docetaxel is used. In another embodiment the antineoplastic agent is selected from the group consisting of: tarceva, Iressa, bevacizumab, SU5416, SU6688 and BAY 43-9006. The length of treatment, and the amounts and administration of said compound of formula 1.0 and the taxane are as described in the embodiments above. The VEGF kinase inhibitor that is an antibody is usually given once per week per cycle. The EGF and VEGF inhibitors that are small molecules are usually given daily per cycle. In another embodiment, the VEGF inhibitor that is an antibody is given on the same day as the taxane, and in another embodiment is administered concurrently with the taxane. In another embodiment, when the EGF inhibitor that is a small molecule or the VEGF inhibitor that is a small molecule is administered on the same day as the taxane, the administration is concurrently with the taxane. The EGF or VEGF kinase inhibitor is generally administered in an amount of about 10 to about 500 mg/m^2.

In another embodiment this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0, an anti-tumor nucleoside derivative, and a platinum coordination compound.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0, an anti-tumor nucleoside derivative, and a platinum coordination compound, wherein said compound of formula 1.0 is administered every day, said anti-tumor nucleoside derivative is administered once per week per cycle, and said platinum coordinator compound is administered once per week per cycle. Although the treatment can be for one to four weeks per cycle, in one embodiment the treatment is for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0, an anti-tumor nucleoside derivative, and a platinum coordination compound, wherein said compound of formula 1.0 is administered every day, said an anti-tumor nucleoside derivative is administered once per week per cycle, and said platinum coordinator compound is administered once every three weeks per cycle. Although the treatment can be for one to four weeks per cycle, in one embodiment the treatment is for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0, gemcitabine, and cisplatin. In another embodiment, said compound of formula 1.0 is administered every day, said gemcitabine is administered once per week per cycle, and said cisplatin is administered once per week per cycle. In one embodiment the treatment is for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0, gemcitabine, and cisplatin. In another embodiment, said compound of formula 1.0 is administered every day, said gemcitabine is administered once per week per cycle, and said cisplatin is administered once every three weeks per cycle. In another embodiment the treatment is for one to seven weeks.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0, gemcitabine, and carboplatin. In another embodiment said compound of formula 1.0 is administered every day, said gemcitabine is administered once per week per cycle, and said carboplatin is administered once per week per cycle. In another embodiment the treatment is for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound of formula 1.0, gemcitabine, and carboplatin. In another embodiment said compound of formula 1.0 is administered every day, said gemcitabine is administered once per week per cycle, and said carboplatin is administered once every three weeks per cycle. In another embodiment the treatment is for one to seven weeks per cycle.

In the above embodiments using gemcitabine, the compound of formula 1.0 and the platinum coordinator compound are administered as described above for the embodiments using taxanes. Gemcitabine is administered in an amount of about 500 to about 1250 mg/m^2. In one embodiment the gemcitabine is administered on the same day as the platinum coordinator compound, and in another embodiment consecutively with the platinum coordinator compound, and in another embodiment the gemcitabine is administered after the platinum coordinator compound.

Another embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient a compound of formula 1.0 and an antineoplastic agent selected from: (1) EGF inhibitors that are antibodies, (2) EGF inhibitors that are small molecules, (3) VEGF inhibitors that are antibodies, and (4) VEGF kinase inhibitors that are small molecules all as described above. The treatment is for one to seven weeks per cycle, and generally for one to four weeks per cycle. The compound of formula 1.0 is administered in the same manner as described above for the other embodiments of this invention. The small molecule antineoplastic agents are usually administered daily, and the antibody antineoplastic agents are usually administered once per week per cycle. In one embodiment the antineoplastic agents are selected from the group consisting of: Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, IMC-1C11, SU5416, SU6688 and BAY 43-9006.

In the embodiments of this invention wherein a platinum coordinator compound is used as well as at least one other antineoplastic agent, and these drugs are administered consecutively, the platinum coordinator compound is generally administered after the other antineoplastic agents have been administered.

Other embodiments of this invention include the administration of a therapeutically effective amount of radiation to the patient in addition to the administration of a compound of formula 1.0 and antineoplastic agents in the embodiments described above. Radiation is administered according to techniques and protocols well know to those skilled in the art.

Another embodiment of this invention is directed to a pharmaceutical composition comprising at least two different chemotherapeutic agents and a pharmaceutically acceptable carrier for intravenous administration. Preferably the pharmaceutically acceptable carrier is an isotonic saline solution (0.9% NaCl) or a dextrose solution (e.g., 5% dextrose).

Another embodiment of this invention is directed to a pharmaceutical composition comprising a compound of formula 1.0 and at least two different antineoplastic agents and a pharmaceutically acceptable carrier for intravenous administration. Preferably the pharmaceutically acceptable carrier is an isotonic saline solution (0.9% NaCl) or a dextrose solution (e.g., 5% dextrose).

Another embodiment of this invention is directed to a pharmaceutical composition comprising a compound of formula 1.0 and at least one antineoplastic agent and a pharmaceutically acceptable carrier for intravenous administration. Preferably the pharmaceutically acceptable carrier is an isotonic saline solution (0.9% NaCl) or a dextrose solution (e.g., 5% dextrose).

Other embodiments of this invention are directed to the use of a combination of at least one (e.g., one) compound of formula 1.0 and drugs for the treatment of breast cancer, i.e., this invention is directed to a combination therapy for the treatment of breast cancer. Those skilled in the art will appreciate that the compounds of formula 1.0 and drugs are generally administered as individual pharmaceutical compositions. The use of a pharmaceutical composition comprising more than one drug is within the scope of this invention.

Thus, another embodiment of this invention is directed to a method of treating (or preventing) breast cancer (i.e., postmenopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and a therapeutically effective amount of at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors, (b) antiestrogens, and (c) LHRH analogues; and said treatment optionally including the administration of at least one chemotherapeutic agent.

The compound of formula 1.0 is preferably administered orally, and in one embodiment is administered in capsule form.

Examples of aromatase inhibitors include but are not limited to: Anastrozole (e.g., Arimidex), Letrozole (e.g., Femara), Exemestane (Aromasin), Fadrozole and Formestane (e.g., Lentaron).

Examples of antiestrogens include but are not limited to: Tamoxifen (e.g., Nolvadex), Fulvestrant (e.g., Faslodex), Raloxifene (e.g., Evista), and Acolbifene.

Examples of LHRH analogues include but are not limited to: Goserelin (e.g., Zoladex) and Leuprolide (e.g., Leuprolide Acetate, such as Lupron or Lupron Depot).

Examples of chemotherapeutic agents include but are not limited to: Trastuzumab (e.g., Herceptin), Gefitinib (e.g., Iressa), Erlotinib (e.g., Erlotinib HCl, such as Tarceva), Bevacizumab (e.g., Avastin), Cetuximab (e.g., Erbitux), and Bortezomib (e.g., Velcade).

Preferably, when more than one antihormonal agent is used, each agent is selected from a different category of agent. For example, one agent is an aromatase inhibitor (e.g., Anastrozole, Letrozole, or Exemestane) and one agent is an antiestrogen (e.g., Tamoxifen or Fulvestrant).

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors, (b) antiestrogens, and (c) LHRH analogues; and administering an effective amount of at least one chemotherapeutic agent.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors, (b) antiestrogens, and (c) LHRH analogues.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors, and (b) antiestrogens.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors and (b) antiestrogens; and at least one chemotherapeutic agent.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and at least one aromatase inhibitor.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, at least one aromatase inhibitor, and at least one chemotherapeutic agent.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0; and (2) at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors that are selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane, (b) antiestrogens that are selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and (c) LHRH analogues that are selected from the group consisting of: Goserelin and Leuprolide; and administering an effective amount of at least one chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0; and (2) at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors that are selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane, (b) antiestrogens that are selected from the group consisting of:

Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and (c) LHRH analogues that are selected from the group consisting of: Goserelin and Leuprolide.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0; and (2) at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors that are selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane, and (b) antiestrogens that are selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0; and (2) at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors that are selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane, (b) antiestrogens that are selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene; and administering an effective amount of at least one chemotherapeutic agents are selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0; and (2) at least one aromatase inhibitor selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0; (2) at least one aromatase inhibitor that is selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane; and (3) administering an effective amount of at least one chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0; (2) at least one aromatase inhibitor; and (3) at least one LHRH analogue.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of:(1) at least one (e.g., one) compound of formula 1.0; (2) at least one antiestrogen ; and (3) at least one LHRH analogue.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0; (2) at least one aromatase inhibitor that is selected from the group consisting of Anastrozole, Letrozole, Exemestane, Fadrozole and Formestane; and (3) at least one LHRH analogue that is selected from the group consisting of: Goserelin and Leuprolide.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of: (1) at least one (e.g., one) compound of formula 1.0; (2) at least one antiestrogen that is selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene; and (3) at least one LHRH analogue that is selected from the group consisting of: Goserelin and Leuprolide.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Anastrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Letrazole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Exemestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and and Fadrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Formestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Raloxifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Goserelin.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said

treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and and Leuprolide.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Anastrozole, and an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Letrozole, and an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Exemestane, and an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Fadrozole, and an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Formestane, and an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Anastrozole, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said

treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Letrozole, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Exemestane, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Fadrozole, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Formestane, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Anastrozole, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Letrozole, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Exemestane, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Fadrozole, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Formestane, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Anastrozole, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Letrozole, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Exemestane, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Fadrozole, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Formestane, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Raloxifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Goserelin, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Leuprolein, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said

treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Anastrozole, an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Letrozole, an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Exemestane, an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Fadrozole, an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Formestane, an antiestrogen selected from the group consisting of: Tamoxifen, Fulvestrant, Raloxifene, and Acolbifene, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Anastrozole, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Letrozole, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Exemestane, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Fadrozole, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Formestane, Tamoxifen, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Anastrozole, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Letrozole, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Exemestane, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Fadrozole, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Formestane, Fulvestrant, and a chemotherapeutic agent selected from the group consisting of: Trastuzumab, Gefitinib, Erlotinib, Bevacizumab, Cetuximab, and Bortezomib.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Goserelin and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Goserelin, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Goserelin, and Raloxifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Goserelin and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Leuprolide, and Tamoxifen.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Leuprolide, and Fulvestrant.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Leuprolide, and Raloxifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Leuprolide and Acolbifene.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Goserelin and Anastrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Goserelin and Letrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said

treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Goserelin and Exemestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Goserelin and Fadrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Goserelin and Formestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Leuprolide and Anastrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Leuprolide and Letrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Leuprolide and Exemestane.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Leuprolide and Fadrozole.

Another embodiment of this invention is directed to a method of treating or preventing breast cancer in a patient in need of such treatment wherein said treatment comprises administering a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Leuprolide and Formestane.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Anastrozole.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Letrozole.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Exemestane.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Tamoxifen.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0 and Fulvestrant.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Anastrozole, and Fulvestrant.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one compound of formula I (e.g., one), Letrozole, and Fulvestrant.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Exemestane, and Fulvestrant.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Anastrozole, and Tamoxifen.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Letrozole, and Tamoxifen.

Another embodiment of this invention is directed to the treatment or prevention of breast cancer in a patient in need of such treatment, said treatment comprising the administration of a therapeutically effective amount of at least one (e.g., one) compound of formula 1.0, Exemestane, and Tamoxifen.

Other embodiments of this invention are directed to any of the above described embodiments for the treatment of Breast Cancer wherein the chemotherapeutic agent is Trastuzumab.

Other embodiments of this invention are directed to any of the above described embodiments for the treatment or prevention of Breast Cancer wherein the method is directed to the treatment of breast cancer.

The compound of formula 1.0, antihormonal agents and chemotherapeutic agents can be administered concurrently or sequentially.

The antihormonal agents and optional chemotherapeutic agents are administered according to their protocols, dosage amounts, and dosage forms that are well know to those skilled in the art (e.g., the Physician's Desk Reference or published literature). For example, for Tamoxifen, Fulvestrant, Raloxifene, Anastrozole, Letrozole, Exemestane, Leuprolide and Goserelin, see the Physician's Desk Reference, 57th Edition, 2003, published by Thomas PDR at Montvale, N.J. 07645-1742, the disclosure of which is incorporated herein by reference thereto.

In general, in the embodiments directed to the methods of treating Breast Cancer: (1) the compound of formula 1.0 can be administered daily (e.g., once per day, and in one embodiment twice a day), (2) the aromatase inhibitors can be administered in accordance with the known protocol for the aromatase inhibitor used (e.g., once per day), (3) the antiestrogens can be administered in accordance with the known protocol for the antiestrogen used (e.g., from once a day to once a month), (4) the LHRH analogue can be administered in accordance with the known protocol for the LHRH analogue used (e.g., once a month to once every three months), and (5) the chemotherapeutic agent can be administered in accordance with the known protocol for the chemotherapeutic agent used (e.g., from once a day to once a week).

Radiation therapy, if administered in the above treatments for breast cancer, is generally administered according to known protocols before administration of the compound of formula 1.0, antihormonal agents and optional chemotherapeutic agents.

Treatment according to the methods of treating breast cancer is continuous (i.e., a continuous dosing schedule is followed). The treatment is continued until there is a complete response, or until the skilled clinician determines that the patient is not benefiting from the treatment (for example, when there is disease progression).

The continuous treatment protocol for breast cancer can be changed to a discontinuous treatment schedule if, in the judgment of the skilled clinician, the patient would benefit from a discontinuous treatment schedule with one or more of the administered drugs. For example, the compound of formula 1.0 can be given using a discontinous treatment schedule while the remaining drugs used in the treatment are given as described herein. An example of a discontinuous treatment protocol for the compound of formula 1.0 is a repeating cycle of three weeks with the compound of formula 1.0 followed by one week without the compound of formula 1.0.

After a complete response is achieved with the breast cancer treatment, maintenance therapy with the compound of formula 1.0 can be continued using the dosing described in the methods of this invention. Maintenance therapy can also include administration of the antihormonal agents using the dosing described in the methods of this invention. Maintenance therapy can just be with the antihormonal agents. For example, after a complete response is achieved, an aromatase inhibitor (e.g., Anastrozole, Letrozole or Exemestane) can be continued for up to five years. Or, for example, an antiestrogen, e.g., Tamoxifen, may be used for up to five years after a complete response is achieved. Or, for example, an antiestrogen (e.g., Tamoxifen) can be used for up to five years after a complete response is achieved followed by the use of an aromatase inhibitor (e.g., Anastrozole, Letrozole or Exemestane) for up to five years.

In the embodiments directed to the treatment of breast cancer described above, the compound of formula 1.0 is administered continuously in a total daily dose of about 100 mg to about 600 mg. Usually this amount is administered in divided doses, and in one embodiment this amount is administered twice a day. In one embodiment the compound of formula 1.0 is dosed twice a day in an amount of about 50 mg to about 300 mg per dose. In another embodiment the compound of formula 1.0 is dosed twice a day in an amount of about 100 mg to about 200 mg per dose. Examples include the compound of formula 1.0 being dosed twice a day at 100 mg per dose. Examples also include the compound of formula 1.0 being dosed twice a day at 200 mg per dose.

Anastrozole is administered p.o. and is dosed once a day in amounts of about 0.5 to about 10 mg per dose, and in one embodiment in an amount of about 1.0 mg per dose.

Letrozole is administered p.o. and is dosed once a day in amounts of about 1.0 to about 10 mg per dose, and in one embodiment in an amount of about 2.5 mg per dose.

Exemestane is administered p.o. and is dosed once a day in amounts of about 10 to about 50 mg per dose, and in one embodiment in an amount of about 25 mg per dose.

Fadrozole is administered p.o. and is dosed twice a day in amounts of about 0.5 to about 10 mg per dose, and in one embodiment in an amount of about 2.0 mg per dose.

Formestane is administered i.m. and is dosed once every two weeks in amounts of about 100 to about 500 mg per dose, and in one embodiment in an amount of about 250 mg per dose.

Tamoxifen is administered p.o. and is dosed once a day in amounts of about 10 to about 100 mg per dose, and in one embodiment in an amount of about 20 mg per dose.

Fulvestrant is administered i.m. and is dosed once a month in amounts of about 100 to about 1000 mg per dose, and in one embodiment in an amount of about 250 mg per dose.

Raloxifene is administered p.o. and is dosed once a day in amounts of about 10 to about 120 mg per dose, and in one embodiment in an amount of about 60 mg per dose.

Acolbifene is administered p.o. and is dosed once a day in amounts of about 5 to about 20 mg per dose, and in one embodiment in an amount of about 20 mg per dose.

Goserelin is administered s.c. and is dosed once a month, or once every three months, in amounts of about 2 to about 20 mg per dose, and in one embodiment in an amount of about 3.6 mg per dose when administered once a month, and in another embodiment in an amount of about 10.8 mg per dose when administered once every three months.

Leuprolide is administered s.c. and is dosed once a month, or once every three months, in amounts of about 2 to about 20 mg per dose, and in one embodiment in an amount of about 3.75 mg per dose when administered once a month, and in another embodiment in an amount of about 11.25 mg per dose when administered once every three months.

Trastuzumab is administered by i.v. and is dosed once a week in amounts of about 2 to about 20 mpk per dose, and in one embodiment in an amount of about 2 mpk per dose. Trastuzumab is generally initially administered in a loading dose that is generally twice the dose of the weekly dose. Thus, for example, a 4 mpk loading dose is administered and then dosing is 2 mpk per dose per week.

Gefitinib is administered p.o. and is dosed once a day in amounts of about 100 to about 1000 mg per dose, and in one embodiment in an amount of about 250 mg per dose.

Erlotinib is administered p.o. and is dosed once a day in amounts of about 100 to about 500 mg per dose, and in one embodiment in an amount of about 150 mg per dose.

Bevacizumab is administered i.v. and is dosed once every two weeks in amounts of about 2.5 to about 15 mg per kilogram of body weight per dose, and in one embodiment in an amount of about 10 mg per kilogram per dose.

Cetuximab is administered i.v. and is dosed once a week in amounts of about 200 to about 500 mg per meter squared dose, and in one embodiment in an amount of about 250 mg per meter squared per dose.

Bortezomib is administered i.v. and is dosed twice a week for 2 weeks followed by a 10 day rest period (21 day treatment cycle) for a maximum of 8 treatment cycles in amounts of about 1.0 to about 2.5 mg per meter squared per dose, and in one embodiment in an amount of about 1.3 mg per meter squared per dose.

Thus in one embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 orally in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, and (2) Anastrozole p.o. in an amount of about 0.5 to about 10 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 orally in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, and (2) Anastrozole in an amount of about 1.0 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 orally in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, and (2) Letrozole p.o. in an amount of about 1.0 to about 10 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 orally in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, and (2) Letrozole p.o. in an amount of about 2.5 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 orally in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, and (2) Exemestane p.o. in an amount of about 10 to about 50 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 orally in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, and (2) Exemestane in an amount of about 25 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 orally in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, and (2) Fulvestrant i.m. in an amount of about 100 to about 1000 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 orally in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, and (2) Fulvestrant i.m. in an amount of about 250 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, and (2) Tamoxifen p.o. in an amount of about 10 to about 100 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, and (2) Tamoxifen p.o. in an amount of about 20 mg per dose wherein each dose is given once a day.

In other embodiments of the invention breast cancer is treated in a patient in need of such treatment wherein said treatment comprises the administration of the compound of formula 1.0, one of the aromatase inhibitors (e.g., Anastrozole, Letrozole, or Exemestane, and in one embodiment Anastrozole), and one of the antiestrogens (e.g., Fulvestrant or Tamoxifen), wherein the compound of formula 1.0, aromatase inhibitor and antiestrogen are administered in the dosages described above.

Thus, for example in another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient : (1) the compound of formula 1.0 p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Anastrozole p.o. in an amount of about 0.5 to about 10 mg per dose wherein each dose is given once a day, and (3) Fulvestrant i.m. in an amount of about 100 to about 1000 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Anastrozole p.o. in an amount of about 1.0 mg per dose wherein each dose is given once a day, and (3)

Fulvestrant i.m. in an amount of about 250 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Letrozole p.o in an amount of about 1.0 to about 10 mg per dose wherein each dose is given once a day, and (3) Fulvestrant in an amount of about 100 to about 1000 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Letrozole p.o. in an amount of about 2.5 mg per dose wherein each dose is given once a day, and (3) Fulvestrant i.m. in an amount of about 250 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Exemestane p.o. in an amount of about 10 to about 50 mg per dose wherein each dose is given once a day, and (3) Fulvestrant i.m. in an amount of about 100 to about 1000 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Exemestane p.o. in an amount of about 25 mg per dose wherein each dose is given once a day, and (3) Fulvestrant i.m. in an amount of about 250 mg per dose wherein each dose is given once a month.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Anastrozole p.o. in an amount of about 0.5 to about 10 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o.in an amount of about 10 to about 100 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Anastrozole p.o. in an amount of about 1.0 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o. in an amount of about 20 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Letrozole p.o. in an amount of about 1.0 to about 10 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o. in an amount of about 10 to about 100 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Letrozole p.o. in an amount of about 2.5 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o. in an amount of about 20 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 50 mg to about 300 mg per dose wherein each dose is administered twice a day, (2) Exemestane p.o. in an amount of about 10 to about 50 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o. in an amount of about 10 to about 100 mg per dose wherein each dose is given once a day.

In another embodiment of this invention breast cancer is treated (or prevented) in a patient in need of such treatment wherein said treatment comprises administering to said patient: (1) the compound of formula 1.0 p.o. in an amount of about 100 to 200 mg per dose, wherein each dose is administered twice a day, (2) Exemestane p.o. in an amount of about 25 mg per dose wherein each dose is given once a day, and (3) Tamoxifen p.o. in an amount of about 20 mg per dose wherein each dose is given once a day.

Those skilled in the art will appreciate that when other combinations of antihormonal agents are used, the individual antihormonal agent is used in the amounts specified above for that individual antihormonal agent.

Other embodiments of the treatment of Breast Cancer are directed to the methods of treating Breast Cancer described above wherein the compound of formula 1.0 is dosed twice a day in an amount of about 100 mg per dose.

Other embodiments of the treatment of Breast Cancer are directed to the methods of treating Breast Cancer described above wherein the compound of formula 1.0 is dosed twice a day in an amount of about 200 mg per dose.

Other embodiments of the treatment of Breast Cancer are directed to the methods of treating Breast Cancer described above wherein a chemotherapeutic agent is administered in addition to the compound of formula 1.0 and antihormonal agent (or antihormonal agents). In these embodiments the dosage ranges of the compound of formula 1.0 and antihormonal agents are as those described above in the combination therapies, or those described above for the individual compound of formula I and antihormonal agents, and the dosages of the chemotherapeutic agents are those described above for the individual chemotherapeutic agent. The dosages for the chemotherapeutic agents are well known in the art.

Other embodiments of this invention are directed to pharmaceutical compositions comprising the compound of formula 1.0 and at least one antihormonal agent and a pharmaceutically acceptable carrier.

Other embodiments of this invention are directed to pharmaceutical compositions comprising the compound of formula 1.0, at least one antihormonal agent, at least one chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Other embodiments of this invention are directed to pharmaceutical compositions comprising the compound of formula 1.0, at least one chemotherapeutic agent, and a pharmaceutically acceptable carrier.

Those skilled in the art will appreciate that the compounds (drugs) used in the methods of this invention are available to the skilled clinician in pharmaceutical compositions (dosage forms) from the manufacturer and are used in those compositions. So, the recitation of the compound or class of compounds in the above described methods can be replaced with a recitation of a pharmaceutical composition comprising the particular compound or class of compounds. For example, the embodiment directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the compound of formula 1.0, a taxane, and a platinum coordination compound, includes within its scope a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a pharmaceutical composition comprising the compound of formula 1.0, a pharmaceutical composition comprising a taxane, and a pharmaceutical composition comprising a platinum coordination compound.

Those skilled in the art will recognize that the actual dosages and protocols for administration employed in the methods of this invention may be varied according to the judgment of the skilled clinician. The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. A determination to vary the dosages and protocols for administration may be made after the skilled clinician takes into account such factors as the patient's age, condition and size, as well as the severity of the disease (e.g.,cancer) being treated and the response of the patient to the treatment.

The amount and frequency of administration of the compound of formula 1.0 and the chemotherapeutic agents (in the methods wherein cancer is treated) will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the disease (e.g., cancer) being treated.

The chemotherapeutic agent can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent can be varied depending on the cancer being treated and the known effects of the chemotherapeutic agent on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents on the patient, and in view of the observed responses of the cancer to the administered therapeutic agents.

The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

The particular choice of chemotherapeutic agent will depend upon the diagnosis of the attending physicians and their judgement of the condition of the patient and the appropriate treatment protocol.

The determination of the order of administration, and the number of repetitions of administration of the chemotherapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the cancer being treated and the condition of the patient.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of an chemotherapeutic agent according to the individual patient's needs, as the treatment proceeds. All such modifications are within the scope of the present invention.

The particular choice of antihormonal agents, optional chemotherapeutic agents and optional radiation will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

The determination of the order of administration, and the number of repetitions of administration of the antihormonal agents, optional chemotherapeutic agents and optional radiation during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the breast cancer being treated and the condition of the patient.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of antihormonal agents, optional chemotherapeutic agents and optional radiation according to the individual patient's needs, as the treatment proceeds. All such modifications are within the scope of the present invention.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of the disease (e.g. for cancer, the relief of cancer-related symptoms (e.g., pain, cough (for lung cancer), and shortness of breath (for lung cancer), inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis). Size of the tumor can be measured by standard methods such as radiological studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparations subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most preferably from about 0.01 mg to about 250 mg according to the particular application.

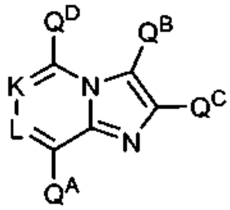
The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill in the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.04 mg/day to about 4000 mg/day, in two to four divided doses.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

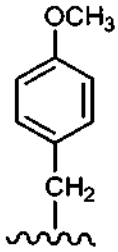
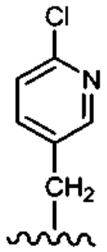
WHAT IS CLAIMED IS:

1. A compound of the formula:

 (1.0)

or the pharmaceutically acceptable salts, esters, and solvates thereof, wherein:

K is selected from the group consisting of:CH, N, -C(alkyl)-, -C(aryl)-, -C(halo)-, and -C(R^C)- wherein R^C is selected from the group consisting of:

 and  ;

L is CH or N;

Q^A is selected from the group consisting of:

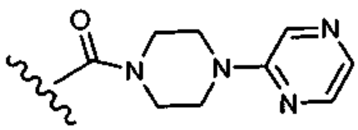
(A) $-C(O)NR^1R^2$;

(B) $-N(R^{14})_2$;

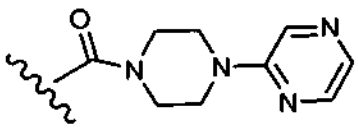
(C) unsubstituted heteroaryl;

(D) substituted heteroaryl, and wherein said substituted heteroaryl is substituted with one or more substituents selected from the group consisting of: (1) halo, (2) heteroaryl, benzo fused heteroaryl, (3) heterocycloalkyl, (4) benzodioxolyl, (5) aryl, (6) substituted aryl wherein the substituent is $-S(O)_2$alkyl, (7) alkyl, (8) $-CF_3$;

(E)

 ;

(F)



substituted with one or more substituents selected from the group consisting of:

(1) $-(\text{alkylene})_{1-6}$-heterocycloalkyl,

(2) aryl,

(3) substituted aryl,

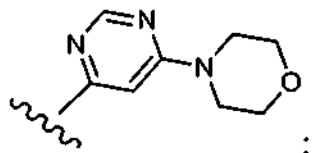
(4) $-C(O)R^{11}$,

(5) –C(O)-aryl (e.g. –C(O)phenyl), and

(6) $-(alkylene)_{1-6}-N(R^{12})_2$, and

wherein said substituted aryl moiety (3) (e.g., substituted phenyl) is substituted with one or more substitutents independently selected from the group consisting of: halo (e.g., Cl and F), and –CN;

(G)



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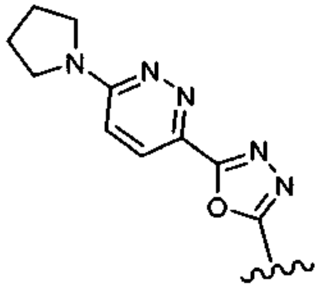
(H)



;

(I)

–NH—pyrimidinyl —— morpholinyl;

(J) H;

(K) –C(O)-heterocycloalkyl-heteroaryl;

(L) –C(O)-piperazinyl-$(alkylene)_{1-6}$-substituted aryl wherein the substituents are independently selected from halo;

(M) –C(O)-heterocycloalkyl-$(alkylene)_{1-6}$-heterocycloalkyl;

(N) –C(O)-piperazinyl-$(alkylene)_{1-6}$-heteroaryl;

(O) alkyl (e.g., C_{1-6}alkyl);

(P) –C(O)-heterocycloalkyl wherein said heterocycloalkyl is substituted with $-(alkylene)_{1-6}-N(R^{12})_2$ wherein each R^{12} is independently selected;

(Q) –C(O)-heterocycloalkyl-$(alkylene)_{1-6}$-(alkyl substituted heterocycloalkyl);

(R) -$(alkylene)_{1-6}$-benzo[1,3]dioxolyl;

(S) $-(alkylene)_{1-6}-N(R^1)(R^2)$ wherein R^1 and R^2 are as defined above,

(T) –NH-heteroaryl-heteroaryl

(U) –NH-(fused heteroarylheteroaryl);

(V) –NH-(substituted heteroaryl);

(W) –NH-heteroaryl-NH-heterocycloalkyl;

(X) biaryl;

(Y) biheteroaryl;

(Z) substituted biaryl; and

(AA) substituted biheteroaryl;

Q^B is selected from the group consisting of:

(A) –C(O)NR^{15}R^{16};

(B) –C(O)-R^{21};

(C) H;

(D) –N(R^{12})$_2$, wherein each R^{12} isindependently selected;

(E) –CH_2OH;

(F) –CH_2OCH_3;

(G) –CH_2SCH_3,

(H) –CH$_2$N(R^B) wherein each R^B is independently selected from the group consisting of: H, alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, and aryl;

(I) –N(R^{12})$_2$ wherein each R^{12} is independently selected;

(J) –NH-C(O)-alkyl;

(K) –NH-C(O)-(hydroxyl substituted alkyl);

(L) –NH-S(O)$_2$-alkyl;

(M) –NH-C(O)-C(=CH_2)CH_2(CH_3)$_2$;

(N) –NH-C(O)-C(O)-CH_2(CH_3)$_2$;

(O) alkyl; and

(P) aryl;

Q^C is selected from the group consisting of:

(A) heteroaryl;

(B) heterocycloalkyl;

(C) H;

(D) alkyl;

(E) –C(O)N(R^{12})$_2$;

(F) cycloalkyl;

(G) halo;

(H) –CN;

(I) -CF_3;

(J) –CH_2CF_3;

(K) –SR^A wherein R^A is selected from the group consisting of: alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, and aryl;

(L) –$N(R^B)_2$ wherein each R^B is independently selected from the group consisting of: H, alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, and aryl;

(M) –OR^A wherein R^A is as defined above;

(N) –$C(O)R^A$ wherein R^A is as defined above;

(O) aryl;

(P) arylalkyl-;

(Q) heteroarylalkyl-;

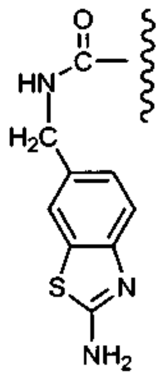
(R) substituted aryl and wherein there are 1 to 3 substituents on said substituted aryl;

(S) substituted heteroaryl;

(T) substituted heteroarylalkyl;

(U) substituted aralkyl;

(V)



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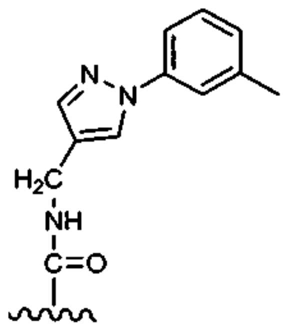
(W)



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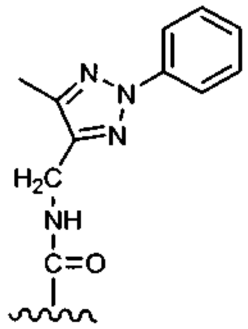
(X)



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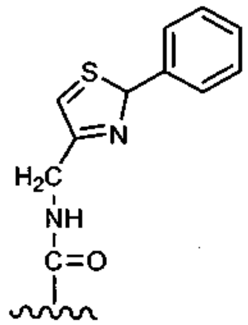
(Y)



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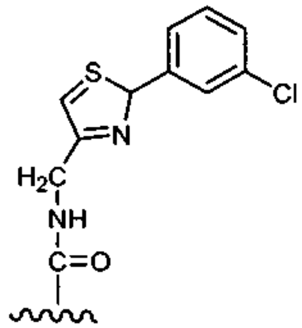
(Z)



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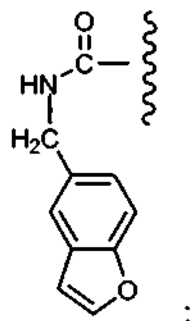

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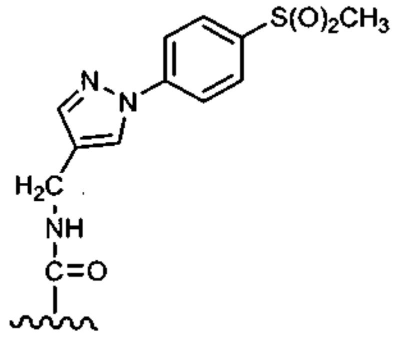

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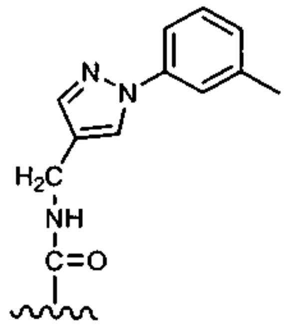


;

Q^D is selected from the group consisting of: H and alkyl;

R^1 and R^2 are each independently selected from the group consisting of:

(1) H;

(2) unsubstituted –(alkylene)$_{1-6}$-benzoheteroaryl;

(3) substituted –(alkylene)$_{1-6}$-benzoheteroaryl, and wherein:

(a) either the alkylene or benzoheteroaryl moieties are substituted, or both the alkylene and benzoheteroaryl moieties are substituted,

(b) when the alkylene moiety is substitued the substitutents are independently selected from the group consisting of: alkyl, cycloalkyl, -C(O)OH, -C(O)Oalkyl, and wherein the substituted alkylene moieties comprise R or S stereochemical centers, and

(c) when the benzoheteroaryl moiety is substituted the substituents are independently selected from the group consisting of: (1) –NH_2, (2) -NH(alkyl), (3) -NHC(O)(alkyl), (4) alkyl, (5) –S(alkyl), and (6) heteroaryl;

(4) unsubstituted –(alkylene)$_{1-6}$-heteroaryl;

(5) substituted –(alkylene)$_{1-6}$-heteroaryl substituted with one or more substitutents independently selected from the group consisting of: halo, -C(O)N(R^6)$_2$,

and $-NHS(O)_2R^7$, wherein each R^6 is independently selected from the group consisting of H and alkyl, and wherein R^7 is alkyl;

(6) unsubstituted –benzoheteroaryl;

(7) substituted –benzoheteroaryl, and wherein said substituted benzoheteroaryl is substituted with one or more substitutents independently selected from the group consisting of: heteroaryl, heterocycloalkyl, and –S(alkyl);

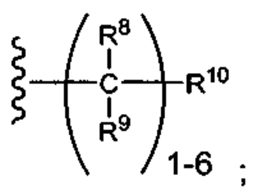
(8) heteroaryl;

(9) substituted heteroaryl substituted with one or more substitutents independently selected from the group consisting of: heteroaryl, heterocycloalkyl, and–S(alkyl);

(10) aryl;

(11) substituted aryl substituted with one or more substitutents independently selected from the group consisting of: heteroaryl, heterocycloalkyl, and –S(alkyl);

(12)



(13) unsubstituted $-(\text{alkylene})_{1\text{-}6}$-heterocycloalkyl;

(14) substituted $-(\text{alkylene})_{1\text{-}6}$-heterocycloalkyl, and wherein said substituted moiety (14) is substituted with one or more substituents selected from the group consisting of $-SO_2R^{13}$, and wherein R^{13} is selected from the group consisting of:

(a) alkyl,

(b) aryl,

(c) substituted aryl,

(d) heteroaryl,

(e) substituted heteroaryl,

(f) $-(\text{alkylene})_{1\text{-}6}$heterocylcoalkyl,

(g) $-(\text{alkylene})_{1\text{-}6}$-heteroaryl,

(h) $-C(O)R^{11}$,

(i) –C(O)aryl,

(j) –(alkylene)$_{1-6}$N(R^{12})$_2$, and

(k) wherein said substituted groups (c) and (e) of said moiety (14) are independently substituted with one or more substitutents independently selected from the group consisting of: (i) halo, (ii) –OH, (iii) –OR^{11}, (iv) –CF$_3$, (v) –S(O)$_2$R^{11}, and (vi) –S(O)$_2$N(R^{12})$_2$;

(15) –(alkylene)$_{1-6}$-bicyclic bridged cycloalkyl;

(16) –(alkylene)$_{1-6}$-bicyclic bridged heterocycloalkyl;

(17) –(alkylene)$_{1-6}$-bicyclic bridged spirocycloalkyl;

(18) –(alkylene)$_{1-6}$-bicyclic bridged spiroheterocycloalkyl;

(19) –(alkylene)$_{1-6}$-(substituted heteroaryl) wherein the substituents on said heteroaryl are independently selected from the group consisting of: -C(O)N(R^{12})$_2$ wherein each R^{12} is independently selected, -NHS(O)$_2$-alkyl;

(20) –cycloalkyl-benzodioxolyl;

(21) –cycloalkyl-(substituted aryl) wherein the substituents are independently selected from the group consisting of methylene dioxy and –S(O)$_2$CH$_3$;

(22) alkyl;

(23) cycloalkyl;

(24) alkyl;

(25) hydroxyl substituted alkyl;

R^8 and R^9 are each independently selected from the group consisting of: H, alkyl, cycloalkyl, C(O)OH, -C(O)OR^{11}, substituted alkyl and substituted cycloalkyl;

R^{10} is selected from the group consisting of:

(a) aryl (e.g., phenyl),

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(e) benzoheteroaryl,

(f) heterocycloalkyl,

(g) substituted heterocycloalkyl,

(h) –piperidinyl-S(O)$_2$-(alkyl substituted heteroaryl),

(i) –piperidinyl-S(O)$_2$-aryl-heteroaryl),

(j) –piperidinyl-C(O)-pyridyl,

(k) –piperidinyl-C(O)-alkyl,

(l) –piperidinyl-(substituted aryl) wherein said substituents are independently selected from the groups consisting of: halo and CN,

(m) –piperidinyl-pyridyl,

(n) benzodioxolyl,

(o) –heteroaryl-NH-cycloalkylalkyl, and

(p) –heteroaryl-NH-cycloalkyl;

wherein said substituted R^8, R^9 and R^{10} groups are substituted with one or more substitutents independently selected from the group consisting of:

(a) halo,

(b) –OH,

(c) $-OR^{11}$,

(d) $-CF_3$,

(e) heterocycloalkyl,

(f) substituted heterocycloalkyl,

(g) heteroaryl,

(h) substituted heteroaryl,

(i) aryl,

(j) substituted aryl,

(k) $-C(O)OR^{11}$,

(l) $-N(R^{12})_2$,

(m) alkyl,

(n) cycloalkyl,

(o) $-SO_2R^{11}$,

(p) –N(alkyl)-cycloalkyl,

(q) –C(O)OH,

(r) benzoheteroaryl, and

(s) substituted benzoheteroaryl,

and wherein said substituted groups (f), (h), and (j) are independently substituted with one or more substitutents independently selected from the group consisting of:

(i) halo,

(ii) –OH,

(iii) $-OR^{11}$,

(iv) $-CF_3$,

(v) $-S(O)_2R^{11}$,

(vi) $-S(O)_2N(R^{12})_2$,

(vii) =O,

(viii) substituted benzoheteroaryl substituted with 1 to 3 groups independently selected from the group consisting of: C_1 to C_6 alkyl, cycloalkyl, $-NH_2$, $-NH(C_1$ to C_6 alkyl), and $-N(C_1$ to C_6 alkyl$)_2$ wherein each alkyl is independently selected,

(ix) alkyl,

(x) CN,

(xi) cycloalkyl,

(xii) –C(O)-morpholinyl,

(xiii) amino,

(xiv) alkylamino,

(xv) and dialkylamino;

R^{11} is alkyl;

each R^{12} is independently selected from the group consisting of H, alkyl, and hydroxyl substituted alkyl;

each R^{14} is independently selected from the group consisting of: H, $-C(O)-(CH_2)_{1-2}$-aryl, substituted aryl, and benzodioxyl, and wherein said substituted aryl is substituted with one or more substituents independently selected from the group consisting of: halo, -OH, $-OR^{11}$ (wherein R^{11} is as previously described), -CN, $-CF_3$, alkyl, $-NH_2$ and $-NO_2$;

R^{15} and R^{16} are each independently selected from the group consisting of:

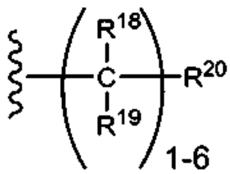
(1) hydroxyl substituted alkyl,

(2) alkyl,

(3) $-SO_2R^{11}$,

(4) unsubstituted $-(\text{alkylene})_{1-6}-R^{17}$ wherein R^{17} is selected from the group consisting of: (a) heterocycloalkyl, (b) heteroaryl, and (c) cycloalkyl,

(5)



,

(6) –C(O)-alkyl,

(7) substituted alkyl wherein said substituents are selected from the group consisting of $-OR^{11}$,

(8) saturated bicyclic rings,

(9) hydroxyl substituted $-(alkylene)_{1-6}$-cycloalkyl,

(10) H,

(11) heterocycloalkyl substituted with heterocycloalkyl,

(12) cycloalkyl, and

(13) cycloalkyl substituted with 1 to 2 –OH groups,

(14) $-(alkylene)_{1-6}$-aryl,

(15) $-(alkylene)_{1-6}$-aryl substituted with 1 to 2 substituents independently selected from the group consisting –OH and alkylamino,

(16) $-(alkylene)_{1-6}$-heteroaryl substituted with 1 to 2 substituents independently selected from the group consisting –OH and alkylamino;

(17) heterocycloalkyl,

(18) substituted heterocycloalkyl,

(19) $-(alkylene)_{1-6}$-heterocycloalkyl wherein said alkylene moiety is substituted with hydroxyl,

(20) $-(alkylene)_{1-6}$-C(O)OH,

(21) fused hydroxyl substituted benzocycloalkyl

(22) fused hydroxyl substituted arylheteroaryl,

(23) hydroxyl-$(alkylene)_{1-6}$-cycloalkyl,

(24) hydroxyl-$(alkylene)_{1-6}$-bridged cycloalkyl,

(25) hydroxyl-$(alkylene)_{1-6}$-spirocycloalkyl,

(26) hydroxyl-$(alkylene)_{1-6}$-bridged heterocycloalkyl,

(27) hydroxyl-$(alkylene)_{1-6}$-spiroheterocycloalkyl, and

(28) heterocycloalkyl;

each R^{18} and each R^{19} is independently selected from the group consisting of: H, alkyl, and hydroxyalkyl-;

R^{20} is selected from the group consisting of:

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) benzo fused heteroaryl,

(e) –(alkylene)$_{1-6}$-heteroaryl,

(f) –(alkylene)$_{1-6}$aryl,

(g) –(alkylene)$_{1-6}$aryl substituted with –OH,

(h) benzoheteroaryl-(alkylene)$_{1-6}$-,

(i) cycloalkylalkyl,

(j) cycloalkyl (e.g., hexyl),

(k) heterocycloalkyl,

(l) –(alkylene)$_{1-6}$aryl substituted with halo,

(m) -(alkylene)$_{1-6}$-S-alkyl,

(n) -(alkylene)$_{1-6}$-O-alkyl,

(o) -(alkylene)$_{1-6}$-N-alkyl,

(p) -(alkylene)$_{1-6}$-cycloalkyl,

and wherein said substituted aryl is substituted with one or more substituents independently selected from the group consisting of: halo, -OH, -OR^{11}, -CN, -CF_3, alkyl, -NH_2 and –NO_2;

R^{21} is selected from the group consisting of:

(1) heterocycloalkyl,

(2) benzo fused cycloalkyl,

(3) cycloalkyl,

(4) multicyclic cycloalkyl ring, and

(5) substituted heterocycloalkyl substituted with one or more substituents independently selected from the group consisting of: (a) hydroxyl substituted alkyl, (b) -OH, (c) -(alkylene)$_{1-6}$C(O)O-(alkyl)$_{1-6}$, (d) aryl, and (e) substituted aryl wherein said substituted aryl is substituted with one or more substitutents independently selected from the group consisting of: halo, and

(6) heterocycloalkyl substituted with 1 to 3 substituents selected from the group consisting of: amino, alkylamino, dialkylamino, and –C(O)alkyl,

(7) heterocycloalkyl,

(8) hydroxy substituted heterocycloalkyl), and

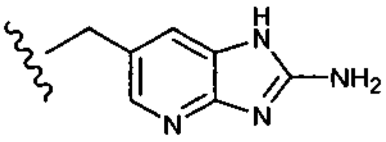
(9) –OH.

2. The compound of Claim 1 wherein K is CH.

3. The compound of Claim 1 wherein L is CH.

4. The compound of Claim 1 wherein K is CH and L is CH.

5. The compound of Claim 1 wherein one of R^1 and R^2 is H, and the other is selected from the group consisting of: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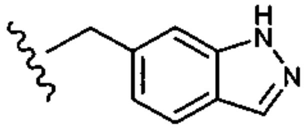
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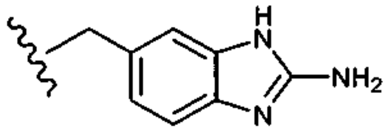
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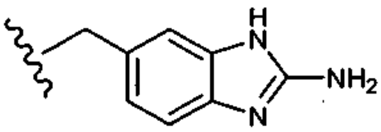
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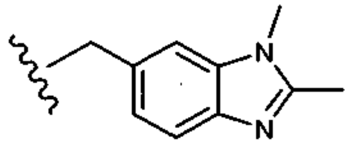
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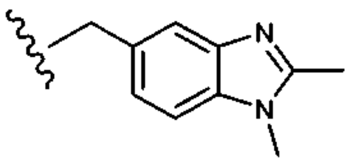
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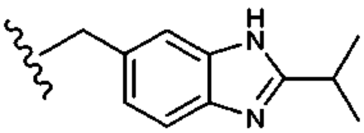
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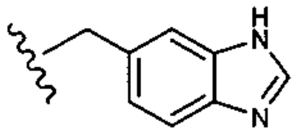
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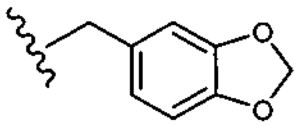
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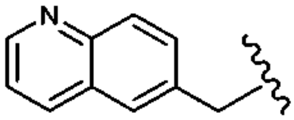
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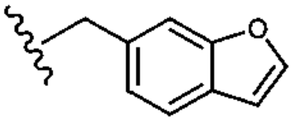
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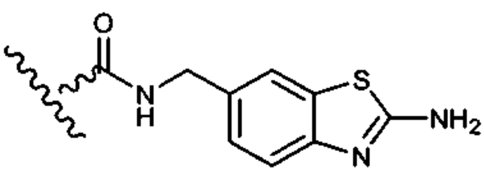
6. The compound of Claim 1 wherein Q^A is selected from the group consisting of: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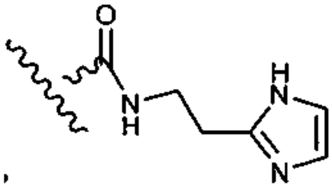
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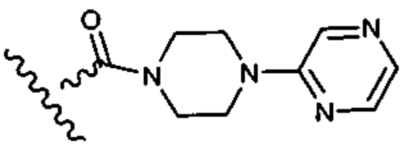
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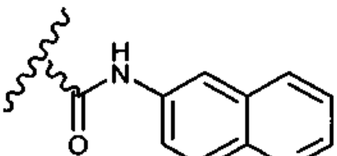
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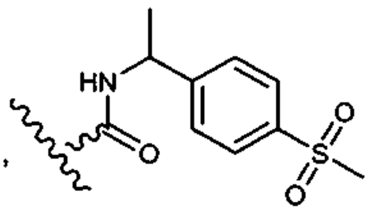
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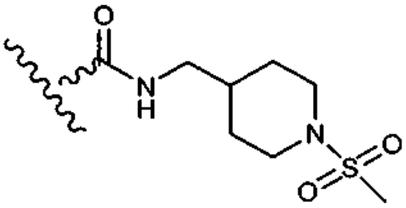
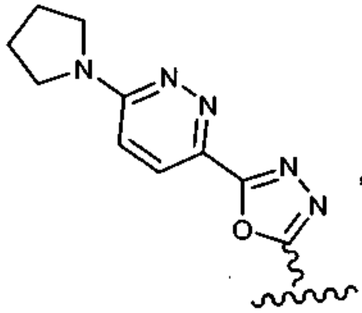
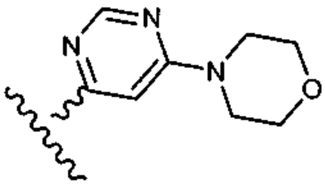
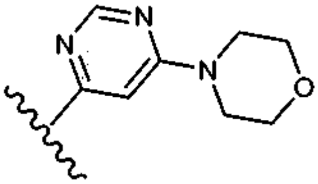
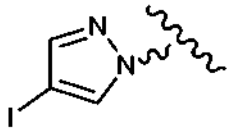
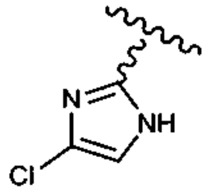
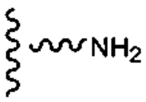
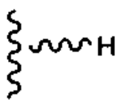
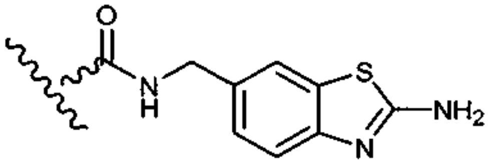
, , ,

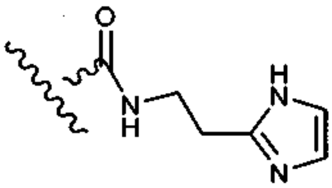
, , ,

 and .

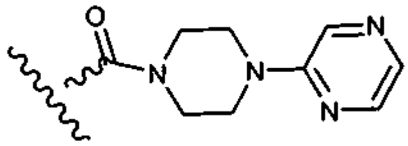
7. The compound of Claim 1 wherein Q^A is:

.

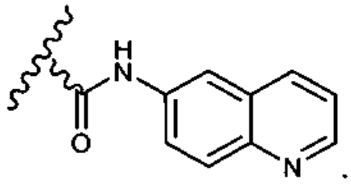
8. The compound of Claim 1 wherein Q^A is:

.

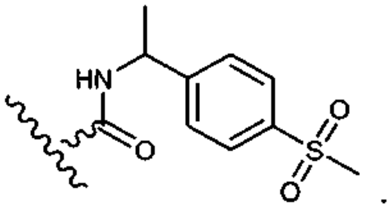
9. The compound of Claim 1 wherein Q^A is:

.

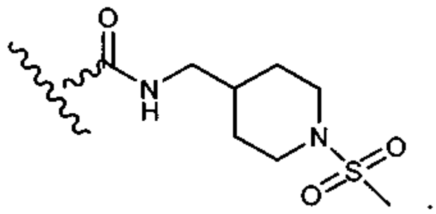
10. The compound of Claim 1 wherein Q^A is:



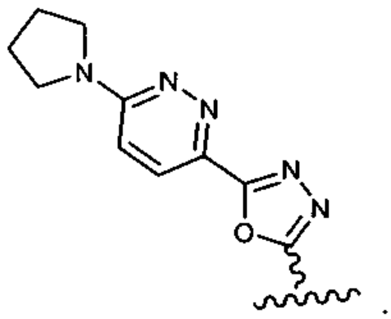
11. The compound of Claim 1 wherein Q^A is:



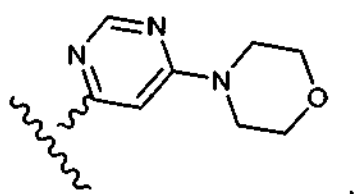
12. The compound of Claim 1 wherein Q^A is:



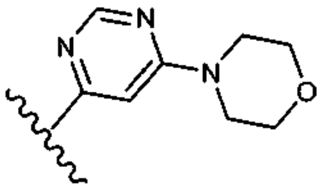
13. The compound of Claim 1 wherein Q^A is:



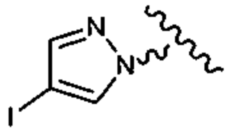
14. The compound of Claim 1 wherein Q^A is:



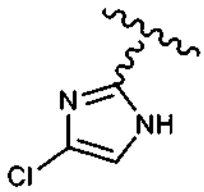
15. The compound of Claim 1 wherein Q^A is:



16. The compound of Claim 1 wherein Q^A is:



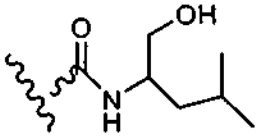
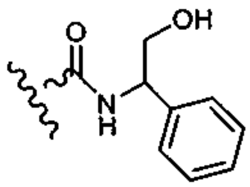
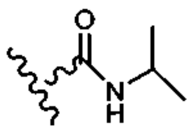
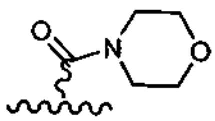
17. The compound of Claim 1 wherein Q^A is:

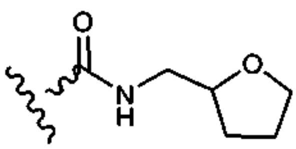
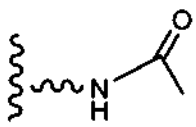
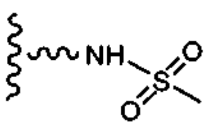


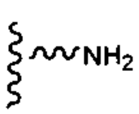
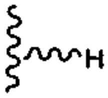
18. The compound of Claim 1 wherein Q^A is $-NH_2$.

19. The compound of Claim 1 wherein Q^A is H.

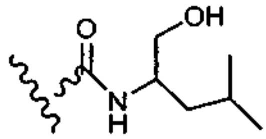
20. The compound of Claim 1 wherein Q^B is selected from the group consisting of:

, , , ,

, , , ,

 and .

21. The compound of Claim 1 wherein Q^B is: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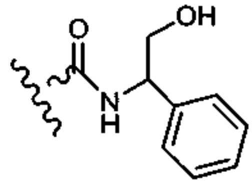
22. The compound of Claim 1 wherein Q^B is: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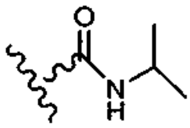
23. The compound of Claim 1 wherein Q^B is: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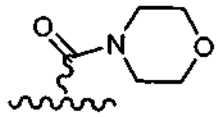
24. The compound of Claim 1 wherein Q^B is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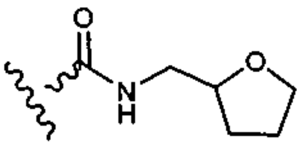
25. The compound of Claim 1 wherein Q^B is: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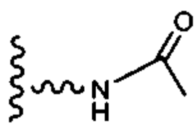
26. The compound of Claim 1 wherein Q^B is: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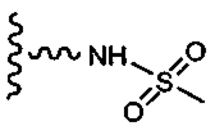
27. The compound of Claim 1 wherein Q^B is: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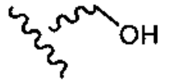
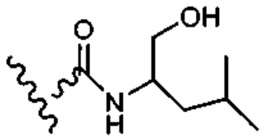
28. The compound of Claim 1 wherein Q^B is:



.

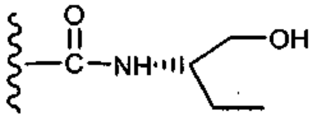
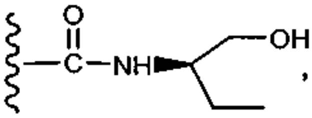
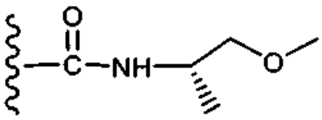
29. The compound of Claim 1 wherein Q^B is $-NH_2$.

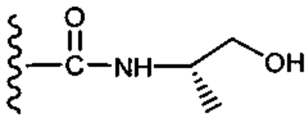
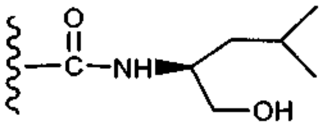
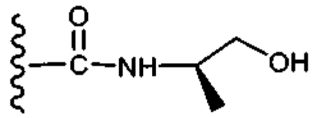


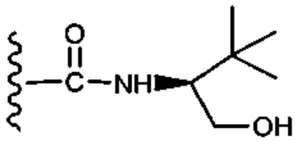
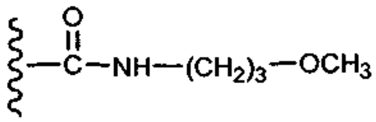
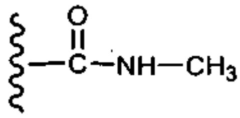
.

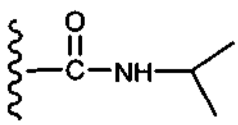
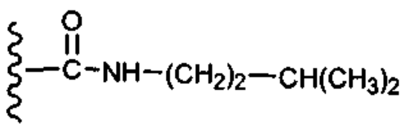
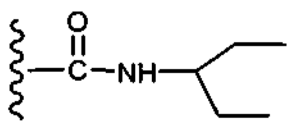
30. The compound of Claim 1 wherein Q^B is H.

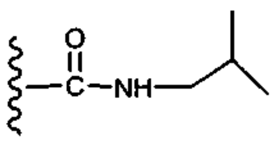
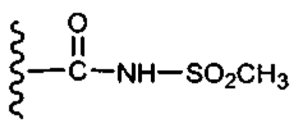
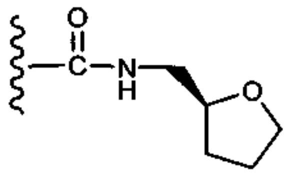
31. The compound of Claim 1 wherein Q^B is selected from the group consisting of:

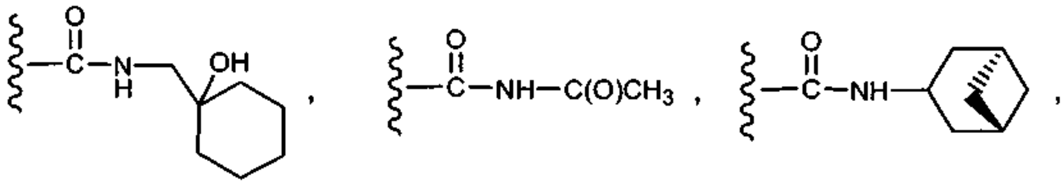
 ,  ,  ,

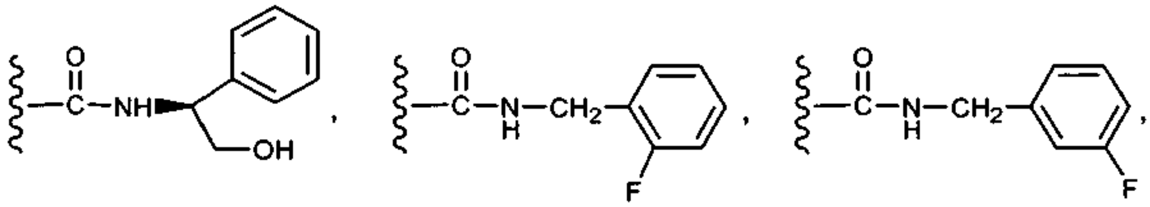
 ,  ,  ,

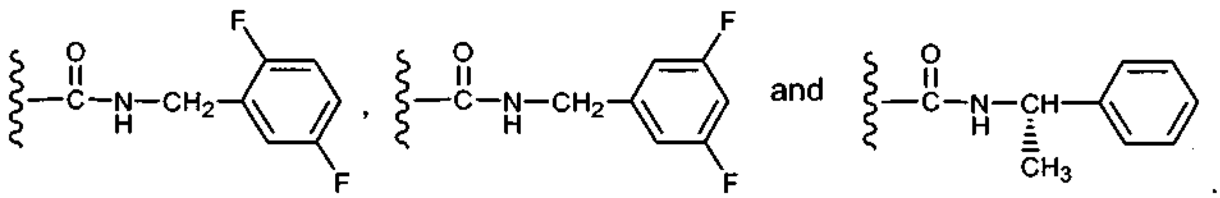
 ,  ,  ,

 ,  ,  ,

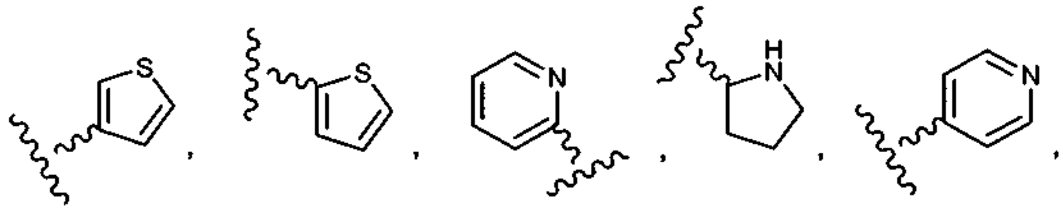
 ,  ,  ,

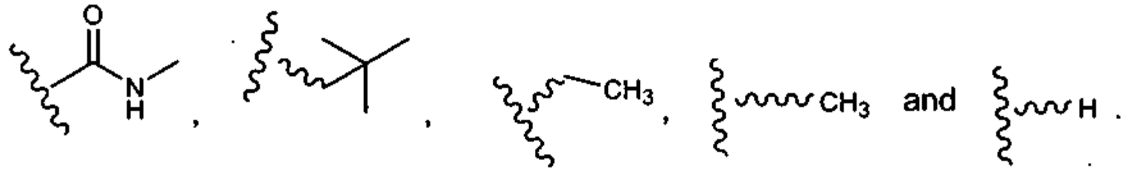




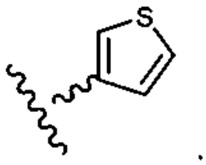


32. The compound of Claim 1 wherein Q^C is selected from the group consisting of:





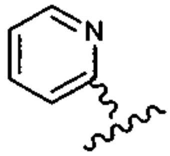
33. The compound of Claim 1 wherein Q^C is:



34. The compound of Claim 1 wherein Q^C is:

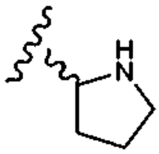
.

35. The compound of Claim 1 wherein Q^C is:



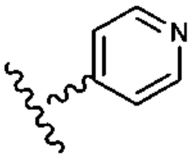
.

36. The compound of Claim 1 wherein Q^C is:



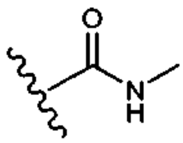
.

37. The compound of Claim 1 wherein Q^C is:



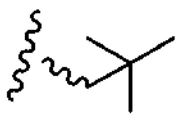
.

38. The compound of Claim 1 wherein Q^C is:



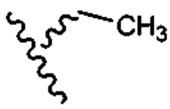
.

39. The compound of Claim 1 wherein Q^C is:



.

40. The compound of Claim 1 wherein Q^C is:



.

41. The compound of Claim 1 wherein Q^C is $-CH_3$.

42. The compound of Claim 1 wherein Q^C is H.

43. The compound of Claim 1 wherein said compound is selected from the group consisting of Compound Numbers: 13-94, 97-101, 111-125, 130, 131, 139, 140, 150, 154-158, 162, 167, 170-246, 271-289, 291-303, 305-307, 321-324, 326-328, 350-354, 404-410, 444-506, 542-546, 573-576, 578, 584, 588, 590, 593, 597, 598-600, 605-629, 635, 647, 650-652, 659, 664-665, 673-680, 686, 691, 692, 699, 703, 720-727, 734, 736, 740-743, 755, 756, 762-776, 780, 784, and 791-794.

44. The compound of Claim 1 wherein said compound is selected from the group consisting of: Compound Numbers: 14, 16, 17, 22, 46, 47, 48, 56, 69, 93, 94, 111-115, 117, 118, 130, 131, 139, 140, 150, 154, -158, 204-206, 209, 213, 215-220, 224, 238, 242, 274, 277, 279, 280, 283, 285, 291, 292, 296, 298, 299, 300, 301, 305, 306, 307, 323, 324, 326, 327, 405, 445, 451, 452, 453, 456, 457, 460-466, 471, 472, 477, 478, 479, 480, 481, 483, 484, 485, 489, 490, 491, 502, 542, 543, 544, 545, 593, 598, 599, 605, 623-629, 647, 650, 651, 652, and 664.

45. The compound of Claim 1 wherein said compound is selected from the group consisting of Compound Numbers: 14, 16, 112, 114, 139, 156, 216, 218, 219, 277, 296, 300, 306, 307, 463, 478, 479, 483, 485, 491, 502, 598, 629, 647, 650, 651, and 652.

46. The compound of Claim 1 wherein said compound is selected from the group consistint of: Compound Numbers: 112, 478, 479, 502, 629, 651, and 652.

47. A pharmaceutical composition comprising an effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

48. A method of treating a JNK1 mediated disease or condition in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound of Claim 1.

49. A method of treating a ERK mediated disease or condition in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound of Claim 1.

50. A method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound of Claim 1.

51. A method of treating a disease or condition in a patient in need of such treatment comprising administereing to said patient an effective amount of at least one compound of Claim 1, and wherein said disease or condition is selected from the group consisting of: inflammation, rheumatoid arthritis, asthma, multiple sclerosis, inflammatory bowel disease, psorisis, diabetes, autoimmune disorders, metabolic diseases, neurological diseases, pain and cardiovascular diseases.

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Full Paper

Synthesis and Antituberculosis Activity of New Hydrazide Derivatives

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The increasing clinical importance of drug-resistant mycobacterial pathogens, especially *Mycobacterium tuberculosis*, has lent additional urgency to microbiological research and new antimycobacterial compound development. For this purpose, new hydrazide derivatives of imidazo[1,2-a]pyridine were synthesized and evaluated for antituberculosis activity. The reaction of 2-[(2-carboxyimidazo[1,2-*a*]pyridine-3-yl)sulfanyl]acetic acid hydrazide with various benzaldehydes gave *N*-(arylidene)-2-[(2-carboxyimidazo[1,2-*a*]pyridine-3-yl)sulfanyl]acetic acid hydrazide derivatives. The chemical structures of the compounds were elucidated by IR, ^{1}H-NMR, FAB-MS spectral data and elemental analysis. Antituberculosis activities of the synthesized compounds were determined by broth microdilution assay, the Microplate Alamar Blue Assay in BACTEC 12B medium. The results were screened *in vitro,* using the BACTEC 460 Radiometric System against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) at 6.25 μg/mL; the tested compounds showed significant inhibition.

Keywords: Antituberculosis activity / Hydrazide / Imidazo[1,2-*a*]pyridine

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Introduction

Tuberculosis (TB) has re-emerged both in industrial and developing countries [1–3]. Further contributing to the increased morbidity is the emergence of new strains of *Mycobacterium tuberculosis* resistant to some or all currently used antitubercular drugs [4, 5]. Particularly multidrug-resistant TB (MDR-TB) is alarming. The standard TB therapy is non-effective in controlling MDR-TB in high MDR-TB incidence areas [6]. There is great fear that the TB situation may get even worse with the spread of HIV worldwide [1] and this is one among other reasons for an urgent need to develop new TB drugs. The Alliance aims to get improved TB drugs to those who need them, drugs, which shorten or simplify treatment of TB or provide a more effective treatment of multidrug-resistant TB; or improve the treatment of latent TB infection or some combination of these [7]. As medicinal chemists, we may handle the problem of obtaining new TB drugs for a fast and better treatment, in two approaches: (i) synthesis of analogues, obtained by modifying or derivating existing chemical structures; (ii) and in case of the multidrug-resistant TB treatment, building the anti-TB strategy on the novelty of the chemical structure for the benefical advantage that the TB organism has not the chance to develop resistant [7, 8].

The heterocyclic hydrazones constitute an important class of biologically active drug molecules, which have attractive attention of medicinal chemists due to their antituberculosis activities [9–12]. On the other hand, a lot of studies were carried out on heterocyclic systems bearing an alkylsulfanyl group as a pharmacophore for antituberculosis activity. QSAR calculations carried out on various types of heterocycles proved that the activity is enhanced with electron-withdrawing substituents. An alkylsulfanyl group bound to an electron-deficient car-

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Abbreviations: growth index (GI); multidrug-resistant TB (MDR-TB); (quantitative) structure-activity relationship ((Q)SAR)

Table 1. Some characteristics of the compounds.

Compound	R_1	R_2	R_3	Yield (%)	Mp. (°C)	M.W.	Formula
IIIa	H	H	Cl	75	192–193	388	$C_{17}H_{13}ClN_4O_3S$
IIIb	H	H	CH_3	72	138–140	368	$C_{18}H_{16}N_4O_3S$
IIIc	H	H	OCH_3	68	160–162	384	$C_{18}H_{16}N_4O_4S$
IIId	H	H	NO_2	75	186–188	399	$C_{17}H_{13}N_5O_5S$
IIIe	CH_3	H	Cl	68	210–212	402	$C_{18}H_{15}ClN_4O_3S$
IIIf	CH_3	H	CH_3	73	190–191	382	$C_{19}H_{18}N_4O_3S$
IIIg	CH_3	H	NO_2	70	226–227	413	$C_{18}H_{15}N_5O_5S$
IIIh	H	CH_3	Cl	74	148–150	402	$C_{18}H_{15}ClN_4O_3S$
IIIi	H	CH_3	CH_3	69	136–137	382	$C_{19}H_{18}N_4O_3S$

bon atom in various heterocycles is responsible for antimycobacterial activity [13–16].

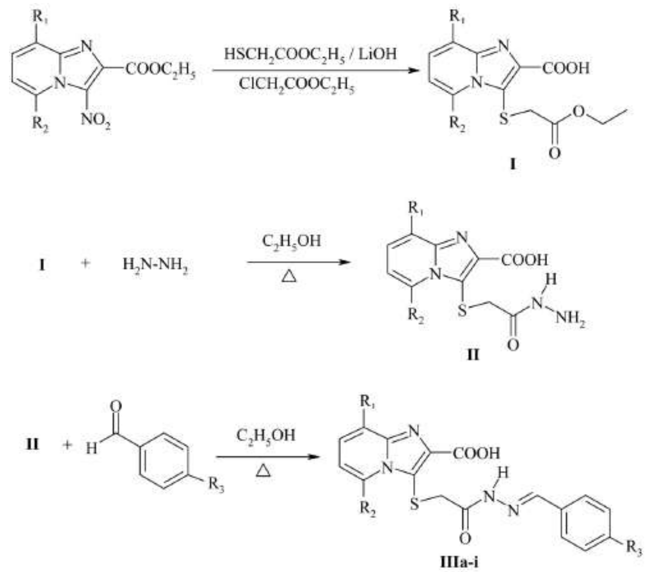
In view of these data, we aimed at the synthesis and antituberculosis evaluations of new *N*-(benzylidene)-2-[(2-carboxyimidazo[1,2-*a*]pyridine-3-yl)sulfanyl]acetic acid hydrazide derivatives. We have chosen imidazo[1,2-*a*]pyridines, which have emerged as potentially interesting drugs, particularly with regard to their antituberculosis activity [17] among the various heterocycles that have attracted the attention as potential antitubercular agents as the basic heterocyclic moiety.

Results and discussion

In this present work, a series of nine new compounds were synthesized. Scheme 1 illustrates the way used for the preparation of target compounds. As starting materials, ethyl 3-nitroimidazo[1,2-*a*]pyridine-2-yl carboxylates were used to produce ethyl 2-[(2-carboxyimidazo[1,2-*a*]pyridine-3-yl)sulfanyl]acetates. The 2-[(2-carboxyimidazo[1,2-*a*]pyridine-3-yl)sulfanyl]acetic acid hydrazides **II** were prepared by reacting ethyl 2-[(2-carboxyimidazo[1,2-*a*]pyridine-3-yl)sulfanyl]acetates **I** with hydrazine hydrate. The condensation of the acid hydrazides with appropriate benzaldehydes resulted in the formation of *N*-(arylidene)-2-[(2-carboxyimidazo[1,2-*a*]pyridine-3-yl)sulfanyl]acetic acid hydrazide derivatives **IIIa–i**. Some characteristics of the synthesized compounds are shown in Table 1.

The structures of the obtained compounds were elucidated by spectral data. In the IR spectra, some significant stretching bands due the N-H, C=O, C=N and C-O-C were at about 3220–3195 cm^{-1}, 1670–1645 cm^{-1}, 1605–1545 cm^{-1} and 1250–1210 cm^{-1}, respectively.

In the ^{1}H-NMR spectra, the signal due to S-CH_2 protons and N=CH proton present in all compounds, appeared at 3.75–3.90 ppm and 8.40–8.60 ppm as singlet, respectively. The NH proton was observed at 12.00–12.40 ppm



Scheme 1. Synthesis of the *N*-(arylidene)-2-[(2-carboxyimidazo[1,2-*a*]pyridine-3-yl)sulfanyl]acetic acid hydrazide derivatives **IIIa–i**.

as a doublet. All the other aromatic and aliphatic protons were observed at the expected regions. All compounds gave satisfactory elemental analyses. Mass spectra (MS (FAB)) of the compounds showed a [M+1] peaks in agreement with their molecular weight.

The antituberculosis activities of the synthesized compounds were screened *in vitro* using a BACTEC 460 radiometric system against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) at 6.25 µg/mL. Rifampicin was used as the test standard. All of the tested compounds showed significant antituberculosis activity as can be inferred from Table 2. The compounds **IIId** and **IIIg** which the 4-nitrobenzylidene derivatives showed the highest inhibitions with 68%. Other compounds showed varying inhibition values between 45–53%.

SAR observation showed that 4-nitro substitution on benzylidene affects the activity.

Table 2. Antituberculosis activity of the compounds.

Compound	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg	IIIh	IIIi	Rifampicin
MIC (μg/mL)	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25	0.25
Inhibition (%)	45	50	48	68	52	47	68	53	49	98

The authors are thankful to the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) in the USA for the in-vitro evaluation of antimycobacterial activity.

The authors have declared no conflict of interest.

Experimental

Chemistry

All reagents were purchased from commercial suppliers and were used without further purification. Melting points were determined by using an Electrothermal 9100 digital melting point apparatus (Barnstead International, Dubuque, IA, USA) and were uncorrected. The compounds were checked for purity by TLC on silica gel 60 F_{254} (Merck, Darmstadt, Germany). Spectroscopic data were recorded on the following instruments: Elemental analyses were performed on a Perkin Elmer EAL 240 elemental analyser (Perkin Elmer, Wellesley, MA, USA), IR (ν, cm^{-1}), Shimadzu 435 IR spectrophotometer (Shimadzu, Tokyo, Japan); ^{1}H-NMR spectra (δ, ppm, Hz) were recorded on a Bruker 250 MHz spectrometer (Bruker, Billerica, MA, USA) in DMSO-d_6 with TMS as an internal standard. MS-FAB$^+$ was recorded on VG Quattro mass spectrometer (Agilent Technologies, Santa Clara, CA, USA).

General procedure for synthesis of the compounds Ethyl 2-[(2-carboxyimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetates I

These compounds were prepared as starting materials in accordance with the method described in the literature [18].

2-[(2-Carboxyimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazides II

These compounds were prepared according to the literature, by reacting ethyl 2-[(2-carboxyimidazo[1,2-*a*]pyridine-3-yl)sulfanyl]acetates **I** with hydrazine hydrate [19].

N-(arylidene)-2-[(2-carboxyimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazides IIIa–i

Equimolar quantities of acid hydrazides **II** (30 mmol) and appropriate benzaldehydes in 25 mL of absolute ethanol were refluxed for 3-5 h. The resulting solid was filtered and recrystallized from ethanol. **IIIa–i**: IR (KBr, cm^{-1}): 3195–3220 (NH), 1645–1670 (CO), 1605–1545 (C=N) and (C=C), 1250–1210 (C-O-C).

N-(4-chlorobenzylidene)-2-[(2-carboxyimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazide IIIa

^{1}H-NMR (250 MHz, DMSO-d_6, δ ppm): 3.85 (s, 2H, S-CH_2), 7.15–7.80 (m, 7H, aromatic protons), 8.60 (s, 1H, N=CH), 8.70–8.85 (m, 1H, aromatic proton), 12.10 (s, 1H, NH). MS (FAB) [M+1]: *m/z* 389. Anal. Calc. for $C_{17}H_{13}ClN_4O_3S$:C, 52.51; H, 3.37; N, 14.41. Found: C, 52.53; H, 3.39; N, 14.43.

N-(4-methylbenzylidene)-2-[(2-carboxyimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazide IIIb

^{1}H-NMR (250 MHz, DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3), 3.80 (s, 2H, S-CH_2), 7.10–7.85 (m, 7H, aromatic protons), 8.55 (s, 1H, N=CH), 8.60–8.80 (m, 1H, aromatic proton), 12.00 (s, 1H, NH). MS (FAB) [M+1]: *m/z* 369. Anal. Calc. for $C_{18}H_{16}N_4O_3S$:C, 58.68; H, 4.38; N, 15.21. Found: C, 58.73; H, 4.39; N, 15.20.

N-(4-methoxybenzylidene)-2-[(2-carboxyimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazide IIIc

^{1}H-NMR (250 MHz, DMSO-d_6, δ ppm): 3.80 (s, 2H, S-CH_2), 3.90 (s, 3H, OCH_3), 7.05–7.75 (m, 7H, aromatic protons), 8.45 (s, 1H, N=CH), 8.60–8.70 (m, 1H, aromatic proton), 12.15 (s, 1H, NH). MS (FAB) [M+1]: *m/z* 385. Anal. Calc. for $C_{18}H_{16}N_4O_4S$:C, 56.24; H, 4.20; N, 14.57. Found: C, 56.21; H, 4.25; N, 14.60.

N-(4-nitrobenzylidene)-2-[(2-carboxyimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazide IIId

^{1}H-NMR (250 MHz, DMSO-d_6, δ ppm): 3.85 (s, 2H, S-CH_2), 7.10–7.80 (m, 3H, imidazopyridine protons), 8.00 (d, *J* = 8.76 Hz, 2H, aromatic protons), 8.35 (d, *J* = 8.78 Hz, 2H, aromatic protons), 8.70–8.85 (m, 2H, N=CH and imidazopyridine proton), 12.40 (s, 1H, NH). MS (FAB) [M+1]: *m/z* 400. Anal. Calc. for $C_{17}H_{13}N_5O_5S$:C, 51.13; H, 3.28; N, 17.54. Found: C, 51.15; H, 3.34; N, 17.51.

N-(4-chlorobenzylidene)-2-[(2-carboxy-8-methylimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazide IIIe

^{1}H-NMR (250 MHz, DMSO-d_6, δ ppm): 2.65 (s, 3H, CH_3), 3.95 (s, 2H, S-CH_2), 7.05–7.65 (m, 6H, aromatic protons), 8.50 (s, 1H, N=CH), 8.60–8.75 (m, 1H, aromatic proton), 12.00 (s, 1H, NH). MS (FAB) [M+1]: *m/z* 403. Anal. Calc. for $C_{18}H_{15}ClN_4O_3S$:C, 53.73; H, 3.73; N, 13.93. Found: C, 53.74; H, 3.72; N, 13.95.

N-(4-methylbenzylidene)-2-[(2-carboxy-8-methylimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazide IIIf

^{1}H-NMR (250 MHz, DMSO-d_6, δ ppm): 2.35 (s, 3H, phenyl-CH_3), 2.60 (s, 3H, CH_3), 3.75 (s, 2H, S-CH_2), 7.10–7.65 (m, 6H, aromatic protons), 8.45 (s, 1H, N=CH), 8.50–8.60 (m, 1H, aromatic proton), 12.05 (s, 1H, NH). MS (FAB) [M+1]: *m/z* 383. Anal. Calc. for $C_{19}H_{18}N_4O_3S$:C, 59.67; H, 4.74; N, 14.65. Found: C, 59.70; H, 4.72; N, 14.65.

N-(4-nitrobenzylidene)-2-[(2-carboxy-8-methylimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazide IIIg

^{1}H-NMR (250 MHz, DMSO-d_6, δ ppm): 2.55 (s, 3H, CH_3), 3.75 (s, 2H, S-CH_2), 7.00–8.20 (m, 6H, aromatic protons), 8.50–8.65 (m, 2H, N=CH and imidazopyridine proton), 12.10 (s, 1H, NH). MS (FAB) [M+1]: *m/z* 414. Anal. Calc. for $C_{18}H_{15}N_5O_5S$:C, 52.30; H, 3.66; N, 16.94. Found: C, 52.34; H, 3.69; N, 16.91.

N-(4-chlorobenzylidene)-2-[(2-carboxy-5-methylimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazide IIIh

^{1}H-NMR (250 MHz, DMSO-d_6, δ ppm): 2.75 (s, 3H, CH_3), 3.90 (s, 2H, S-CH_2), 7.00–7.70 (m, 6H, aromatic protons), 8.45 (s, 1H, N=CH), 8.50–8.70 (m, 1H, aromatic proton), 12.10 (s, 1H, NH). MS (FAB) [M+1]: *m/z* 403. Anal. Calc. for $C_{18}H_{15}ClN_4O_3S$:C, 53.73; H, 3.73; N, 13.93. Found: C, 53.65; H, 3.69; N, 13.94.

N-(4-methylbenzylidene)-2-[(2-carboxy-5-methylimidazo[1,2-a]pyridine-3-yl)sulfanyl]acetic acid hydrazide IIIi

^{1}H-NMR (250 MHz, DMSO-d_6, δ ppm): 2.30 (s, 3H, phenyl-CH_3), 2.75 (s, 3H, CH_3), 3.85 (s, 2H, S-CH_2), 7.15–7.65 (m, 6H, aromatic protons), 8.40 (s, 1H, N=CH), 8.45–8.65 (m, 1H, aromatic proton), 12.15 (s, 1H, NH). MS (FAB) [M+1]: *m/z* 383. Anal. Calc. for $C_{19}H_{18}N_4O_3S$:C, 59.67; H, 4.74; N, 14.65. Found: C, 59.65; H, 4.70; N, 14.60.

Microbiology

In-vitro evaluation of antimycobacterial activity against Mycobacterium tuberculosis $H_{37}Rv$

Antituberculotic activities of the compounds were tested at the center of Tuberculosis Antimicrobial Acquisiton & Coordinating Facility (TAACF). Compounds were tested for *in-vitro* antituberculosis activity against *Mycobacterium tuberculosis* H_{37}Rv (ATCC 27294) at 6.25 μg/mL, in BACTEC 12B medium using a broth microdilution assay, the Microplate Alamar Blue Assay (MABA). Compounds exhibiting fluorescence are tested in the BACTEC 460 Radiometric System [20].

BACTEC radiometric method of susceptibility testing

Inocula for susceptibility testing were either from a positive BACTEC isolation vial with a growth index (GI) of 500 and more, or suspension of organism isolated earlier on conventional medium. The culture was well mixed with a syringe and 0.1 mL of a positive BACTEC culture was added to each of the vials containing the test drugs. The drug vials contained rifampicin (0.25 μg/mL). A control vial was inoculated with a 1 : 100 microdilution of the culture. A suspension equivalent to a Mc-Farland No.1 standard was prepared in the same manner as a BACTEC positive vial, when growth from a solid medium was used. Each vial was tested immediately on a BACTEC instrument to provide CO_2 in the headspace. The vials were incubated at 37°C and tested daily with a BACTEC instrument. When the GI in the control read at least 30, the increase in GI (ΔGI) from the previous day in the control was compare with that in the drug vial. The following formula was used to interpret results:

$$\Delta\text{GI control} > \Delta\text{GI drug} = \text{Susceptible}$$

$$\Delta\text{GI control} < \Delta\text{GI drug} = \text{Resistant}$$

If a clear susceptibility pattern (the difference of ΔGI of control and the drug bottle) was not seen at the time, the control ΔGI is 30, the vials were read for one or two additional days to establish a definite pattern of ΔGI differences.

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PLoS MEDICINE

OPC-67683, a Nitro-Dihydro-Imidazooxazole Derivative with Promising Action against Tuberculosis In Vitro and In Mice

D5

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ABSTRACT

Background

Tuberculosis (TB) is still a leading cause of death worldwide. Almost a third of the world's population is infected with TB bacilli, and each year approximately 8 million people develop active TB and 2 million die as a result. Today's TB treatment, which dates back to the 1970s, is long and burdensome, requiring at least 6 mo of multidrug chemotherapy. The situation is further compounded by the emergence of multidrug-resistant TB (MDR-TB) and by the infection's lethal synergy with HIV/AIDS. Global health and philanthropic organizations are now pleading for new drug interventions that can address these unmet needs in TB treatment.

Methods and Findings

Here we report OPC-67683, a nitro-dihydro-imidazooxazole derivative that was screened to help combat the unmet needs in TB treatment. The compound is a mycolic acid biosynthesis inhibitor found to be free of mutagenicity and to possess highly potent activity against TB, including MDR-TB, as shown by its exceptionally low minimum inhibitory concentration (MIC) range of 0.006–0.024 μg/ml in vitro and highly effective therapeutic activity at low doses in vivo. Additionally, the results of the post-antibiotic effect of OPC-67683 on intracellular *Mycobacterium tuberculosis* showed the agent to be highly and dose-dependently active also against intracellular *M. tuberculosis* H37Rv after a 4-h pulsed exposure, and this activity at a concentration of 0.1 μg/ml was similar to that of the first-line drug rifampicin (RFP) at a concentration of 3 μg/ml. The combination of OPC-67683 with RFP and pyrazinamide (PZA) exhibited a remarkably quicker eradication (by at least 2 mo) of viable TB bacilli in the lung in comparison with the standard regimen consisting of RFP, isoniazid (INH), ethambutol (EB), and PZA. Furthermore, OPC-67683 was not affected by nor did it affect the activity of liver microsome enzymes, suggesting the possibility for OPC-67683 to be used in combination with drugs, including anti-retrovirals, that induce or are metabolized by cytochrome P450 enzymes.

Conclusions

We concluded that based on these properties OPC-67683 has the potential to be used as a TB drug to help combat the unmet needs in TB treatment.

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Abbreviations: BRM, bacterial reverse mutation; CFU, colony-forming unit; DMSO, dimethylsulfoxide; EB, ethambutol; HPLC, high-performance liquid chromatography; ICR, Institute of Cancer Research; INH, isoniazid; LTBI, latent tubercle bacilli infection; MDR-TB, multidrug-resistant tuberculosis; MIC, minimum inhibitory concentration; PZA, pyrazinamide; RFP, rifampicin; SM, streptomycin; TB, tuberculosis

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Introduction

Tuberculosis (TB) is still a leading cause of death worldwide [1]. Almost a third of the world's population is infected with TB bacilli, and each year approximately 8 million people develop active TB and 2 million die as a result [2]. Today's TB treatment, which dates back to the 1970s, is long and burdensome, requiring at least 6 mo of multidrug chemotherapy, typically consisting of rifampicin (RFP), isoniazid (INH), ethambutol (EB), and pyrazinamide (PZA) given under clinically observed conditions. The situation is further complicated by the emergence of multidrug-resistant TB (MDR-TB) and by the infection's lethal synergy with HIV/AIDS [3–6]. Patients with MDR-TB must be treated with a combination containing second-line drugs that are less effective, more expensive, and more toxic. TB's lethal synergy with HIV/AIDS puts HIV-positive individuals with latent tubercle bacilli infection (LTBI) at a 30× to 50× greater risk of developing active TB, giving rise to TB as the number one killer among patients with AIDS [6].

The pharmaceutical industry, however, has generally shown little interest in developing new, more effective drugs to address these needs, and, as a result, no new anti-TB agent with a novel mechanism of action has been launched since the introduction of RFP in 1966. Consequently, global health and philanthropic organizations are now pleading for new chemotherapy interventions that can shorten the total duration of therapy, provide improved efficacy against MDR-TB, safely treat patients co-infected with HIV/AIDS, and target LTBI [6,7].

We initiated a program to screen for potent anti-TB agents that have a new structure and mechanism able to inhibit the biosynthesis of mycolic acid, and found nitro-dihydro-imidazooxazole derivatives to exhibit such activity. Nitro-heterocyclic compounds, including various 5- and 2-nitro-imidazoles and 5-nitrofurans, are known to be effective against a variety of protozoan and bacterial infections in humans and animals [8]. These compounds, however, are also known to commonly possess mutagenicity. CGI-17341 (Figure 1), a nitroimidazooxazole derivative, has been reported to have anti-tubercular activity [9,10], but the compound was not developed because of its mutagenic properties. We focused our search on new nitro-dihydro-imidazooxazoles with anti-tubercular activity that had no mutagenicity by performing the bacterial reverse mutation (BRM) test [11]. About 95% of the compounds we screened earlier that had mono- or di-alkyl substituents at 2-position were mutagenic. However, after introducing heteroatoms to the substituent, we were able to successfully decrease the mutagenicity rate to 16%. Among the non-mutagenic derivatives, we found OPC-67683 to have potent anti-TB activity. We then further evaluated OPC-67683 to determine whether the compound could help address the unmet needs of TB treatment.

Methods

Culture Medium

Cultures of *Mycobacterium tuberculosis* and *M. bovis* BCG were grown in Middlebrook 7H9 broth (BBL, http://www.bd.com) and Middlebrook 7H11 agar medium (BBL), respectively. Both types of media were prepared according to the manufacturer's directions.

Drug Preparation for In Vitro Studies

OPC-67683, PA-824, and CGI-17341 were synthesized at Otsuka Pharmaceutical (http://www.otsuka.global.com); RFP, INH, EB, streptomycin (SM), and PZA were purchased from Sigma (http://www.sigmaaldrich.com). OPC-67683, RFP, INH, PZA, and PA-824 were each dissolved in dimethylsulfoxide (DMSO), and the solutions were diluted serially with DMSO in 2-fold dilutions to desired concentrations. EB and SM were dissolved in distilled water, and the solutions were serially diluted with distilled water in 2-fold dilutions to desired concentrations.

Drug Preparation for In Vivo Studies

OPC-67683, PA-824, RFP, INH, EB, and PZA were each pestled in a mortar and dissolved or suspended in 5% gum arabic solution using an ultrasonic generator. Two-fold dilutions were then conducted using 5% gum arabic solution to adjust to the desired concentrations.

Strains

M. tuberculosis ATCC 25618 (H37Rv), *M. tuberculosis* ATCC 35838 (H37Rv-R-R), *M. tuberculosis* ATCC 35822 (H37Rv-H-R), *M. tuberculosis* ATCC 35837 (H37Rv-E-R), *M. tuberculosis* ATCC 35820 (H37Rv-S-R), *M. tuberculosis* ATCC 35801 (Erdman), and *M. tuberculosis* ATCC 35812 (Kurono) were purchased from American Type Culture Collection (http://www.atcc.org). *M. bovis* IID 982 (BCG Tokyo) was purchased from the Institute of Medical Science, University of Tokyo. A total of 67 *M. tuberculosis* strains used in this study were isolated in Japan, Myanmar, Thailand, Cambodia, Indonesia, Vietnam, and China.

BRM Test

The BRM test was performed in accordance with OECD Guideline 471 using *Salmonella tyiphimurium* TA98, TA100, TA1535, and TA1537, and *Escherichia coli* WP2 *uvrA* [11]. Each bacterial strain was pre-cultured at 37 °C for 18 h using a nutrient broth (Nissui Pharmaceutical; http://www.nissui-pharm.co.jp/index_e.html). After adjustment to 2.4 at OD660 nm, each bacterial suspension was added to a test tube containing the designated compound in the absence or presence of rat liver microsome (S9) mix. After a 20-min incubation at 37 °C, top agar was added to each test tube and the contents were poured into minimum essential medium (Oriental Yeast; http://www.oyc.co.jp/e/index.htm). The number of revertants was counted 48 h after incubation at 37 °C.

Susceptibility Testing

Susceptibility testing was performed using a procedure previously reported [12,13]. Bacteria stocks preserved in a deep freezer were each dissolved and adjusted to approximately 10^6 colony-forming units (CFU)/ml. Drug-containing plates were inoculated with the designated bacterial suspension to approximately 10^6 CFU/ml using a multipoint inoculator (Sakuma Seisakusho; http://homepage1.nifty.com/sakuma2000). Each plate was incubated at 37 °C for 14 d and analyzed to determine the minimum inhibitory concentration (MIC). The MIC was expressed as the lowest concentration that inhibited visible growth of organism on the agar medium after incubation.

For the evaluation of susceptibility against clinically isolated strains, resistance was determined based on the following criteria recommended by the National Committee

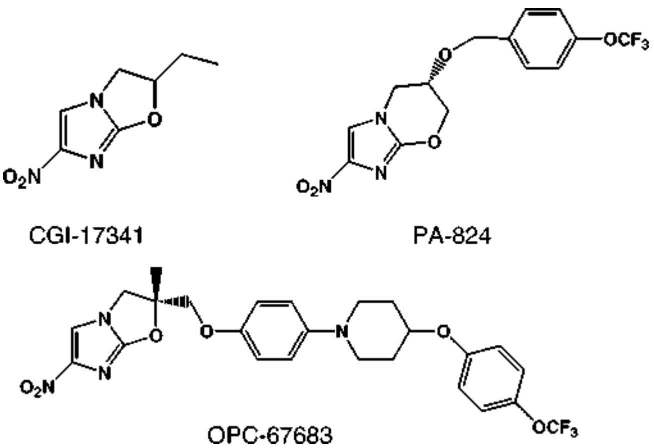

Figure 1. Structure of CGI-17341, PA-824, and OPC-67683

OPC-67683: (*R*)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-*b*]oxazole.

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for Clinical Laboratory Standards [14]: 1.0 μg/ml for RFP, 1.0 μg/ml for INH, 7.5 μg/ml for EB, and 10 μg/ml for SM. We calculated the concentrations at which 90% of the susceptible strains were inhibited (MIC_{90}) and the 95% confidence intervals using the probit method.

Inhibitory Activity against Mycolic Acid Biosynthesis

M. bovis BCG cell culture was apportioned to each assay tube at a volume of 0.98 ml, and then 0.01 ml of the test sample solution or DMSO (vehicle control) was added. Then, 0.01 ml of 2-^{14}C acetic acid sodium salt was added to each tube at 1 mCi/tube (37 Bq/tube), followed by incubation at 37 °C for 60 min. The ^{14}C-labeled cells were harvested by centrifugation at $2{,}000 \times g$ for 10 min and hydrolyzed by 2 ml of 10% potassium hydroxide/methanol (20% potassium hydroxide:methanol = 1:1, vol/vol) at 37 °C for 1 h. After incubation, 1 ml of 6 M hydrochloric acid was added and mixed gently. Then, 5 ml of n-hexane was added, followed by extraction by shaking for 20 min. Separating upper-phase centrifugation ($1{,}000 \times g$ for 5 min) was then performed, and 4 ml of the upper hexane phase was removed and transferred to another tube and dried at 100 °C. For methyl esterization, 1 ml of benzene-methanol-concentrated sulfuric acid (10:20:1, vol/vol/vol) was added and incubated at 100 °C for 1 h for drying. Then, 0.2 ml of n-hexane was added and mixed to extract ^{14}C-labeled fatty acid and mycolic acid. The extracted fatty acid and the mycolic acid subclasses were separated onto a thin-layer plate of Silicagel 60 F254 (thin-layer chromatography plate, Merck Japan; http://www.merck.co.jp/eng/index.html). 0.01 ml of extracted hexane phase was applied to the plate and allowed to develop to a diameter of 4 cm in the first solvent (heptan–diethylether–acetic acid [94:5:1, vol/vol/vol]) and 8 cm in the second solvent (petroleum ether–acetic acid [98:2, vol/vol]). Three thin-layer chromatography plates were fixed with an imaging plate (BAS-SR, Fujifilm; http://www.fujifilm.com) and analyzed by the following procedures: ^{14}C-labeled fatty acid and mycolic acid were detected using a BAS-2500 imaging system (Fujifilm). The radioactivity of each mycolic acid subclass was calculated as photo-stimulated luminescence using Image Gauge software (Version 2.54).

Statistical analysis was conducted, using SAS software (R.8.1, SAS Institute; http://www.sas.com), on the values of percent of control that were calculated automatically using Image Gauge software (Version 2.54) based on the result of each photo-stimulated luminescence. The significance level of the test was set at 5%. IC_{50} values (concentration required to inhibit by 50%) and 95% confidence intervals were calculated by linear regression analysis with logarithmic transformed concentrations.

Analysis of Metabolites Produced after Mixing OPC-67683 and *M. bovis* BCG Tokyo

15 μl of ^{14}C OPC-67683 (0.5 mg/ml:1 μCi/μl) was added to 585 μl of 7H9/TN-ADC broth or bacterial culture and incubated for 48 h. After incubation, a 2-fold volume of acetonitrile was added and mixed well. The lysate was centrifuged for 5 min at 15,000 rpm, and the supernatant was analyzed using high-performance liquid chromatography (HPLC) with flow scintillation analyzer to determine the metabolite pattern. In a parallel experiment, 0.1 ml of the supernatant was added to the vial containing 5 ml of Scintillation Cocktail (Ultima Gold, Perkin Elmer; http://www.perkinelmer.com). The pellet was suspended in 600 μl of 2 M sodium hydroxide and incubated for 1 h at 60 °C, and 0.1 ml of the suspension was added to the vial containing the Scintillation Cocktail. These samples were measured using a Scintillation Counter (LS5000CE, Beckman; http:/www.beckmancoulter.com) to confirm the existence of covalently binding radioactive molecules.

Determination of the Structure of Metabolite Produced after Mixing OPC-67683 and *M. bovis* BCG Tokyo

75 μl of OPC-67683 (0.5 mg/ml) was added to 2,925 μl of 7H9/TN-ADC broth or *M. bovis* BCG Tokyo bacterial culture and incubated for 72 h. After incubation, a 2-fold volume of acetonitrile was added and mixed well. The lysate was centrifuged for 5 min at 15,000 rpm, and the supernatant was then analyzed using LC-MS/MS to determine the structure of the detected metabolite produced by mixing OPC-67683 with *M. bovis* BCG Tokyo. The identified metabolite was synthesized at Otsuka Pharmaceutical, and the fragment pattern of the metabolite was then compared with that of another compound newly synthesized based on the predicted structure.

Activity against Intracellular Mycobacteria

Human THP-1 monocytic cells were differentiated into macrophages by treatment with 100 ng/ml phorbol 12-myristae 13-acetate (PMA) in RPMI-1640 medium and were distributed at a portion of 1×10^6/ml after a 2-d incubation. The differentiated macrophages were then inoculated with 6.88 $\log_{10}$ CFU of *M. tuberculosis* H37Rv for 4 h, washed twice with the medium to roughly remove the non-infecting bacteria, and then treated with 20 μg/ml SM for 20 h to kill the remaining viable extracellular bacteria. The starting CFU count in the cells was 6.42 $\log_{10}$ CFU. The cells were subsequently treated with the designated test compound for 4 h and were then washed twice with fresh medium to remove the added test compound. After an additional 68-h culture, the cells were lysed using 0.1% SDS, and the viable bacteria were counted in 7H11 agar plates to determine the potency against intracellular mycobacteria.

Plasma Levels in an Experimental Mouse Model of TB

Mice were anesthetized by an intramuscular administration with a 0.05-ml solution containing ketamine and xylazine (Ketalar 50 [Sankyo; http://www.sankyo.co.jp/english]/Serakutaru 2% [Bayer; http://www.bayer.com])/sterile physiological saline solution = 8:3:9), infected by an intratracheal inoculation with a 0.05-ml cell suspension (1,010 CFU) of *M. tuberculosis* Kurono using feeding needle and micro-syringe, and housed for 28 d prior to the initiation of administration. The designated compound dissolved or suspended in 5% gum arabic was then administered orally. Blood samples (approximately 1 ml) at each time-point were collected into a heparinized syringe from the abdominal post cava under ether anesthesia. The blood samples were then centrifuged (3,000 rpm, at 5 °C) to extract the plasma. The plasma (0.1 ml) was mixed with acetonitrile (0.2 ml) for RFP and with ethanol (0.3 ml) for INH, EB, and PZA. For OPC-67683, the plasma obtained was filtered through a 0.22-μm filter, and then 0.1 ml of the filtered plasma was mixed with 0.5 ml of 0.5 M carbonate buffer (pH 10) and 5 ml of diethyl ether. After shaking for 10 min, the organic layer (4 ml) was dried using nitrogen gas at 40 °C and dissolved with 0.2 ml of methanol/water/formic acid (50/50/0.1). The samples were analyzed using HPLC and high-performance liquid chromatography–electrospray ionization–tandem mass spectrometry (LC-ESI-MS/MS).

Therapeutic Efficacy

For evaluation of the therapeutic efficacy of OPC-67683, we designed three experiments that used various mouse models of TB, as described below. In each experiment, the designated compound dissolved or suspended in 5% gum arabic was administered orally once daily. At the end of the treatment period, the mice were euthanized (exsanguination through the abdominal inferior vena cava) under ether anesthesia, and the lung was aseptically excised. A lung homogenate for each mouse was prepared by pestling the lung evenly with a glass homogenizer after adding sterile distilled water to the excised lungs, and the homogenate was then diluted further with distilled water. A smear plate for each lung homogenate was then prepared by spreading 0.1 ml of each diluted solution on a 7H11 agar plate using a spreader. After spreading the homogenate solution, all plates were incubated at 37 °C and counted for formed colonies after 14 d.

Therapeutic efficacy in an experimental mouse model of chronic TB. In order to examine the therapeutic efficacy of OPC-67683 and to determine the therapeutic dose range, an experimental mouse model of chronic TB was established by inoculating Institute of Cancer Research (ICR) mice with *M. tuberculosis* Kurono through the caudal vein and allowing the infection to develop for 28 d. OPC-67683, RFP, INH, EB, SM, or PZA was then administered once daily for 28 d to examine the change in viable bacterial count in the lung. ICR mice were inoculated intravenously with 8.6×10^4 CFU of *M. tuberculosis* Kurono. After a 28-d period, the mice were assigned to groups (n = 5/group) using a stratified randomization method based on the body weight of each infected mouse. The test compounds were then administered orally once daily for 28 d (OPC-67683: 40 to 0.156 mg/kg, RFP: 20 to 1.25 mg/kg, INH: 20 to 1.25 mg/kg, EB: 160 to 20 mg/kg, SM: 160 to 20 mg/kg, PZA: 320 to 40 mg/kg, and PA-824: 40 to 1.25 mg/kg [2-fold dilutions]). CFU counts were performed as described above. All lungs were homogenized with 5 ml of sterile distilled water.

Statistical analysis was conducted using SAS software (R.8.1) on the number of viable bacteria in the lung of mice surviving until necropsy on the 57th day after inoculation, and on the number at the start of the treatment, which was on the 29th day after inoculation. The significance level of the test was set at 5%. A test for dose dependency was performed using linear regression analysis based on log-transformed values of the viable bacterial counts in the lung. When dose dependency was confirmed, the Williams' test (lower-tailed) was subsequently performed, and when dose dependency was not confirmed, the Dunnett's test (two-tailed) was subsequently performed against each of the control groups.

Therapeutic efficacy in an experimental TB model using immunocompromised mice. To examine whether immunity relates to the mechanism of action in vivo, we performed experiments using BALB/c nude mice, which lack both conventional $CD4^+$ and $CD8^+$ T cells. The anti-tubercular activity of OPC-67683 in nude mice was compared with that in immunocompetent mice. BALB/c nude mice and BALB/c mice were inoculated intravenously with 2.04×10^4 CFU of *M. tuberculosis* Kurono. 1 d after inoculation, the mice were assigned to groups (n = 5/group) using a stratified randomization method based on the body weight of each infected mouse. OPC-67683 was then administered orally once daily for 10 d (OPC-67683: 10 to 0.313 mg/kg [2-fold dilutions]). CFU counts were performed as described above. All lungs were homogenized with 5 ml of sterile distilled water.

Therapeutic efficacy in combination with conventionally used drugs. A new regimen that included OPC-67683 was evaluated and compared with a global standard regimen to determine the best regimen for reducing the treatment duration in an experimental mouse model of chronic TB. ICR mice were inoculated intratracheally under anesthesia with 855 CFU of *M. tuberculosis* Kurono, and left for 28 d to allow the animals to develop chronic TB. Grouping (n = 6/group) was conducted by a stratified randomization method based on the body weight of each infected mouse. The test regimens were then administered orally for 2 mo in the combination of OPC-67683, RFP, and PZA, or RFP, INH, EB, and PZA as an intensive treatment, and for an additional 2 mo in the combination of OPC-67683 and RFP or 4 mo in the combination of RFP and INH as a maintenance treatment. The doses used in this experiment provided plasma levels in mice similar to those seen at the standard doses used in humans: for RFP, we used 5 mg/kg; for INH, 10 mg/kg; for EB, 100 mg/kg; and for PZA, 100 mg/kg. We set the dose for OPC-67683 at 2.5 mg/kg.

Necropsy was performed on days 29, 57, 85, 113, 141, 169, and 177 relative to the inoculation for the standard regimen and vehicle control groups and on days 29, 57, 85, 113, and 141 for the new-regimen groups. A lung homogenate for each mouse from a drug-treated group was prepared by pestling the lung evenly with a glass homogenizer after adding to the excised lungs 5 ml of sterilized distilled water on day 29 and 2 ml of sterilized distilled water on the day of necropsy. Lung homogenates for all vehicle control groups were prepared by pestling the lung evenly with a glass homogenizer after adding 5 ml of sterilized distilled water to the excised lungs. Smear plates of lung homogenate samples from the groups after 2–6

Table 1. Bacterial Reverse Mutation Test for OPC-67683

Bacterial Strain	S9 mix	Compound	Revertants/Plate					
			5,000	2,500	1,250	625	312.5	0 μg/plate
S. typhimurium TA98	−	OPC-67683 AF-2(0.1 μg/plate)	31	37	34	29	29	29 473
	+	OPC-67683 2AA(0.5 μg/plate)	35	31	30	31	31	36 92
S. typhimurium TA100	−	OPC-67683 AF-2(0.01 μg/plate)	94	90	87	77	85	98 547
	+	OPC-67683 2AA(1 μg/plate)	119	112	107	108	116	108 1103
S. typhimurium TA1535	−	OPC-67683 NaN_3(0.5 μg/plate)	6	7	6	9	6	6 174
	+	OPC-67683 2AA(2 μg/plate)	9	8	5	6	5	6 188
S. typhimurium TA1537	−	OPC-67683 ACR(80 μg/plate)	63	61	54	62	60	64 953
	+	OPC-67683 2AA(2 μg/plate)	74	63	66	72	73	81 238
E. coli WP2 uvr A	−	OPC-67683 AF-2(0.01 μg/plate)	24	24	20	25	23	30 225
	+	OPC-67683 2AA(10 μg/plate)	29	23	25	20	23	33 1122

AF-2, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide; 2AA, 2-aminoanthracene; NaN_3, sodium azide; ACR, 9-aminoacridine.
doi:10.1371/journal.pmed.0030466.t001

mo of treatment were prepared by spreading all of the lung homogenate on 7H11 agar plates.

Statistical analysis was conducted using SAS software (R.8.1) on the viable bacteria number in the lungs of mice surviving until necropsy after the inoculation. The significance level of the test was set at 5%. The viable bacterial count in the lungs of mice anatomized at days 57, 85, 113, and 141 were log-transformed for comparing the new regimen with the standard regimen using the two-tailed Dunnett's test. The mean values and 95% confidence intervals were calculated for evaluating the new regimen.

In Vitro Metabolism of OPC-67683 in Human and Animal Liver Microsomes

The study was undertaken to investigate the metabolites produced by the metabolic reactions of OPC-67683 using human, rat, mouse, dog, rabbit, and monkey liver microsomes. Pooled human liver microsomes (20 mg/ml) from ten donors were prepared at the Biomedical Research Institute, Human and Animal Bridge Discussion Group (Chiba, Japan) [15]. Human liver samples were legally procured from the National Disease Research Interchange (http://www.ndriresource.org/) through the international partnership with the Human and Animal Bridge Discussion Group. The study was conducted in accordance with the Declaration of Helsinki.

The incubation mixtures contained 100 mM phosphate buffer (pH 7.4), 100 μM OPC-67683, 2.5 mM β-NADPH, 2.5 mM β-NADH, and 1 mg/ml microsomal protein in a final incubation volume of 0.5 ml. OPC-67683 was dissolved in DMSO, and the concentration of the organic solvent was 1% (v/v) in the reaction system. The reactions were performed in duplicate in a shaking water bath at 37 °C for 2 h. The incubation mixtures were extracted with acetonitrile and ethyl acetate, and the samples were analyzed by HPLC and LC-ESI-MS/MS.

Effect of OPC-67683 on Cytochrome P450–Mediated Reactions in Human Liver Microsomes

7-ethoxyresorufin *O*-deethylase activity by CYP1A1/2, coumarin 7-hydroxylase activity by CYP2A6, 7-benzyloxyresorufin *O*-debenzylase activity by CYP2B6, tolbutamide methylhydroxylase activity by CYP2C8/9, S-mephenytoin 4′-hydroxylase activity by CYP2C19, bufuralol 1′-hydroxylase activity by CYP2D6, chlorzoxazone 6-hydroxylase activity by CYP2E1, and testosterone 6β-hydroxylase and nifedipine oxidized activities by CYP3A4 were determined as previously reported [16].

Standard incubation mixtures of 0.5 ml contained microsomal protein (0.1–0.5 mg), 0.1 M potassium phosphate buffer (pH 7.4), 0.1 mM EDTA, NADPH-generating system (2.5 mM β-NADP, 25 mM glucose-6-phosphate, 2 units of glucose-6-phosphate dehydrogenase, and 10 mM magnesium chloride), and substrates with or without OPC-67683. OPC-67683 was dissolved in DMSO and added to incubations at a volume of 5 μl. Substrates were dissolved in the following solvents: 7-ethoxyresorufin and 7-benzyloxyresorufin in DMSO; coumarin, bufuralol, and nifedipine in ethanol; tolbutamide, *S*-mephenytoin and testosterone in methanol; and chlorzoxazone in 1% (w/v) aqueous solution. The substrate solutions were added to incubations at a volume of 5 μl. The enzyme incubations were carried out in duplicate, and formations of metabolites were determined by HPLC.

Assay methods were validated in this study. The calibration curves were established for resorufin (0.2–200 nM, $r = 0.9996$), 7-hydroxycoumarin (0.05–5 μM, $r = 0.9998$), 4-hydroxytolbutamide (0.05–10 μM, $r = 0.9998$), 4-hydroxymephenytoin (0.025–5 μM, $r = 0.9996$), 1′-hydroxybufuralol (0.025–5 μM, $r = 0.9995$), 6-hydroxychlorzoxazone (0.25–100 μM, $r = 0.9994$), 6β-hydroxytestosterone (0.03–30 μM, $r = 0.9994$), and oxidized nifedipine (0.1–25 μM, $r = 0.9998$).

7-ethoxyresorufin (0.5 μM), coumarin (2 μM), 7-benzyloxyresorufin (1.5 μM), tolbutamide (400 μM), *S*-mephenytoin (100 μM), bufuralol (20 μM), chlorzoxazone (100 μM), testosterone (100 μM), and nifedipine (50 μM) were selected as the concentrations of the substrates for the determination of residual activity in the presence of OPC-67683 (1–100 μM). The concentrations of the substrates were approximately the K_m values for the enzymes as previously reported [17]. Selective Cytochrome P450 inhibitors were used in this study to confirm the validity of the assays. 7,8-benzoflavone [18], furafylline [19], orphenadrine [20], quercetin [21], sulfaphenazole [22], tranylcypromine [23], quinidine [24], diethyldithiocarbamate [25], and ketoconazole [26], which are inhibitors of CYP1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4, respectively, inhibited the respective enzyme

Table 2. In Vitro Anti-Mycobacterial Activity of OPC-67683 Compared with RFP, INH, EB, SM, CGI-17341, and PA-824

Type Strain	MIC (μg/ml)						
	OPC-67683	RFP	INH	EB	SM	CGI-17341	PA-824
M. tuberculosis ATCC 25618 (H37Rv)	0.012	0.78	0.1	1.56	1.56	0.2	0.2
M. tuberculosis ATCC 35838 (H37Rv-R-R)	0.006	>100	0.1	1.56	0.78	0.05	0.1
M. tuberculosis ATCC 35822 (H37Rv-H-R)	0.012	0.39	>100	3.13	0.78	0.2	0.05
M. tuberculosis ATCC 35837 (H37Rv-E-R)	0.012	0.2	0.2	50	0.78	0.2	0.2
M. tuberculosis ATCC 35820 (H37Rv-S-R)	0.012	0.78	0.1	3.13	>100	0.2	0.2
M. tuberculosis ATCC 35812 (Kurono)	0.012	0.39	0.1	3.13	0.78	0.2	0.2

Susceptibility of OPC-67683 against standard *M. tuberculosis.*

doi:10.1371/journal.pmed.0030466.t002

activities. Diethyldithiocarbamate is also known to be a specific inhibitor of CYP2A6 [18], and the present study confirmed the potent inhibitory capability of this compound on CYP2A6-mediated metabolism.

Other Information

The care and handling of the animals was in accordance with "Guidelines for Animal Care and Use in Otsuka Pharmaceutical Co., Ltd." The aspects of experiments related to biosafety were performed according to standards set forth in "Biosafety manuals in Microbiological Research Institute and 3rd Institute of New Drug Discovery, Otsuka Pharmaceutical Co., Ltd."

Results

BRM Test

The mutagenic potential of OPC-67683 was evaluated in the absence and presence of S9 mix using the BRM test in accordance with OECD Guideline 471. As shown in Table 1, OPC-67683 did not show mutagenicity.

Susceptibility Testing

The MICs against standard strains are shown in Table 2. At concentrations ranging from 0.006 to 0.012 μg/ml, OPC-67683 inhibited the growth of both drug-susceptible and drug-resistant *M. tuberculosis*. The MICs of OPC-67683 were, respectively, four to 64, two to 32, 128 to 256, 64 to 512, eight to 16, and four to 16 times lower than those of RFP, INH, EB, SM, CGI-17341, and PA-824. These results indicate that OPC-67683 possesses the most potent anti-mycobacterial activity against both drug-susceptible and drug-resistant strains.

The anti-tubercular activity was also evaluated on 67 clinically isolated strains. The MIC_{90} values (range) of OPC-67683, RFP, INH, EB, and SM were, respectively, 0.012 μg/ml (0.006–0.024 μg/ml), 0.288 μg/ml (0.05–0.78 μg/ml), 0.099 μg/ml (0.05–0.78 μg/ml), 3.636 μg/ml (0.78–6.25 μg/ml), and 2.938 μg/ml (0.39–6.25 μg/ml). Based on these results, the MIC_{90} values of OPC-67683 were about 24, eight, 303, and 244 times lower than those of RFP, INH, EB, and SM, respectively. The results of our evaluation indicated that OPC-67683 inhibited the growth of the clinically isolated drug-susceptible *M. tuberculosis* at the same range as on standard strains, and also showed activity against the clinically isolated strains resistant to the currently used anti-TB drugs RFP, INH, EB, or SM. These results indicate that OPC-67683 exhibits anti-mycobacterial activity on both drug-susceptible and drug-resistant strains and that it has no cross-resistance with any of the currently used anti-TB drugs. These data are shown in Table 3.

In addition, the efficacy of OPC-67683 in combination with currently used anti-TB drugs RFP, INH, EB, and SM was examined in vitro using the checkerboard method. These results are shown in Table 4. The results showed OPC-676783 to have no antagonistic activity in combination with any of the drugs tested.

Table 3. MIC_{90} of OPC-67683 against Drug-Susceptible and Drug-Resistant *M. tuberculosis*

Organism Group (Number of Strains)	MIC (μg/ml)	
	MIC_{90}	95% Confidence Intervals
RFP-susceptible *M. tuberculosis* (31)	0.01248	0.01097–0.01535
RFP-resistant *M. tuberculosis* (36)	0.01221	0.01050–0.01583
INH-susceptible *M. tuberculosis* (31)	0.01194	0.01054–0.01452
INH-resistant *M. tuberculosis* (36)	0.01279	0.01094–0.01679
EB-susceptible *M. tuberculosis* (56)	0.01213	0.01081–0.01440
EB-resistant *M. tuberculosis* (11)	0.01341	0.01073–0.02450
SM-susceptible *M. tuberculosis* (49)	0.01203	0.01077–0.01416
SM-resistant *M. tuberculosis* (18)	0.0134	0.01068–0.02298

Susceptibility of OPC-67683 against 67 strains of clinically isolated *M. tuberculosis*: Resistant strains were selected based on the recommendations of the National Committee For Clinical Laboratory Standards [14] using the following criteria: 1.0 μg/ml for RFP, 1.0 μg/ml for INH, 7.5 μg/ml for EB, and 10 μg/ml for SM. We calculated the concentrations at which 90% (MIC_{90}) of the susceptible strains are inhibited. MIC_{90} and 95% confidence intervals were calculated using the actual data obtained by the probit method.

doi:10.1371/journal.pmed.0030466.t003

Inhibitory Activity against Mycolic Acid Biosynthesis

^{14}C-labeled fatty acid and mycolic acid were detected using the BAS-2500 imaging system (unpublished data). The percent with respect to the control of each mycolic acid subclass was calculated automatically, and IC_{50} was calculated using SAS software. The results indicated that both OPC-67683 and INH inhibited mycolic acid synthesis, but the manner of action differed between the two compounds: OPC-67683 inhibited the synthesis of methoxy- and keto-mycolic acid, with IC_{50} values of 0.021 to 0.036 μg/ml, but not the synthesis of α-mycolic acid at concentrations up to 0.25 μg/ml, while INH inhibited all mycolic acid subclasses, with IC_{50} values of 0.630 to 1.851 μg/ml. The IC_{50} and 95% confidence interval values are shown in Table 5.

Table 4. In Vitro Synergistic Activity of OPC-67683 and Existing TB Drugs against Clinically Isolated *M. tuberculosis*

Drug Combination	Number of Test Strains for which FIC Index Is:			
	Synergistic	Partially Synergistic	Additive	Indifferent
OPC-67683 and RFP	1 (3.7%)	24 (88.9%)	2 (7.4%)	—
OPC-67683 and INH	—	12 (44.4%)	5 (18.5%)	10 (37.0%)
OPC-67683 and EB	3 (11.1%)	21 (77.8%)	3 (11.1%)	—
OPC-67683 and SM	—	7 (25.9%)	10 (37.0%)	10 (37.0%)

In vitro synergistic activity of OPC-67683 and existing TB drugs against clinically isolated *M. tuberculosis*: The checkerboard procedure was performed based on the MIC values of 27 test strains of clinically isolated *M. tuberculosis* established by the agar dilution method. The level of synergy was determined by calculating the fractional inhibitory concentration (FIC) index based on the following formula: FIC of drug A = MIC of drug A in combination ÷ MIC of drug A alone; FIC of drug B = MIC of drug B in combination ÷ MIC of drug B alone; and FIC index = FIC of drug A + FIC of drug B. Results of FIC index were interpreted as follows: $\leq$0.5: synergy, $>$0.5 to 0.75: partial synergy, $>$0.75 to 1.0: additive effect, $>$1.0 to 4.0: indifference, and $>$4.0: antagonism. We calculated the FIC index value for each concentration of two-drug combination and the minimum value was adopted.
doi:10.1371/journal.pmed.0030466.t004

Analysis of Metabolites Produced after Mixing OPC-67683 and *M. bovis* BCG

After mixing OPC-67683 with *M. bovis* BCG Tokyo, we identified only one main metabolite, and this metabolite eluted faster than OPC-67683. No metabolites, however, were observed after mixing OPC-67683 with an experimentally obtained OPC-67683-resistant *M. bovis* BCG Tokyo strain. These results are shown in Figure 2A. The supernatant was analyzed using LC-MS/MS to determine the structure of the identified metabolite. We found the mass number of the identified metabolite to be 490 and predicted this structure to be a desnitro-imidazooxazole. We then synthesized a desnitro-imidazooxazole and performed a product ion scan with the identified metabolite and the newly synthesized compound. We observed product ions in 200, 352, 378, and 406 m/z in each experiment. Structural analysis of the main metabolite indicated that the structure was a desnitro-imidazooxazole possessing the same substituent as that of OPC-67683. The MS spectrum is displayed in Figure 2B.

In addition, when we treated the drug-susceptible strain with the radioactive OPC-67683, none of the radioactivity was recovered after the addition of acetonitrile. About 20% of the total radioactivity was distributed to the cell components, and this phenomenon was not observed with an OPC-67683-resistant strain. These data are shown in Table 6.

Activity against Intracellular Mycobacteria in Human Macrophages

A study was conducted to confirm the post-antibiotic effect of OPC-67683 on intracellular *M. tuberculosis* in THP-1 cells, and the results were compared with RFP, INH, and PA-824. OPC-67683 was shown to be highly active against intracellular *M. tuberculosis* H37Rv after 4-h pulsed exposures in a dose-dependent manner. The data are shown in Figure 3. The intracellular activity of OPC-67683 at a concentration of 0.1 μg/ml was similar to that of RFP of 3 μg/ml, but was superior to INH and PA-824, which both showed poor activity during the 4-h pulsed exposure. These results indicated that even with limited contact with the bacteria within the cells, OPC-67683 might be able to effectively kill the intracellular mycobacteria.

Plasma Levels in an Experimental Mouse Model of TB

As shown in Table 7, OPC-67683 exhibited the lowest plasma concentration but longest half-life among the tested reference drugs. The C_{max} and AUC_t values for RFP, EB, and PZA in mouse plasma at the tested dose were similar to those in human at clinical doses. The C_{max} value for INH in mouse plasma was also similar to that in humans, but the AUC_t in the mouse was lower than that in humans. A comparison of these parameters between mouse and human plasma is summarized in Figure 4C [27–29].

Therapeutic Efficacy

Therapeutic efficacy in an experimental mouse model of chronic TB. The viable bacterial count in the OPC-67683-treated groups decreased dose-dependently, and the therapeutic effects of the compound were observed and compared with those of the reference drugs. The results are shown in Figure 4A and Table S1. The dose groups that showed a significant decrease in pulmonary viable bacterial count when compared with the vehicle control group were

Table 5. IC_{50} of OPC-67683 and INH against Mycolic Acid Synthesis

Compound	Subclass Mycolic Acid and Fatty Acid	IC50 (μg/ml)	95% Confidence Interval (μg/ml)
OPC-67683	Fatty acid	>0.25	—
	α-Mycolic acid	>0.25	—
	Methoxy-mycolic acid	0.036	0.020–0.068
	Keto-mycolic acid	0.021	0.009–0.059
INH	Fatty acid	>4	—
	α-Mycolic acid	1.851	1.109–3.090
	Methoxy-mycolic acid	0.63	0.537–0.738
	Keto-mycolic acid	0.69	0.422–1.129

The IC_{50} (concentration required to inhibit activity by 50%) of OPC-67683 against mycolic acid synthesis in *M. bovis* BCG was determined and compared with that of INH, a well-known inhibitor of mycolic acid synthesis. ^{14}C-labeled acetic acid was incorporated to mycolic acid by incubation with *M. bovis* BCG cell cultures in the presence of OPC-67683 or INH as a reference. ^{14}C-labeled fatty acid and mycolic acid subclasses were detected using thin-layer chromatography (TLC, $n = 3$), and analyzed by BAS-2500 (Fujifilm). The radioactivity of each fatty acid and mycolic acid subclasses was calculated using photo-stimulated luminescence, expressed as the percentage of incorporation in untreated controls, and statistical analysis was conducted by linear regression analysis to calculate IC_{50} values and 95% confidence intervals (significance level: 5%).
doi:10.1371/journal.pmed.0030466.t005

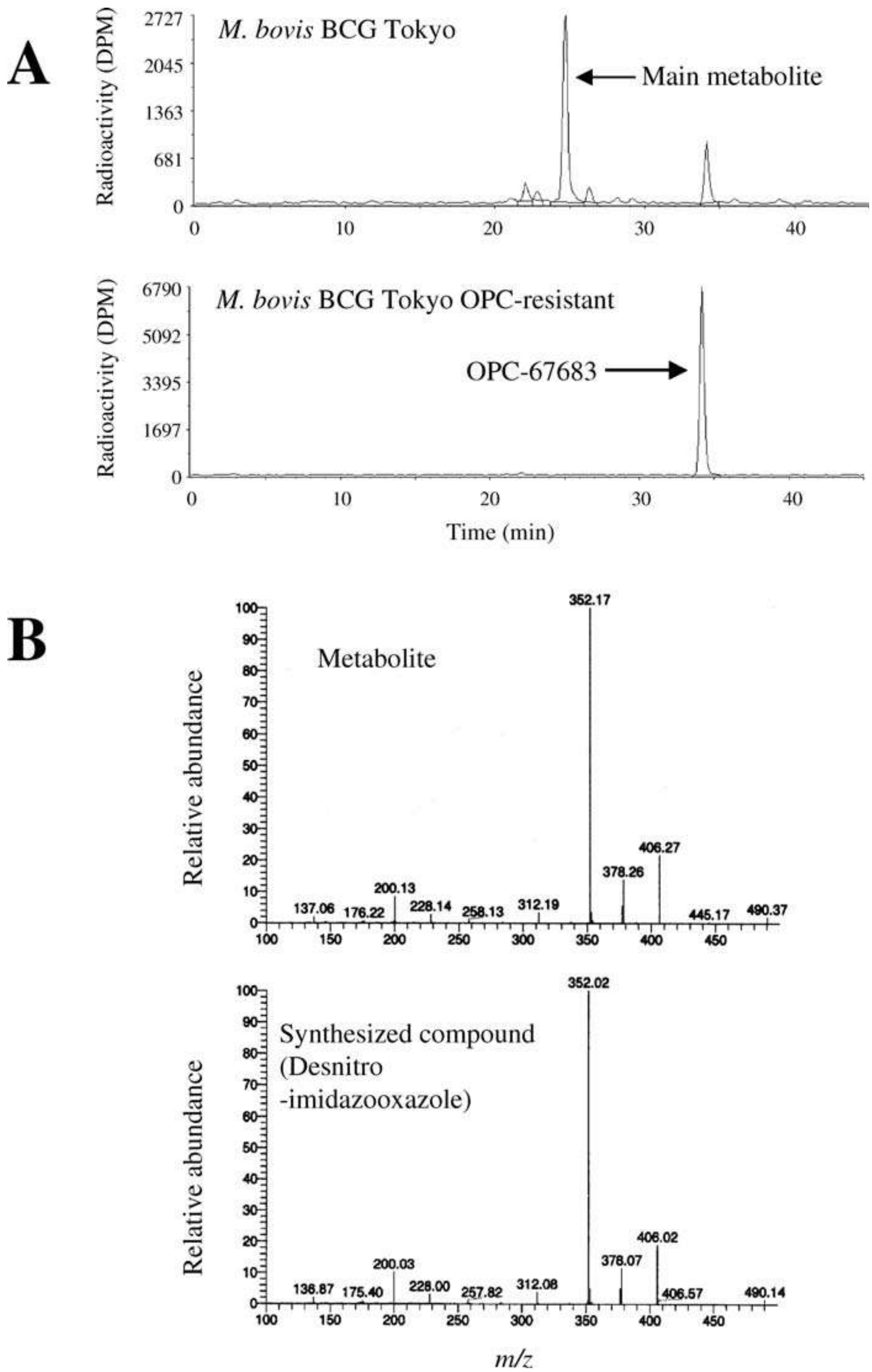


Figure 2. Analysis of Metabolites Produced after Mixing OPC-67683 and *M. bovis* BCG

(A) 15 μl of ^{14}C OPC-67683 (0.5mg/ml: 0.056 μCi/μl) was added to 585 μl of 7H9/TN-ADC broth or bacterial culture and incubated for 48 h. After incubation, a 2-fold volume of acetonitrile was added and mixed well. The lysate was centrifuged for 5 min at 15,000 rpm. The supernatant was analyzed using HPLC with flow scintillation analyzer to determine the metabolite pattern.

(B) The identified metabolite (desnitro-imidazooxazole) was synthesized at Otsuka Pharmaceutical, and the fragment pattern of the metabolite by electrospray ionization mass spectroscopy was then compared with that of another compound newly synthesized based on the predicted structure.

doi:10.1371/journal.pmed.0030466.g002

0.313, 0.625, 1.25, 2.5, 5, 10, 20, and 40 mg/kg for OPC-67683; 3.5, 5, 10, and 20 mg/kg for RFP; 2.5, 5, 10, and 20 mg/kg for INH; 160 mg/kg for EB, 20, 40, 80, and 160 mg/kg for SM; and 80, 160, and 320 mg/kg for PZA.

The doses of OPC-67683, RFP, INH, EB, SM, and PZA that could produce a CFU reduction of at least 95% in this experimental mouse model were 0.625, 3.5, 5, >160, 40, and 160 mg/kg, respectively.

Therapeutic efficacy in an experimental TB model using immunocompromised mice. These results are shown in Figure 4B.

The pulmonary CFU counts of the OPC-67683-treated

Table 6. Analysis of OPC-67683-Susceptible and -Resistant *M. bovis* BCG Using Radio-Labelled OPC-67683

Sample	Total DPM		Percent	
	Supernatant	Pellet	Sample DPM (Supernatant)/ Control DMP (Supernatant)	Sample DPM (Pellet)/ Control DMP (Supernatant)
Control	823295.30	24558.06	100	3
M. bovis BCG Tokyo	678566.21	182886.84	82	22
M. bovis BCG Tokyo OPC-resistant	862893.41	43158.12	105	5

15 μl of ^{14}C OPC-67683 (0.5mg/ml:0.056 μCi/μl) was added to 585 μl of 7H9/TN-ADC broth or bacterial culture and incubated for 48 h. After incubation, a 2-fold volume of acetonitrile was added and mixed well. The lysate was centrifuged for 5 min at 15,000 rpm and 0.1 ml of the supernatant was added to the vial containing 5 ml of Scintillation Cocktail (Ultima Gold, PerkinElmer). The pellet was suspended in 600 μl of 2 M NaOH and incubated for 1 h at 60 °C, and 0.1 ml of the suspension was added to the vial containing 5 ml Scintillation Cocktail. These samples were measured using a Scintillation Counter (LS5000CE, Beckman).
doi:10.1371/journal.pmed.0030466.t006

BALB/c nude mice and immunocompetent mice were reduced dose-dependently, and significant decreases were observed at doses of 0.313, 0.625, 1.25, and 2.5 mg/kg. The efficacy profiles of OPC-67683 were similarly excellent in both types of mice.

Therapeutic efficacy in combination with conventionally used drugs. The eradication rate of a new regimen containing OPC-67683 was compared with that of the standard regimen. The OPC-67683-containing regimen exerted a rapid and consistent reduction during the first 3 mo (Figure 4D). At 3 mo after the start of treatment, only one colony was detected in one of the six animals; at 4 mo, no colonies were detected in any of the six animals. In contrast, at 6 mo for the standard regimen, colonies were detected in four out of five mice. These results suggest that a new regimen containing OPC-67683 could dramatically reduce the treatment duration by at least 2 mo.

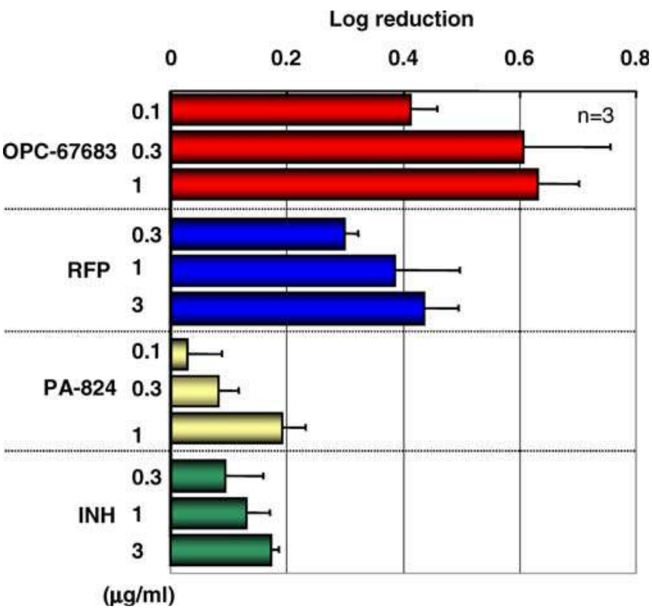


Figure 3. Effect of Pulsed Exposures to OPC-67683, RFP, INH, and PA-824 on the Intracellular Growth of *M. tuberculosis* H37Rv within THP-1 Cells
Infected cells were incubated with the test compound for 4 h, washed, cultured until 68 h at 37 °C, plated on 7H11 agar, and counted for colonies after 16 d of growth at 37 °C. Values represent mean ± S.D ($n = 3$).
doi:10.1371/journal.pmed.0030466.g003

In Vitro Metabolism in Human and Animal Liver Microsomes

The current study was conducted to investigate the metabolites produced by in vitro metabolism of OPC-67683 using human and animal liver microsomes and to investigate the in vitro ability of OPC-67683 to affect the metabolism of substrates for CYP1A1/2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. The results are shown in Table 8.

The HPLC and LC-ESI-MS/MS data demonstrated that the major metabolites were hardly detected in the incubation mixture OPC-67683 with human, rat, mouse, dog, rabbit, and monkey liver microsomes. OPC-67683 was stable in the in vitro metabolism of human and animal liver microsomes. These results suggest that OPC-67683 is not metabolized by the CYP enzymes.

OPC-67683 had neither stimulatory nor inhibitory effects on CYP1A1/2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 activities at concentrations up to 100 μM, indicating that OPC-67683, at the expected therapeutic concentrations, would not be predicted to cause clinically significant interactions with other CYP-metabolized drugs.

Discussion

With the several disadvantages to the current TB drug regimen, there are a number of expectations for a new anti-TB drug. An ideal new drug should be safe and able to shorten the treatment duration, be effective against MDR-TB, treat TB patients co-infected with HIV, and effectively address LTBI. We have performed our TB research program with these expectations in mind.

To shorten the duration of treatment, we focused our search on finding more powerful anti-TB agents, as history has shown that the introduction of more potent drugs can effectively reduce the required duration of treatment, as was the case with RFP and PZA. For improved efficacy against MDR-TB, we screened for compounds with a new structure and mechanism of action. Furthermore, to target LTBI, we

Table 7. Plasma Concentration of OPC-67683, RFP, INH, EB, and PZA after Oral Administration in Mice Infected with *M. tuberculosis* Kurono

Compound (Dose; mg/kg)	Concentration (μg/ml)											C_{max} (μg/ml)	AUC_t (μg · h/ml)	t_{max} (h)	$t_{1/2}$ (h)
	0.083 h	0.25 h	0.5 h	1 h	2 h	4 h	6 h	8 h	12 h	16 h	24 h				
OPC-67683 (2.5)	N.T.	N.T.	N.T.	0.133 ±0.030	0.193 ±0.040	0.220 ±0.020	0.297 ±0.083	0.167 ±0.028	0.166 ±0.049	N.T.	0.049 ±0.012	0.297	4.13	6	7.6
RFP (5)	N.T.	N.T.	3.33 ±0.87	4.49 ±1.04	4.52 ±1.90	3.82 ±0.70	5.10 ±1.63	3.18 ±0.68	N.T.	0.660 ±0.260	N.T.	5.10	48.2	6	3.4
INH (10)	2.17 ±0.435	3.06 ±0.779	2.28 ±0.390	1.92 ±0.478	0.740 ±0.202	0.253 ±0.057	N.T.	N.D.	N.T.	N.T.	N.T.	3.06	4.55	0.25	1.0
EB (100)	0.055 ±0.049	1.30 ±0.939	3.17 ±0.392	3.51 ±1.13	2.51 ±1.01	1.02 ±0.202	N.T.	0.612 ±0.325	N.T.	N.T.	N.T.	3.51	12.2	1	2.8
PZA (100)	49.6 ±11.2	59.1 ±14.1	63.2 ±28.9	60.2 ±18.7	35.5 ±6.45	18.4 ±3.09	N.T.	0.815 ±0.580	N.T.	N.T.	N.T.	63.2	197	0.5	1.1

Each value represents mean ± SD ($n = 3$).
Each pharmacokinetic parameter was calculated by WINNONLIN (Version 4.1).
N.D., not detected (<0.05 μg/ml for INH); N.T., not tested.
doi:10.1371/journal.pmed.0030466.t007

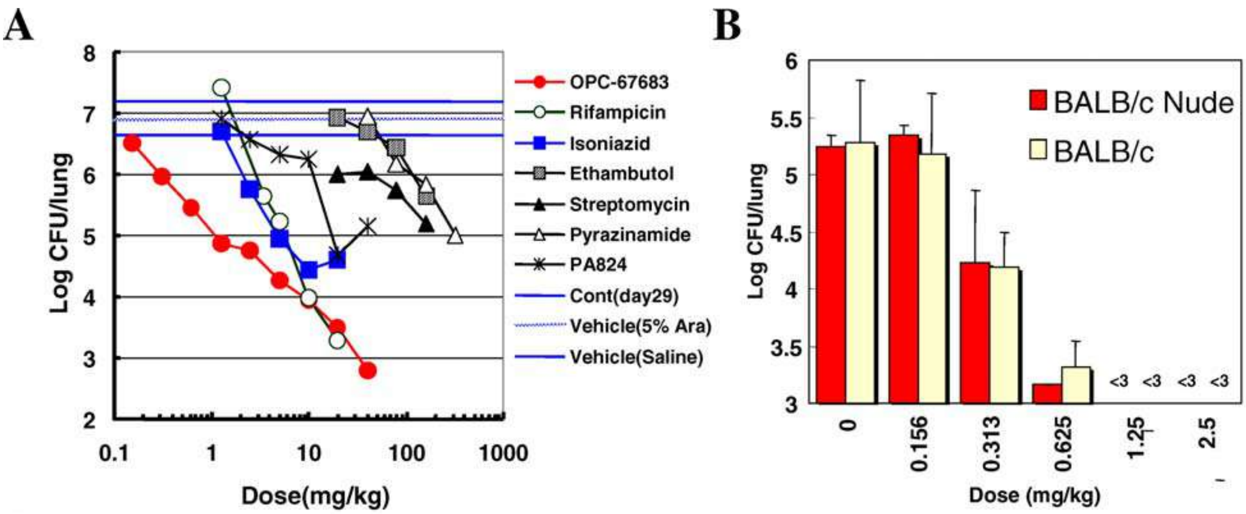
focused on compounds with activity against intracellular *M. tuberculosis*.

Mycobacteria are well known to be wax-rich bacteria, and a main component of the wax is mycolic acid, which is detected only in mycobacteria and not in gram-positive or gram-negative bacteria or in mammalian cells. Genome research of tubercle bacilli has verified this lipid richness, showing there to be almost 250 distinct enzymes involved in the lipid metabolism of tubercle bacilli [30]. In view of the important role of mycolic acid in mycobacteria, we searched for a compound that could inhibit mycolic acid synthesis and demonstrate potent anti-TB activity in vitro. We found OPC-67683 to have both inhibitory activity on mycolic acid biosynthesis and potent in vitro activity against *M. tuberculosis*, as indicated by its low MIC range across many strains, including MDR-TB. The IC_{50} values of OPC-67683 for mycolic acid subclasses were lower than those of INH, and these results correlated well with the in vitro anti-tubercular activity of OPC-67683 and INH. The anti-tubercular activity of nitro-imidazooxazole derivatives correlated well with their inhibitory activity against mycolic acid biosynthesis [11]. We therefore concluded that the inhibitory activity of OPC-67683 against mycolic acid synthesis was a mechanism of action attributable to killing mycobacteria at least as potently as INH.

As *M. tuberculosis* can grow not only facultatively but also as intracellular organisms that survive and multiply in macrophages of the infected host, we consider it important that a compound is also able to kill intracellular TB and that such activity should correlate with a shortened treatment duration and could be an important factor in the treatment of LTBI. We therefore examined the killing activity against intracellular TB in macrophage-derived THP-1 cells. Among the tested compounds, OPC-67683 demonstrated the most potent killing activity. The killing activity of OPC-67683 at 0.1 μg/ml was similar to that of RFP at 3 μg/ml and was superior to that of INH and PA-824. The intracellular potency of antibiotics is commonly evaluated in vitro using continuous exposure rather than in animal models due to their often-rapid elimination, depending on the plasma half-life. OPC-67683 was able to demonstrate potent in vitro killing ability even at short exposure times. These results indicate that OPC-67683 would likely exert strong antibiotic activity against intracellular TB in patients even at short exposure times, which could be an advantage in intermittent treatment.

PA-824 has been reported to be a prodrug metabolized to its active form by mycobacterium [31]. Recently, Manjunatha et al reported that Rv3547 acts as the catalytic enzyme for PA-824, but the role of Rv3547 within mycobacterium is not yet clear [32]. Similarly, OPC-67683 also requires metabolic activation by *M. tuberculosis* in order for the anti-TB activity to be exerted. Experimentally isolated OPC-67683-resistant mycobacterium did not metabolize the compound. We confirmed a mutation in the Rv3547 gene among the resistant organisms, indicating Rv3547 to be a key enzyme involved in activating OPC-67683, as it was for PA-824 (unpublished data). According to Manjunatha et al, the metabolites of PA-824 have not yet been identified. With OPC-67683, however, the main metabolite produced in the presence of *M. tuberculosis* was identified as a non-active desnitro-imidazooxazole. This result suggests that Rv3547 possesses a reduction potency of the nitro residue and that an intermediate between OPC-67683 and the desnitro-imidazooxazole could be the active form. After mixing radioactive OPC-67683 with viable mycobacterium, nearly 20% of the radioactive substances were not recovered. In contrast, after treating OPC-67683-resistant mycobacterium, nearly 100% of radioactivity was recovered. The action mechanism of metronidazole derivatives against *H. pylori* has been reported to be due to the production of a radical intermediate [33]. This information suggests the possibility that a radical intermediate that appears as the intermediate for the metabolism of a nitro residue covalently binds to the target molecule. If this hypothesis is correct, it could well explain the strong post-antibiotic effect seen with OPC-67683 against intracellular mycobacterium, a property considered necessary to kill latent TB.

The therapeutic efficacy of OPC-67683 was evaluated in vivo in an experimental chronic TB mouse model. In this



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Compound	mouse			human		
	Dose (mg/kg)	Cmax (μg/mL)	AUCt (μg.h/mL)	Dose	Cmax (μg/mL)	AUCt (μg.h/mL)
OPG67683	2.5	0.297	4.13			
RFP	5	5.10	48.2	450mg	5.5	29.7
INH	10	3.06	4.55	300mg	4.5	22.9
EB	100	3.51	12.1	850mg	3.7	13.0
PZA	100	63.2	198	1-2g	59.33	

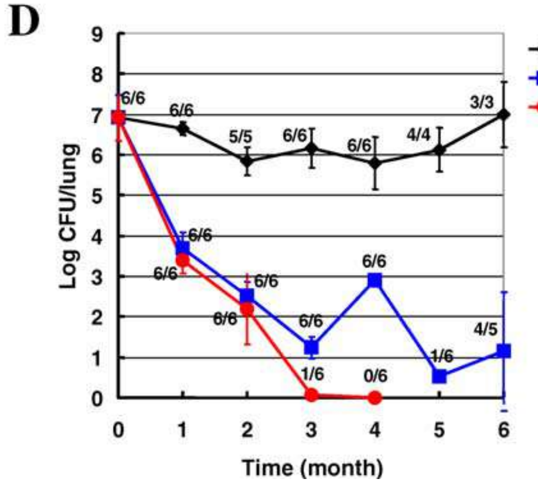

Figure 4. Effects of OPC-67683 in an Experimental Mouse Model of TB

(A) ICR mice were inoculated intravenously with *M. tuberculosis* Kurono. After 28 d, test compounds were administered orally once daily for 28 d (OPC-67683: 40–0.156 mg/kg, RFP: 20–1.25 mg/kg, INH: 20–1.25 mg/kg, EB: 160–20 mg/kg, SM: 160–20 mg/kg, PZA: 320–40 mg/kg, and PA-824: 40–1.25 mg/kg; 2-fold dilution). Mean value ($n = 5$) of $\log_{10}$ CFU was plotted.

(B) BALB/c standard and nude mice were inoculated intravenously with *M. tuberculosis* Kurono. From the following day, OPC-67683 was administered orally once daily for 10 d (OPC-67683: 10–0.313 mg/kg, 2-fold dilution). The bar was expressed as mean value and SD ($n = 5$) of $\log_{10}$ CFU.

(C) The doses of conventional drugs used for evaluating regimen are summarized in this table. The doses set up for using the plasma C_{max} achieved in mice TB model is equivalent to that achieved in humans at the clinical dose.

(D) ICR mice were inoculated intratracheally with *M. tuberculosis* Kurono. After 28 d, mice were treated for 2 mo with a combination of OPC-67683, RFP, and PZA (ORZ), or RFP, INH, EB, and PZA (RHEZ) (intensive treatment), and for an additional 2 mo with OPC-67683 and RFP or 4 mo with RFP and INH (maintenance treatment) (OPC-67683: 2.5 mg/kg, RFP: 5 mg/kg, INH: 10 mg/kg, EB: 100 mg/kg, and PZA: 100 mg/kg). Mean value and SD bar ($n = 6$) of $\log_{10}$ CFU was plotted. The fraction refers to the number of mice in which at least one colony was detected of the total number of surviving mice.

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model, OPC-67683 exhibited the most potent anti-tubercular activity in comparison with the reference compounds. The viable bacterial counts in the lung were markedly reduced dose-dependently by OPC-67683 at 0.313 mg/kg and higher. A 95% reduction in bacterial load was achieved at 0.625 mg/kg. Furthermore, the efficacy of OPC-67683 in a TB model established using immunodeficient mice was similar to that seen using standard mice.

Treatment of TB requires combination therapy not only to shorten the treatment duration but also to prevent the development of resistance. The effects of OPC-67683 in combination with currently used TB drugs were therefore evaluated both in vitro and in vivo. OPC-67683 did not exert antagonistic effects in any of the tested combinations, and produced partial synergistic or synergistic effects when combined with RFP or EB in vitro. A combination regimen containing OPC-67683, RFP, and PZA produced a steady rapid reduction in bacterial load over the first 3 mo. These results suggest that a new regimen containing OPC-67683 could possibly be effective in shortening the clinical treatment duration.

Multiple-drug therapy is a common clinical practice, particularly in patients with concomitant diseases or conditions. However, whenever two or more drugs are administered concurrently, the possibility of drug interactions exists. Many drug interactions are clinically caused by inhibition of drug-metabolizing enzymes, such as CYPs, leading to decreased metabolic clearance and increased exposure to the inhibited drug [34–36]. Rifamycin derivatives such as RFP usually induce CYP3A4 enzymes, remarkably reducing the

Table 8. Effect of OPC-67683 on CYP1A1/2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 Mediated Reactions in Human Liver

CYP	Reaction	OPC-67683 or In hibitor	Percent of Control		
			Concentration (μM)		
			10	30	100
CYP1A1/2	7-Ethoxyresorufin O-deethylation	OPC-67683	98.4	102.5	98.6
		Furafylline			32.3
		7,8-Benzoflavone			3.8
CYP2A6	Coumarin 7-hydroxylation	OPC-67683	103.1	97.8	100.8
		Diethyldithiocarbamate			38.2
CYP2B6	7-Benzyloxyresorufin O-debenzylation	OPC-67683	118.3	112.8	122.3
		Orphenadrine			118.8
CYP2C8/9	Tolubutamide methylhydroxylation	OPC-67683	107.2	107.8	108.5
		Sulfaphenazole			25.5
		Quercetin			30.6
CYP2C19	S-mephenytoin 4′ -hydroxylation	OPC-67683	113.3	106.5	107.6
		Tranylcypromine			16.6
CYP2D6	Bufuralol 1′ -hydroxylation	OPC-67683	99.1	103.3	97.8
		Quinidine			0.0
CYP2E1	Chlorzoxazone 6-hydroxylation	OPC-67683	110.8	112.4	112.5
		Diethyldithiocarbamate			55.0
CYP3A4	Testosterone 6β̃-hydroxylation	OPC-67683	117.7	117.7	115.6
		Ketoconazole			0.5
CYP3A4	Nifedipine oxidation	OPC-67683	101.3	99.9	100.3
		Ketoconazole			3.4

The substrate concentrations used for each assay were 0.5 μM 7-ethoxyresorufin, 2 μM coumarin, 1.5 μM 7-benzyloxyresorufin, 400 μM tolbutamide, 100 μM S-mephenytoin, 20 μM bufuralol, 100 μM chlorzoxazone, 100 μM testosterone, and 50 μM nifedipine. Enzyme incubations and metabolite analysis were carried out in triplicate. Each value represents the mean.
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bioavailability of the drug itself as well as other CYP-intermediated drugs, including protease inhibitors, which are indispensable in the treatment of HIV/AIDS [37]. It is therefore important that a new TB drug does not induce nor is affected by metabolic enzymes. With this in mind, we studied the interactions between OPC-67683 and metabolic enzymes. Our results showed that OPC-67683 was hardly metabolized when exposed to human and animal liver microsomes and did not have inductive, stimulatory, or inhibitory effects on CYP enzyme activities at concentrations up to 100 μM, indicating that OPC-67683, at the expected therapeutic concentrations, would not be expected to cause clinically significant interactions with other CYP-metabolized drugs, such as rifamycin derivatives. These results, together with data supporting non-compromised anti-TB activity in immunodeficient animals, suggest that OPC-67683 could be useful in treating TB patients who are also co-infected with HIV/AIDS.

We conclude that OPC-67683 possesses qualities that could help address the unmet needs in TB chemotherapy, i.e., the need for shortened treatment duration, effectiveness against MDR-TB, ability to be used safely in HIV/AIDS patients, and the treatment of LTBI. An early Phase II clinical study to confirm the efficacy in patients is now ongoing.

Furthermore, the Global Alliance for TB Drug Development is aiming to establish an entirely new regimen containing the best combination of new drugs [38]. Development and integration of these drugs into the regimen individually would normally be done in series, taking at least six years for each drug. We therefore attach importance to including an evaluation of the effects of OPC-67683 in combination with not only conventional drugs but also new drugs as early as possible in order to contribute data necessary for establishing the best regimen needed to address the unmet needs in TB treatment.

Supporting Information

Table S1. Viable Count in Lung of Each Group of OPC-67683, RFP, INH, EB, SM, PZA, and PA-824 after 4 wk of Treatments on the Experimental Chronic TB Model in Mice

Found at doi:10.1371/journal.pmed.0030466.st001 (43 KB DOC).

Acknowledgments

We thank F. Tabusa and T. Sumida for their helpful discussions and expertise in their respective fields of medicinal chemistry and screening toxicology, and H. Ishikawa for his unrelenting support in bringing this TB drug project to a reality. We also acknowledge the many researchers, particularly M. Teshima, K. Ohguro, T. Hasegawa, and Y. Haraguchi, T. Koga, and several other staff members of Otsuka Pharmaceutical, the sponsoring company, for their many hours of dedication that have helped move OPC-67683 to its current stage. We also thank V. Lawlor for his editorial support.

Author contributions. All listed authors actively participated in the studies related to OPC-67683 described in this manuscript. M. Matsumoto established a strategy for screening for all synthesized compounds, and was instrumental in selecting and evaluating OPC-67683 through conducting susceptibility tests, establishing the inhibitory activity of OPC-67683 on mycolic acid biosynthesis, and carrying out all in vivo studies involving OPC-67683 in collaboration with H. Hashizume, T. Tomishige, and M. Kawasaki. H. Hashizume was responsible for conducting the bacteria reverse mutation testing and the absorption study in mice. T. Tomishige looked after determining the intracellular activity of OPC-67683 and confirming the potency in the immunosuppressive animal model. M. Kawasaki conducted the studies related to the mechanism of action, susceptibility testing, experimental isolation of resistant strains, confirmation of a mutation in the Rv3547 gene in OPC-67683-resistant strains, and identification of metabolites. H. Tsubouchi and M. Komatsu coordinated the overall activities involved in synthesizing the many

novel derivatives for selecting potent antituberculosis agents, and, together with H. Sasaki, synthesized and supplied the derivatives used for in vitro and in vivo evaluations. They also established the facile and practical synthesis method for the intermediates to synthesize many target compounds and supplied derivatives for the screening toxicity test in animals in large scale. H. Sasaki assumed a main role in synthesising various compounds, including OPC-67683. Y. Shimokawa was in charge of the drug interaction studies.

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Editors' Summary

Background. One-third of the world's population is infected with *Mycobacterium tuberculosis,* the bacterium that causes tuberculosis (TB). Most infected people are healthy—the bacteria can remain latent for years, hidden within cells in the body. However, every year 8 million people develop active TB, a chronic disease that usually affects the lungs, and 2 million people die. For most of the second half of the 20th century, TB was in decline because of the powerful antibiotics that were developed from the 1940s onwards. The standard treatment for TB—four antibiotics that have to be taken several times a week for at least six months to flush out any latent *M. tuberculosis* bacteria—was introduced in the late 1970s and saved many lives. Recently, however, efforts to eradicate TB have been set back by the HIV/AIDS epidemic—people with damaged immune systems are very susceptible to TB—and the emergence of multi-drug resistant (MDR) bacteria.

Why Was This Study Done? The treatment for TB is long and unpleasant, and patients who develop MDR-TB have to be treated with second-line drugs that are less effective, more expensive, and more toxic. In addition, for people infected with both HIV and TB, some antiretroviral and anti-TB drugs cannot be used at the same time. Many drugs are either activated or removed by enzymes in the liver, so combinations of these two classes of drugs sometimes alter liver function in a way that causes clinical problems. There is, therefore, an urgent need for new, effective anti-TB drugs that attack *M. tuberculosis* in a different way than do existing drugs. Such drugs should ideally be active against MDR *M. tuberculosis*, work quickly at low doses, be active against latent bacteria, and have minimal effects on the liver so that they can be used in patients co-infected with HIV. In this study, the researchers investigated a chemical called OPC-67683.

What Did the Researchers Do and Find? The researchers identified a compound that inhibited the production of mycolic acid—an essential component of the cell wall of *M. tuberculosis*—and they tested its ability to kill the organism. They then tested in detail its ability to inhibit bacterial growth in dishes of antibiotic-sensitive and MDR *M. tuberculosis* and isolates from patients. OPC-67683 inhibited the growth of all these bugs at lower concentrations than the four antibiotics used in the standard TB treatment. It also killed bacteria hidden within human cells as well as or better than these drugs. Next, the researchers treated mice infected with *M. tuberculosis* with OPC-67683. They found that it reduced the number of bacteria in the lungs of both normal and immunocompromised mice at lower concentrations than the standard drugs. Furthermore, when combined with two of the standard drugs, it reduced the time taken to clear bacteria from the lungs by the standard drug regimen by two months. Finally, the researchers showed that OPC-67683 had no effects on the liver enzymes that metabolize antiretrovirals, and, conversely, that the activity of OPC-67683 was not affected by liver enzymes. Thus, this agent is unlikely to cause clinical problems or lose its efficacy in HIV patients who are receiving antiretroviral drugs.

What Do These Findings Mean? These results from laboratory and animal experiments suggest that OPC-67683 could possibly fulfill the criteria for a new anti-TB drug. OPC-67683 is active against MDR-TB. It is also active against intracellular TB, which the authors postulate could be a positive link with the effective treatment of latent TB, and it works quickly in animals when combined with existing anti-TB drugs. Importantly, it also disables *M. tuberculosis* in a unique way and does not appear to have any major effects on the liver that might stop it from being used in combination with antiretrovirals. All these preclinical characteristics now need to be checked in people—many drugs do well in preclinical studies but fail in patients. These clinical studies need to be expedited given the upsurge in TB, and, write the researchers, OPC-67683 needs to be tested in combination with both conventional drugs and other new drugs so that the best regimen of new drugs for the treatment of TB can be found as soon as possible.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0030466.

- US National Institute of Allergy and Infectious Diseases patient fact sheet on tuberculosis
- US Centers for Disease Control and Prevention information on tuberculosis
- MedlinePlus encyclopedia entry on tuberculosis
- NHS Direct Online patient information on tuberculosis from the UK National Health Service
- World Health Organization information on the global elimination of tuberculosis
- Global Alliance for TB Drug Development information on why new TB drugs are needed

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Fused Heterocycles: Synthesis of Some New Imidazopyridines as Anti-Mycobacterial Agents

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The reaction of semicarbazones bearing an imidazo[1,2-*a*]pyridine ring system with mercaptoacetic acid was investigated. The anti-mycobacterial activity of the compounds thus obtained were evaluated against *Mycobacterium tuberculosis* $H_{37}Rv$, using rifampin as the standard. Only **IVe** showed activity at 6.25 μg mL^{-1}.

Key Words: Imidazo[1,2-*a*]pyridine, semicarbazones, 4-thiazolidinone, antituberculous activity.

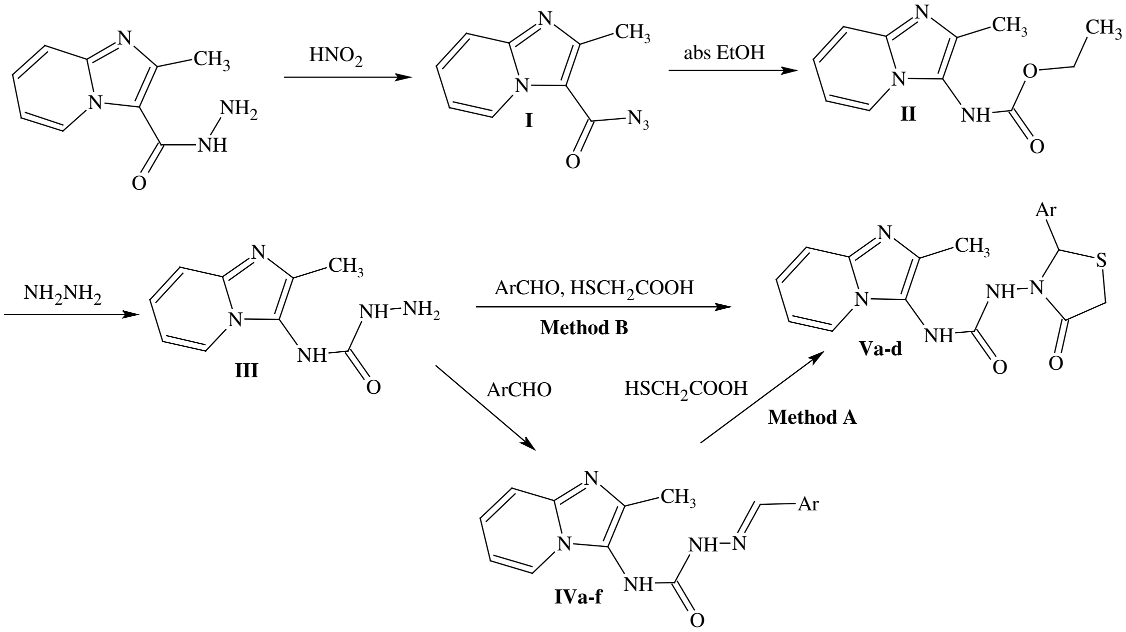
Introduction

Tuberculosis (TB) remains a major cause of death worldwide. The emergence of multi-drug resistant TB (MDR-TB) is most alarming. Up to 4% of all TB cases worldwide are resistant to more than one anti-tubercular drug because of incomplete or partial therapy.[1,2] Isonicotinic acid hydrazide (INH) is one of the primary drugs, in combination with ethambutol, rifampin and streptomycin, for treating TB, but the treatment of the disease is still a major health problem due to multi-drug resistant bacterial strains. New anti-mycobacterial agents, different from currently available first-line drugs, are urgently needed. This is an additional reason why many laboratories are seeking new anti-tubercular agents that could confer greater selectivity and lower toxicity.[3] We recently reported the synthesis of some imidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazides as structural analogues of INH, related compounds, and their anti-mycobacterial activity.[4,5] Continuing our search for new anti-tubercular agents we have now synthesized some new semicarbazones (**IVa-f**) and 4-thiazolidinones (**Va-d**) incorporating an imidazo[1,2-*a*] pyridine moiety. These compounds were characterized by their elemental and spectral analyses (IR, ^{1}H-NMR, and mass spectra).

*Corresponding author

Experimental

Melting points were determined with an Electrothermal 9200 apparatus in open capillary tubes and are uncorrected. IR spectra were recorded on KBr disks, using a Perkin Elmer 1600 FT-IR spectrophotometer. ^{1}H-NMR spectra were obtained in DMSO-d_6, with Bruker AC 200 and Inova (500 MHz) spectrophotometers using TMS as the internal standard. EI and APCI mass spectra were determined with VG Zab Spec and LC/MSD Diod-Array instruments. Elemental analyses were performed on a Leco 932 CHNS-O elemental analyzer. The starting materials were either commercially available or synthesized according to the references cited.



Ar= C_6H_5 (**IVa**), p-C_6H_4Cl (**IVb**), p-$C_6H_4CH_3$ (**IVc**), p-$C_6H_4OCH_3$ (**IVd**), p-$C_6H_4NO_2$ (**IVe**), 5-nitro-2-furyl (**IVf**)
Ar= C_6H_5 (**Va**), p-C_6H_4Cl (**Vb**), p-$C_6H_4CH_3$ (**Vc**), p-$C_6H_4OCH_3$ (**Vd**)

Scheme. Synthetic pathway for the preparation of **I-V**.

2-Methylimidazo[1,2-*a*]pyridine-3-carbonyl azide (I)

In 80 mL of cold water were dissolved 0.02 mol of 2-methylimidazo[1,2-*a*]pyridine-3-carbohydrazide[4] and 0.02 mol of $NaNO_2$. Dropwise, 20 mL of HCl (25%) was added, maintaining the temperature below 15 °C. The solution was stirred for 15 min, neutralized with Na_2CO_3, and then the solid thus obtained was filtered, and dried and recrystallized from $CHCl_3$.

Yield: 85.67%, m.p.: 102-5 °C. IR ν_{max} (cm^{-1}): 2149 (N≡N), 1646 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.50 (3H, s, CH_3); 7.27 (1H, dd, $J_{5,6}$=$J_{6,7}$= 7 Hz, C_6-H); 7.68 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.74 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 9.34 (1H, d, $J_{5,6}$= 7 Hz, C_5-H). EIMS (%): 201 ($M^{+\cdot}$, 21.01), 144 (base peak). Anal. for $C_9H_7N_5O$: Calc. C: 53.73, H: 3.51, N: 34.81. Found C: 53.48, H: 3.98, N: 34.37.

Ethyl (2-methylimidazo[1,2-*a*]pyridine-3-yl)carbamate (II)

In 25 mL of absolute EtOH was refluxed 0.02 mol of **I** for 2.5 h; then EtOH was removed in vacuo. The product thus obtained was recrystallized from EtOH (96%).

Yield: 84.61%, m.p.: 72-8 °C. IR ν_{max} (cm^{-1}): 3273 (NH), 1694 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 1.23 (3H, t, $OCH_2\mathbf{CH_3}$); 2.37 (3H, s, CH_3); 4.12 (2H, q, $O\mathbf{CH_2}CH_3$); 6.87 (1H, dd, $J_{5,6}$=$J_{6,7}$= 7 Hz, C_6-H); 7.20 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.43 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.96 (1H, d, $J_{5,6}$= 7 Hz, C_5-H); 9.12 (1H, s, NH). EIMS (%): 219 ($M^{+\cdot}$, 83.17), 119 (base peak). Anal. for $C_{11}H_{13}N_3O_2.H_2O$: Calc. C: 55.69, H: 6.37, N: 17.71. Found C: 55.00, H: 5.86, N: 17.96.

N-(2-Methylimidazo[1,2-*a*]pyridine-3-yl)hydrazinecarboxamide (III)

In 20 mL of hydrazine (98%) was refluxed 0.02 mol of **II** for 2 h. The precipitate formed after cooling was filtered, washed with water, dried and recrystallized from EtOH (96%).

Yield: 43.70%, m.p.: 222-5 °C. IR ν_{max} (cm^{-1}): 3304, 3161 (NH), 1643 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.22 (3H, s, CH_3); 4.35 (2H, s, $NHCONHN\mathbf{H_2}$); 6.84 (1H, dd, $J_{5,6}$=$J_{6,7}$= 7 Hz, C_6-H); 7.16 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.59 (1H, s, N**H**CONHNH$_2$); 7.74 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.89 (1H, d, $J_{5,6}$= 7 Hz, C_5-H); 8.31 (1H, s, NHCON**H**NH$_2$). EIMS (%): 205 ($M^{+\cdot}$, 46.18), 144 (base peak). Anal. for $C_9H_{11}N_5O$: Calc. C: 52.67, H: 5.40, N: 34.13. Found C: 52.81, H: 5.39, N: 34.39.

General procedure for the preparation of aromatic aldehyde N-(2-methyl imidazo [1,2-*a*]pyridin-3-yl)semicarbazones (IVa-f)

For 2-6 h, 0.01 mol of **III**, 0.011 mol of appropriate aromatic aldehyde, and 25 mL of EtOH (96%) were refluxed. The solid that separated was filtered and recrystallized from EtOH or washed with EtOH (96%).

IVa. Yield: 60.00%, m.p.: 223-5 °C. IR ν_{max}(cm^{-1}): 3304, 3161 (NH), 1689 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.27 (3H, s, CH_3); 6.88 (1H, dd, $J_{5,6}$= 6 Hz, $J_{6,7}$= 7 Hz, C_6-H); 7.21 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.39-7.45 (4H, m, C_8-H and phenyl 3,4,5-H); 7.86-7.89 (2H, m, phenyl 2,6-H); 7.99-8.01 (2H, m, C_5-H and N=CH); 9.07 (1H, s, **NH**CONHN); 10.99 (1H, s, NHCO**NH**N). EIMS (%): 293 ($M^{+\cdot}$, 66.45), 78 (base peak). Anal. for $C_{16}H_{15}N_5O$: Calc. C: 65.52, H: 5.15, N: 23.88. Found C: 65.51, H: 4.92, N: 23.51.

IVb. Yield: 81.34%, m.p.: 242-4 °C. IR ν_{max} (cm^{-1}): 3369, 3170 (NH), 1685 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.26 (3H, s, CH_3); 6.87 (1H, dd, $J_{5,6}$= $J_{6,7}$= 7 Hz, C_6-H); 7.33 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.44 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.46 (1H, d, J= 8 Hz, phenyl 3,5-H); 7.90 (2H, d, J= 8 Hz, phenyl 2,6-H); 7.96-7.99 (2H, m, C_5-H and N=CH); 9.07 (1H, s, N**H**CONHN); 10.97 (1H, s, NHCON**H**N). EIMS (%): 329 (M^{+2}, 14.69), 327 ($M^{+\cdot}$, 39.62), 173 (base peak). Anal. for $C_{16}H_{14}ClN_5O$: Calc. C: 58.63, H: 4.31, N: 21.37. Found C: 58.70, H: 3.89, N: 21.51.

IVc. Yield: 84.25%, m.p.: 202-7 °C. IR ν_{max} (cm^{-1}): 3369, 3201(NH), 1687 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.26 (3H, s, CH_3); 2.33 (3H, s, phenyl 4-CH_3); 6.86 (1H, dd, $J_{5,6}$= 6 Hz, $J_{6,7}$= 7 Hz, C_6-H); 7.15-7.24 (3H, m, C_7-H and phenyl 3,5-H); 7.33 (2H, d, J= 8 Hz, phenyl 2,6-H); 7.44 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.96-7.98 (2H, m, C_5-H and N=CH); 8.92 (1H, s, N**H**CONHN); 10.76 (1H, s, NHCON**H**N). EIMS (%): 307 ($M^{+\cdot}$, 54.31), 134 (base peak). Anal. for $C_{17}H_{17}N_5O$: Calc. C: 66.43, H: 5.58, N: 22.79. Found C: 66.07, H: 5.51, N: 22.39.

IVd. Yield: 87.09%, m.p.: 188-92 °C. IR ν_{max} (cm^{-1}): 3307, 3194 (NH), 1690 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.26 (3H, s, CH_3); 3.80 (3H, s, phenyl 4-OCH_3); 6.85 (1H, dd, $J_{5,6}$=$J_{6,7}$= 7 Hz, C_6-H); 6.96 (2H, d, J= 9 Hz, phenyl 3,5-H); 7.18 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.44 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.78 (2H, d, J= 9 Hz, phenyl 2,6-H); 7.93-7.98 (2H, m, C_5-H and N=CH); 8.90 (1H, s, N**H**CONHN); 10.69 (1H, s, NHCONH**H**N). EIMS (%): 323 ($M^{+\cdot}$, 27.48), 150 (base peak). Anal. for $C_{17}H_{17}N_5O_2$: Calc. C: 63.15, H: 5.30, N: 21.66. Found C: 63.34, H: 4.93, N: 21.48.

IVe. Yield: 73.41%, m.p.: 228-33 °C. IR ν_{max}(cm^{-1}): 3379, 3197 (NH), 1684 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.27 (3H, s, CH_3); 6.87 (1H, dd, $J_{5,6}$= $J_{6,7}$= 7 Hz, C_6-H); 7.21 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.45 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.99 (1H, d, $J_{5,6}$= 7 Hz, C_5-H); 8.08 (1H, s, N=CH); 8.10 (2H, d, J= 9 Hz, phenyl 2,6-H); 8.25 (2H, d, J= 9 Hz, phenyl 3,5-H); 9.22 (1H, s, N**H**CONHN); 11.26 (1H, s, NHCON**H**N). EIMS (%): 338 ($M^{+\cdot}$, 39.30), 173 (base peak). Anal. for $C_{16}H_{14}N_6O_3.H_2O$: Calc. C: 53.92, H: 4.52, N: 23.58. Found C: 54.24, H: 4.33, N: 24.65.

IVf. Yield: 56.50%, m.p.: 206 °C. IR ν_{max} (cm^{-1}): 3364, 3213 (NH), 1694 (C=O). ^{1}H-NMR (200 MHz) δ (ppm): 2.24 (3H, s, CH_3); 6.79 (1H, dd, $J_{5,6}$=$J_{6,7}$= 7 Hz, C_6-H); 7.14 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.22 (1H, d, J= 4 Hz, furan 3-H); 7.36 (1H, d, $J_{7,8}$= 9 Hz, C_8-H); 7.70 (1H, d, J= 4 Hz, furan 4-H); 7.83 (1H, s, N=CH), 7.92 (1H, d, $J_{5,6}$= 7 Hz, C_5-H); 8.99 (1H, s, **NH**CONHN); 11.25 (1H, s, NHCO**NH**N). APCI MS (%): 329 ($[M+H]^+$, 53.6), 79 (base peak). Anal. for $C_{14}H_{12}N_6O_4.1.5H_2O$: Calc. C: 47.98, H: 4.31, N: 23.98. Found C: 47.48, H: 4.17, N: 24.26.

General procedure for the preparation of 1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-3-(4-oxo-2-aryl-1,3-thiazolidin-3-yl)ureas (Va-d)

Method A

A mixture of **IVa-d** (0.01 mol) and $HSCH_2COOH$ (0.25 mol) was heated under reflux for 4 h in dry benzene (30 mL) using a Dean-Stark trap. Excess benzene was evaporated in vacuo. The residue was triturated with saturated $NaHCO_3$ until CO_2 evaluation ceased and was then left to stand overnight. The solid thus obtained was filtered and washed with H_2O.

Method B

The appropriate aromatic aldehyde (0.011 mol) was added to a solution of **III** (0.01 mol) in dry benzene (30 mL) and the mixture was heated under reflux for 4 h using a Dean-Stark trap. After cooling, $HSCH_2COOH$ (0.15 mol) was added dropwise to the solution and the resulting mixture was refluxed for 2-4 h. The compounds were purified using the procedure described in Method A.

Va. Yield: 13.08% (Method A), 34.50% (Method B), m.p.: 233-6 °C. IR ν_{max} (cm^{-1}): 3295, 3154 (NH), 1700, 1674 (C=O). ^{1}H-NMR (500 MHz) δ (ppm): 2.13 (3H, s, CH_3); 3.76, 3.85 (2H, dd, J= 16 Hz, thiazolidinone CH_2); 5.83 (1H, s, thiazolidinone CH); 6.86 (1H, d, $J_{5,6}$= 6 Hz, C_6-H); 7.18 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 8 Hz, C_7-H); 7.38-7.48 (6H, m, C_8-H and phenyl 2,3,4,5,6-H), 7.76 (1H, s, C_5-H); 8.41 (1H, s, **NH**CONH); 8.94 (1H, s, NHCO**NH**). APCI MS (%): 368 ($[M+H]^+$, base peak). Anal. for $C_{18}H_{17}N_5O_2S.0.5H_2O$: Calc. C: 57.42, H: 4.81,N: 18.60. Found C: 57.27, H: 4.38, N: 18.49.

Vb. Yield 55.00% (Method A), 51.68% (Method B), m.p.: 244 °C. IR ν_{max} (cm^{-1}): 3395, 3263 (NH), 1700, 1674 (C=O). ^{1}H-NMR (500 MHz) δ (ppm): 2.25 (3H, s, CH_3); 3.86, 3.88 (2H, dd, J= 16 Hz, thiazolidinone CH_2); 5.86 (1H, s, thiazolidinone CH); 6.86 (1H, dd, $J_{5,6}$= 6 Hz, $J_{6,7}$= 7 Hz, C_6-H); 7.19 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 8 Hz, C_7-H); 7.41 (1H, d, $J_{7,8}$= 8 Hz, C_8-H); 7.48-7.53 (4H, m, phenyl 2,3,5,6-H); 7.76

(1H, s, C_5-H); 8.64 (1H, s, **NH**CONH); 9.09 (1H, s, NHCO**NH**). APCI MS (%): 404 ($[M+H]^{+2}$, 16.85); 402($[M+H]^{+}$, 49.44), 174 (base peak). Anal. for $C_{18}H_{16}ClN_5O_2S$: Calc. C: 53.80, H: 4.01, N: 17.43. Found C: 53.22, H: 4.11, N: 17.32.

Vc. Yield 17.04% (Method A), 40.00% (Method B), m.p.: 272 °C. IR ν_{max} (cm^{-1}): 3307, 3268 (NH), 1700, 1675 (C=O). ^{1}H-NMR (500 MHz) δ (ppm): 2.13 (3H, s, CH_3); 2.34 (3H, s, phenyl 4-CH_3); 3.75, 3.84 (2H, dd, J= 15 Hz, thiazolidinone CH_2), 5.81 (1H, s, thiazolidinone CH); 6.86 (1H, s, C_6-H); 7.19 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 9 Hz, C_7-H); 7.23 (2H, d, J= 8 Hz, phenyl 3,5-H); 7.37 (2H, s, phenyl 2,6-H); 7.41 (1H, d, J= 9 Hz, C_8-H); 7.76 (1H, s, C_5-H); 8.37 (1H, s, **NH**CONH); 8.90 (1H, s, NHCO**NH**). APCI MS (%): 382 ($[M+H]^{+}$, 3.6%), 79 (base peak). Anal. for $C_{19}H_{19}N_5O_2S.0.5H_2O$: Calc. C: 58.59, H: 5.18, N: 17.68. Found C: 58.61, H: 4.66, N: 18.09.

Vd. Yield 22.22% (Method A), 38.75% (Method B), m.p.: 242 °C. IR ν_{max} (cm^{-1}): 3256, 3213 (NH), 1704, 1674 (C=O). ^{1}H-NMR (500 MHz) δ (ppm): 2.14 (3H, s, CH_3); 3.73-3.83 (5H, m, phenyl 4-OCH_3 and thiazolidinone CH_2); 5.81 (1H, s, thiazolidinone CH); 6.85 (1H, s, C_6-H); 6.97 (2H, d, J= 8 Hz, phenyl 3,5-H); 7.19 (1H, dd, $J_{6,7}$= 7 Hz, $J_{7,8}$= 8 Hz, C_7-H); 7.36-7.42 (3H, m, C_8-H and phenyl 2,6-H); 7.75 (1H, s, C_5-H); 8.43 (1H, s, **NH**CONH); 8.94 (1H, s, NHCO**NH**). APCI MS (%): 398 ($[M+H]^{+}$, base peak). Anal. for $C_{19}H_{19}N_5O_3S$: Calc. C: 57.42, H: 4.82, N: 17.62. Found C: 56.95, H: 4.73, N: 17.76.

Antituberculous Activity

Anti-mycobacterial screening was conducted at 6.25 μg mL^{-1}against *M. tuberculosis* H_{37}Rv using the BACTEC 460 radiometric system at the National Institute of Allergy and Infectious Diseases, USA. Compounds resulting in inhibition < 90% (MIC > 6.25 μg mL^{-1}, MIC rifampin 0.031 μg mL^{-1}) were not evaluated further.[6] Only **IVe** showed anti-tuberculous activity (8% inhibition) at the tested concentration.

Results and Discussion

The synthetic pathway followed in the preparation of the compounds is outlined in the Scheme. The starting material, 2-methylimidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazide, was obtained by a previously described method.[4]

In the first stage of the study 2-methylimidazo[1,2-*a*]pyridine-3-carbonyl azide (**I**) was obtained by reacting 2-methylimidazo[1,2-*a*]pyridine-3-carbohydrazide with nitrous acid. Compound **I** was refluxed in absolute ethanol to gain ethyl 2-(methylimidazo[1,2-*a*]pyridin-3-yl)carbamate (**II**), which was then reacted with hydrazine to afford N-(2-methylimidazo[1,2-*a*]pyridin-3-yl)hydrazinecarboxamide (**III**). Condensation of **III** with the appropriate aromatic aldehydes in ethanol yielded the corresponding aldehyde semicarbazones **IVa-f**. The semicarbazones were reacted with mercaptoacetic acid in dry benzene (Method A) to give cyclocondensation products **Va-d**. On the other hand, refluxing a mixture of **III** and the appropriate aromatic aldehydes, together with mercaptoacetic acid in dry benzene (Method B), also produced the target compounds, **V,** but in higher yields, except **Vb**.

The IR spectrum of **I** displayed a strong band at 2149 cm^{-1} due to N_3 stretching. Characteristic N-H and C=O absorptions at 3271 cm^{-1} and 1694 cm^{-1}, and loss of N_3 absorption at 2149 cm^{-1} supported the formation of **II**. The N-H and C=O absorption peaks were observed in the 3304-3161 cm^{-1} region and at 1643 cm^{-1} in the spectrum of **III**. The IR spectra of **IVa-f** exhibited C=O bands in the 1684-1694 cm^{-1} region. A new strong band in the 1700-1704 cm^{-1} region in the spectra of **Va-d** provided firm support for the cycloaddition reaction. ^{1}H-NMR spectra of compounds **Va-c** displayed 2 doublets at about 3.76-3.88 ppm (except **Vd**, a multiplet together with OCH_3 resonance) due to the inequivalance of the SCH_2 protons. The singlet of N=CH at about 7.83-8.05 ppm in the spectra of **IVa-f** was shifted upfield to 5.81-5.86 ppm by the loss of the sp^2 character of the involved C atom. The mass spectra of all the compounds were relatively simple and showed their peaks due to molecular ions. All attempts to obtain the nitro derivatives (**V**) failed. This can be explained by the electronic effects of the nitro group (negative resonance and inductive effects) making the benzylic carbon atom more nucleophilic for the reaction with the sulfhydryl group.

All the compounds were evaluated for anti-tuberculous activity using the BACTEC method; only **IVe** showed activity (8% inhibition) at 6.25 μg mL^{-1}.

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Amide bond formation: beyond the myth of coupling reagents

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Amide bond formation is a fundamentally important reaction in organic synthesis, and is typically mediated by one of a myriad of so-called coupling reagents. This critical review is focussed on the most recently developed coupling reagents with particular attention paid to the pros and cons of the plethora of "acronym" based reagents. It aims to demystify the process allowing the chemist to make a sensible and educated choice when carrying out an amide coupling reaction (179 references).

Introduction

Amide bonds play a major role in the elaboration and composition of biological systems, representing for example the main chemical bonds that link amino acid building blocks together to give proteins. Amide bonds are not limited to biological systems and are indeed present in a huge array of molecules, including major marketed drugs. For example, Atorvastatin **1**, the top selling drug worldwide since 2003, blocks the production of cholesterol and contains an amide bond (Fig. 1),[1] as do Lisinopril **2** (inhibitor of angiotensin converting enzyme),[2] Valsartan **3** (blockade of angiotensin-II receptors),[3] and Diltiazem **4** (calcium channel blocker used in the treatment of angina and hypertension).[4]

Amide bonds are typically synthesised from the union of carboxylic acids and amines; however, the unification of these two functional groups does not occur spontaneously at ambient temperature, with the necessary elimination of water only taking place at high temperatures (*e.g.* >200 °C),[5] conditions typically detrimental to the integrity of the substrates. For this reason, it is usually necessary to first activate the carboxylic acid, a process that usually takes place by converting the –OH of the acid into a good leaving group prior to treatment with the amine (Scheme 1). Enzymatic catalysis has also been investigated for the mild synthesis of amides and the organic chemist may find some of these methods useful as an alternative to traditional methods.[6,7]

In order to activate carboxylic acids, one can use so-called coupling reagents, which act as stand-alone reagents to generate compounds such as acid chlorides, (mixed) anhydrides, carbonic anhydrides or active esters. The choice of coupling reagent is however critical. For example, in medicinal chemistry library-based synthesis, amides are often generated using broad ranges of substrates with varying reactivities (*e.g.* anilines, secondary amines, bulky substrates). A coupling reagent needs to be able to cope with this whole portfolio of reactivity. Many reviews on coupling reagents have been published,[8–14] illustrating their importance in the synthetic armoury of the synthetic chemist, but these reviews have often failed to offer a critical view on the subject making the choice of reagent difficult. An important issue is that many of the coupling reagents reported have not been compared to others, making any real evaluation impossible. As many groups have reported "new" reagents as being wonderful and better than others, the chemist looking at the field of coupling reagent for

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Professor Bradley's research interests are focused on the application of the tools and techniques of chemistry to address biological problems and needs, typically with a high-throughput twist. Two themes dominate at this time: the development of non-DNA based microarray platforms for cell and enzymatic based assays and the development of chemistries that enable efficient cellular delivery of proteins, nucleic acids, sensors and small molecules.

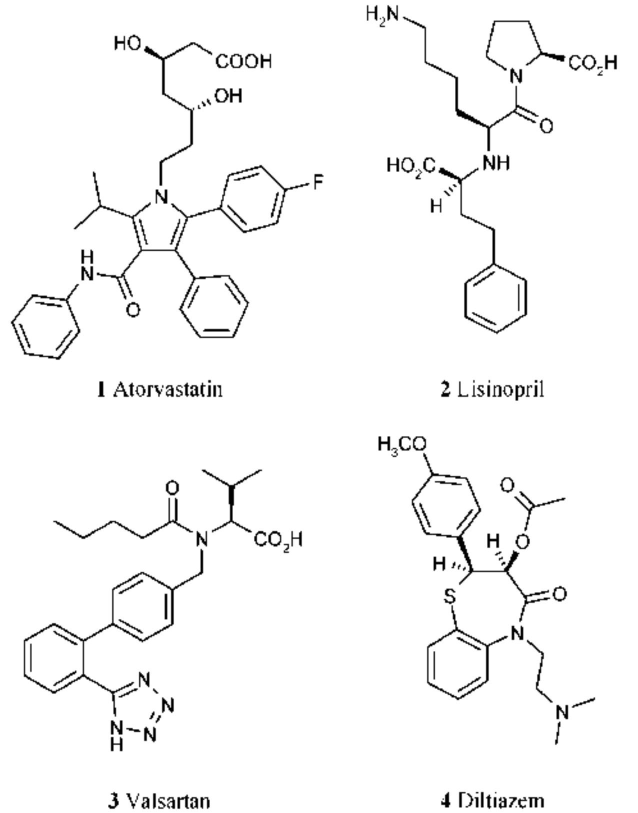
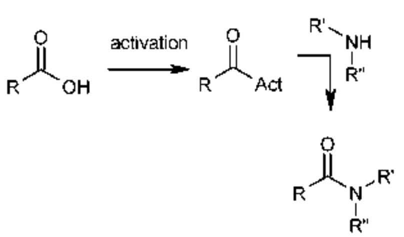


Fig. 1 Examples of top drugs containing an amide bond. These examples are just a small selection of drugs containing amide bonds illustrating the importance of this functional group.



Scheme 1 Principle of the activation process for amide-bond formation.

the first time can be completely lost. The process can be made even more complicated as epimerisation, usually through an oxazoline intermediate, may take place during amide bond formation. Thus, when coupling reagents are evaluated, several tests that have been developed to assess the extent of epimerisation (see Table 1) should be carried out.

1. Coupling using carbodiimides

1.1 Dicyclohexylcarbodiimide

Carbodiimides were the first coupling reagents to be synthesised. Dicyclohexylcarbodiimide (DCC, **5**) has been used for coupling since 1955,[21] and the mechanism for coupling carboxylic acids to amines is shown in Scheme 2.

The first step involves the reaction of the carboxylic acid with DCC to form the *O*-acylurea **6**. This intermediate can then yield a number of different products:

- The amide *via* direct coupling with the amine (the by-product formed, dicyclohexylurea (DCU **7**), is usually insoluble in the reaction solvent and can be removed *via* filtration).
- Formation of an *N*-acylurea **8** by-product
- Formation of the carboxylic acid anhydride which subsequently yields the amide by reaction with the amine (needs 2 equiv. of acid).

When using DCC, oxazolone formation can take place after generation of the *O*-acylurea leading to epimerisation,[19] especially important when activating acid groups in the α position of an amide bond.

In addition to peptide synthesis, carbodiimides (often with *N*-hydroxysuccinimide as an additive) have been used extensively in nanotechnology for the functionalisation of monolayers on surfaces and nanoparticles.[22,23]

1.2 Use of additives

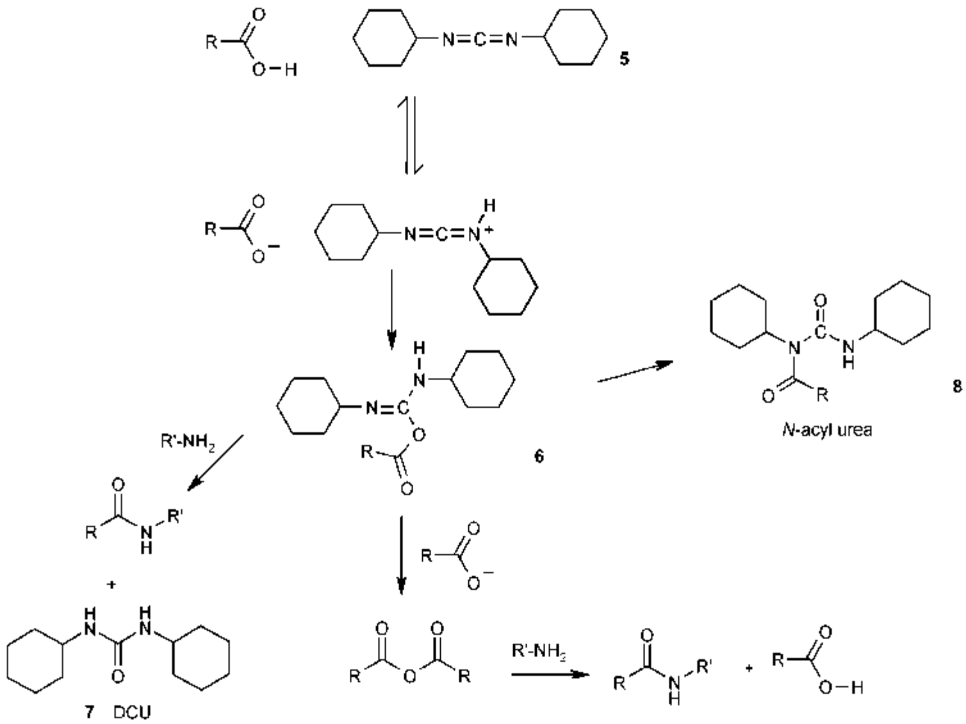
In order to reduce the epimerisation level when using carbodiimides as coupling reagents, Koenig and Geiger introduced 1-hydroxy-1*H*-benzotriazole (HOBt) **9** as an additive,[24,25] showing that, when using this additive, yields were higher and epimerisation levels lower. For example, when coupling Z-Gly-Phe-OH to H-Val-OMe, the epimerisation levels dropped from 35% to 1.5%.

HOBt **9** is believed to work by initially reacting with the *O*-acylurea **6** to give the OBt active ester **10**, which enhances the reactivity of the "activated ester" by encouraging/stabilising the approach of the amine *via* hydrogen bonding (Scheme 3). However, HOBt can yield by-products, thus it catalyses the formation of diazetidine **11** (Scheme 4).[26]

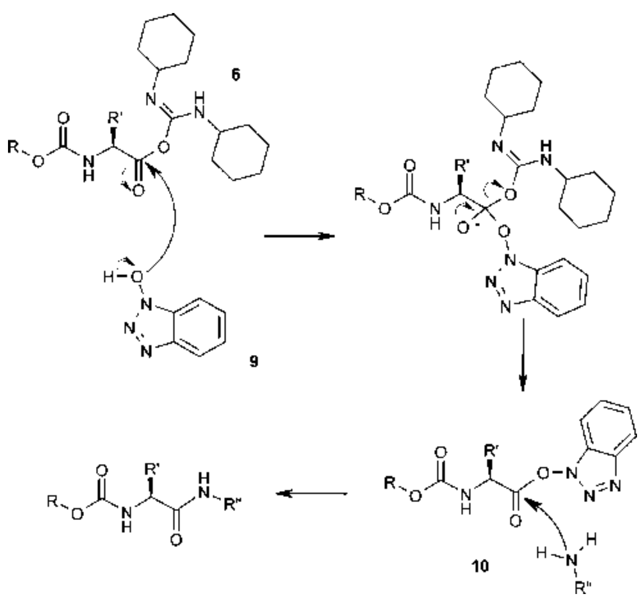
In 1994, Carpino reported a related additive, 1-hydroxy-7-azabenzotriazole (HOAt) **12** (Fig. 2), which was even more efficient than HOBt **9** in terms of yield, kinetics and reduced epimerisation levels.[27] For example epimerisation during coupling of Z-Val-OH and H-Val-OMe using DCC **5** dropped from 41.9% with HOBt **9** to 14.9% with HOAt **12**, while during the coupling of Z-PheVal-OH to H-Ala-OMe using

Table 1 Common epimerisation tests used for coupling reagent evaluation involving amino acids

Entry	Author	Acid	Amine	Analysis method
1	Young[15]	*Z*-Leu-OH	H-Gly-OEt	Optical rotation
2	Weinstein[16]	Ac-Phe-OH	H-Ala-OMe	NMR
3	Bodansky[17]	Ac-*iso*Leu-OH	H-Gly-OMe	Chiral HPLC
4	Anteunis[18]	Z-Gly-Phe-OH	H-Val-OMe	HPLC or NMR
5	Anderson[19]	Z-Gly-Phe-OH	H-Gly-OEt	Fractional crystallisation
6	Izumiya[20]	Z-Gly-Ala-OH	H-Leu-OBz	Hydrogenation followed by HPLC



Scheme 2 Coupling using DCC.



Scheme 3 Mechanism of activation by 1-hydroxy-1*H*-benzotriazole when used as an additive with DCC.

EDC, it dropped from 4.1% with HOBt **9** to under 2% with HOAt **12**.[27]

Much work has been carried out on the benefit of using additives. In particular, Carpino studied various isomers of HOAt concluding that the 7-isomer was the most efficient.[28] Albericio also showed that copper(II) complexes with HOAt **11** or HOBt **9** were efficient additives in lowering the epimerisation level.[29]

However, safety considerations when using benzotriazoles (and variants) need to be carefully considered as these compounds display explosive properties.[30,31]

1.3. Other carbodiimides

Since the application of DCC to amide bond formation, many carbodiimides, including DIC **13** (diisopropylcarbodiimide), have been reported and this field has been reviewed.[26] In particular, attention has focused on so-called water-soluble carbodiimides, as the ureas formed when using DCC **5** or the popular diisopropylcarbodiimide DIC **13** can sometimes be difficult to remove. Sheehan investigated several derivatives **14–17**, and concluded that coupling was more efficient when using tertiary amine carbodiimides rather than quaternary derivatives (*e.g.* **14** > **16**).[32,33]

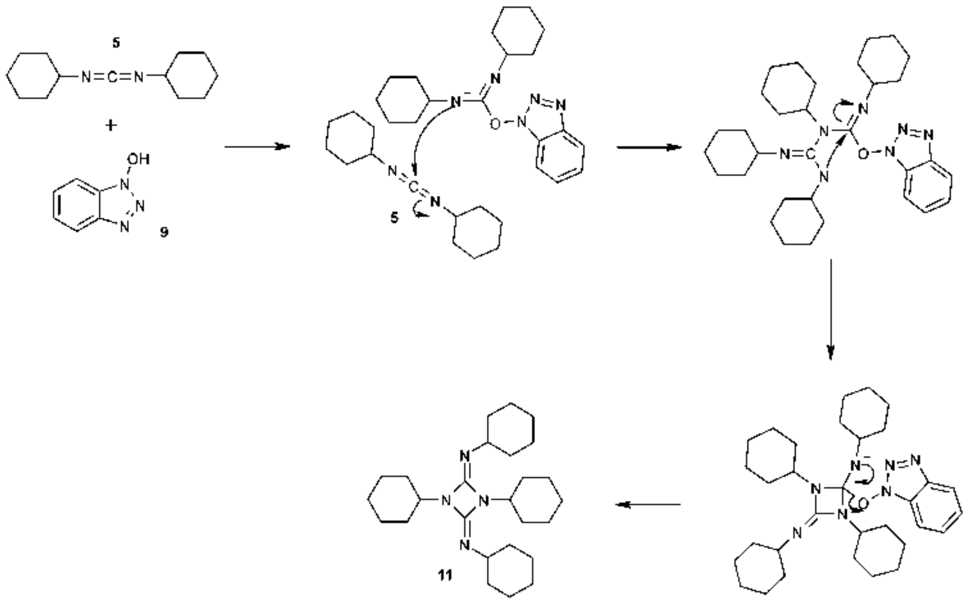
Carpino compared DIC **13** to EDC **20** and analogues **18–19**,[34] and also compared DIC **13** to some unsymmetrical alkyl/aryl carbodiimides such as phenyl ethyl carbodiimide (PEC **21**) and phenyl isopropyl carbodiimide (PIC **22**) (Fig. 3, Table 2). Overall, when using HOAt as an additive, DIC gave the best results for peptide segment coupling.

Other carbodiimides, BMC **23** and BEC **24** have been proposed by Izdebski, but these reagents showed no benefit over DIC **13**.[35]

Another so-called "water extractable" carbodiimide, BDDC **25** was synthesised and its efficiency was comparable to DCC **5** and EDC **20**.[36]

2. Coupling reagents based on 1*H*-benzotriazole

Several "salts" are often associated with reagents based on 1*H*-benzotriazoles, including uronium/aminium, phosphonium and immonium salts (Fig. 4).



Scheme 4 Formation of the diazetidine by-product when using DCC/HOBt.

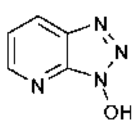


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Fig. 2 Structure of 1-hydroxy-7-azabenzotriazole.

2.1 Uronium/aminium salts

Many coupling reagents are based on the HOBt/HOAt system and uronium/aminium salts.[37] Uronium **26** and aminium **27** isomers of these reagents have been structurally identified and the true forms is probably a mater of debate depending on solvent, isolation method and counter anion *etc.* (Fig. 5).[38] Coupling reagents based on uronium salts were first reported as the *O*-isomer (**26**). However, Carpino showed by X-ray crystallography that HATU **28a** and HBTU **28b** were in fact the *N*-isomer (**27**).[38]

These reagents react with carboxylic acids to form OAt/OBt active esters, which then react with amines (Scheme 5).

A side-reaction can often take place with the amine reacting with the coupling reagent to form a guanidinium by-product **29** (Scheme 6),[14] thus order of addition and timing are crucial.

Comparative studies using HBTU[39] **28b** and TBTU[40] **30b** showed that the counter-anion had no practical influence on the outcome of coupling reactions using these reagents (Fig. 6). Carpino showed that the best results were obtained with HOAt, and many coupling reagents started to be based on this additive such as HATU **28a** and TATU **30a**.[27] It has been proven that coupling reagents based on HOAt (compared to HOBt) give faster, more efficient couplings with less epimerisation.[41] Much work has been carried out with variation of the substituents, yielding HAPyU **31** (also named BBC by Chen[42]) and TAPipU **32** with relatively little impact on the outcome of couplings.[43] Other modifications include HAPipU[37] **33a**, HBPipU[44] **33b**, HAMDU[37] **34a**, HBMDU[37] **34b** (also named BOI), and HAMTU[37] **35**. Overall the structural differences between these reagents did not appear to be based on rational considerations and were merely a screening of different substituents. Reagents **33–35** gave poor coupling results because the reagents were too reactive and degraded before coupling could take place.

Carpino modified the HOAt ring to form 5,6-benzo (**36**) and 4,5-benzo (**37**) derivatives,[45] which showed no real benefit over classical methods. In fact when used as additives with DIC, the epimerisation was higher than when using HOAt as additive.

More recently, derivatives HCTU **40a** and TCTU **40b** based on 6-chloro-HOBt were developed by Albericio,[46] but these reagents have not been directly compared to other coupling reagents.

Scientists at Argonaut also reported a 6-chloro-HOBt-based reagent, ACTU **40c**,[47] which was compared to DIC **13**. Some results were very disappointing as a simple, unhindered acid (phenylacetic acid) was only activated to 36%. This result was only improved to 70% when using an excess of acid, demonstrating that ACTU is a fairly poor coupling reagent.

Recently El-Faham developed some new reagents based on "immonium salts".[48] However, according to the terminology used in coupling reagents, these belong to the aminium/uronium salt-based class. Based on HOAt-/HOBt-rings, HAM_2PyU **41a**, HBM_2PyU **41b**, HAM_2PipU **42a**, HBM_2PipU **42b**, HAE_2PyU **43a**, HBE_2PyU **43b**, HAE_2PipU **44a**, HBE_2PipU **44b**, HATeU **45a** and HBTeU **45b** were synthesised. El-Faham firstly investigated the stability of these new reagents both in solution and in the solid state. Solids and solutions (in DMF) were stable for 3–4 weeks when kept under an inert atmosphere. However, like most coupling reagents, the reagents degraded rapidly when left in solution in the presence of a base. Thus, coupling involving hindered or poorly reactive substrates can be expected to be poor as longer reaction time are typically required for these substrates. Efficiency of the reagents was tested by measuring the

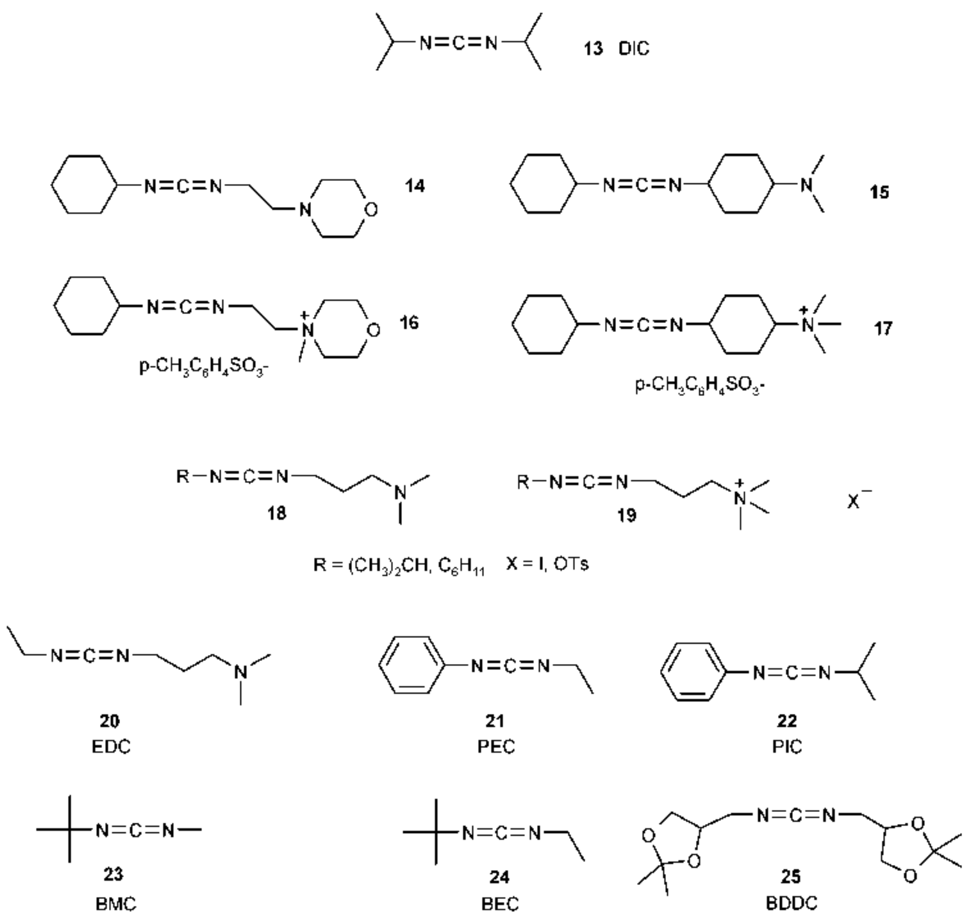

Fig. 3 Structure of some common carbodiimides.

Table 2 Results obtained when coupling Z-Phe-Val-OH to H-Pro-NH_2 with various carbodiimides and HOAt as an additive[34]

Entry	Coupling reagent	Yield (%)	LDL (%)
1	DIC	86	2.1
2	PEC	91	5.6
3	PIC	89	9.6
4	EDC	85	4.7
5	EDC·HCl	81	4.1

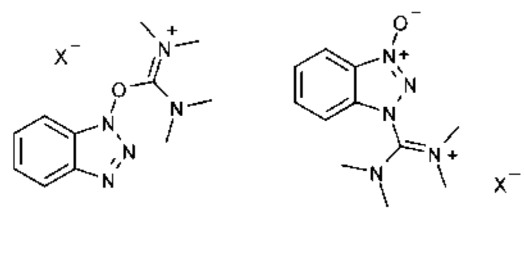

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Fig. 5 Aminium and uronium isomers.

half-life of the activated esters of Z-Aib-OH in the presence of 4-chloroaniline. HOAt-based reagents HAM$_2$PyU **41a**, HAM$_2$PipU **42a**, HAE$_2$PyU **43a**, HAE$_2$PipU **44a**, HATeU **45a** reacted more quickly than the HOBt-based reagents HBM$_2$PyU **41b**, HBM$_2$PipU **42b**, HBE$_2$PyU **43b**, HBE$_2$PipU **44b**, HBTeU **45b**. However no yields were given, which makes the direct comparison of the reagents impossible. Indeed, the activated esters might be hydrolysed rather than coupled to the poorly nucleophilic 4-chloroaniline. Epimerisation was low (Anteunis test) when the reagents were used in the presence of collidine but was as high as 11.8% in the presence of DIPEA when using HBTeU **45b**. Overall it was not evident

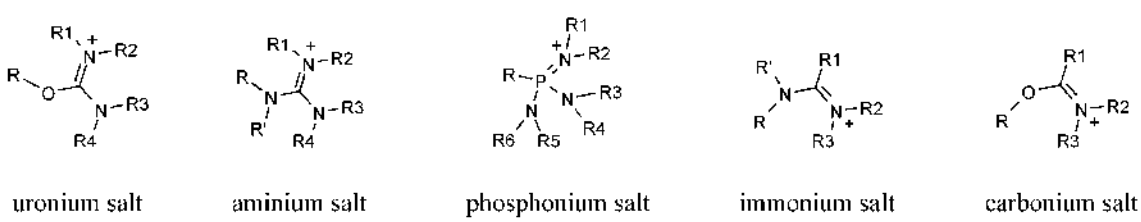
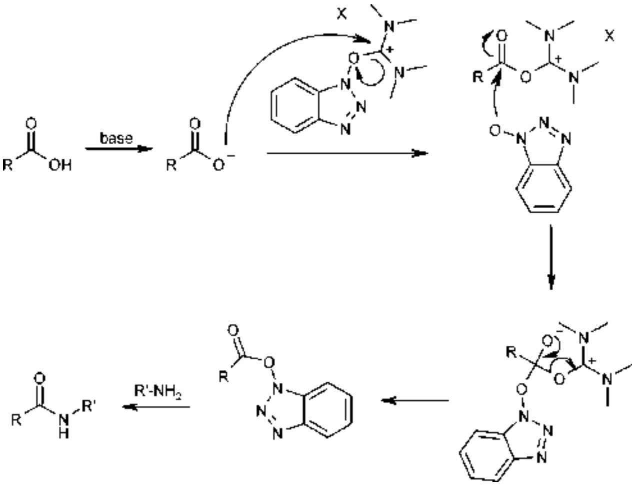
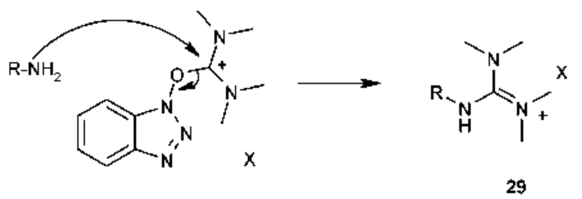


Fig. 4 Salts associated with reagents based on 1*H*-benzotriazole.



Scheme 5 Activation process using uronium/aminium type reagents.



Scheme 6 Guanidinium formation with aminium/uronium type coupling reagents.

that any of the new reagents reported were beneficial over a reagent like HATU **28a**.

Recently, El-Faham reported further development of such coupling reagents.[49] HDMA **46a**, HDMB **46b**, and 6-HDMCB **47** were evaluated and little variation on epimerisation levels was noticed, but HDMA **46a** proved to give higher yields for the synthesis of Fmoc-Val-Val-NH_2 compared to HATU **28a**. Other reagents such as 6-HDMFB **48**, 4-HDMA **49**, HDMTA **50a** and HDMTB **50b** were also synthesised.[50] Overall there was hardly any difference between the different reagents. HDMB **46b** displayed the best hydrolytic stability while having better solubility than HATU **28a**. Morpholino derivatives HDMA **46a** and HDMB **46b** showed better efficiency than their thio analogues HDMTA **50a** and HDMTB **50b**.

2.2 Phosphonium salts

Another family of coupling reagents based on HOBt/HOAt uses a phosphonium group. Phosphonium salts have the advantage of not yielding guanidinium by-products *via* reaction of the coupling reagent with amines. The first HOBt/HOAt-phosphonium salt introduced was BOP **51b**,[51] but its use has been limited due to the carcinogenicity and respiratory toxicity associated with HMPA generated when BOP **51b** is used in coupling reactions, leading to the development of the pyrrolidino derivative PyBOP **52b**.[52] Carpino prepared AOP[37] **51a** and PyAOP[37,53] **52a** and compared them to BOP **51b** and PyBOP **52b**, and showed that the aza-derivatives were more reactive.

For the synthesis of thioamides, Hoeg-Jensen developed phosphonium coupling reagents based on 6-nitro HOBt (Fig. 7).[54] PyNOP **53**, PyFOP **54** and NOP **55** were used successfully for the formation of thioamides, with good thioamide/amide selectivity but their solubility in organic solvents was poor. Moreover, the results obtained with PyBOP were very similar to PyNOP **53**, PyFOP **54** and NOP **55**.

In a recent patent, PyClock **56** was disclosed as a new coupling reagent.[55] However hydrolysis was shown to be worse than PyBOP **52b** in the absence of base after 6 h and this was also worse in the presence of a tertiary base as around 88% had been hydrolysed after 1 h compared to 81% for PyBOP **52b** under these conditions. The efficiency of PyClock **56** was evaluated *via* the solid-phase synthesis of three pentapeptides which incorporated hindered/*N*-methylated aminoacids (Table 3).

2.3 Immonium salts

Li designed and synthesised immonium/carbonium type coupling reagents,[56,57] such as BOMI **57**,[56,58–61] BDMP **58**,[56,60,61] BPMP **59**, BMMP **60**, and AOMP[56,59] **61** (Fig. 8). BOMI **57** and BDMP **58** showed the best results, achieving >90% conversion within 10 min during the coupling of Z-Gly-Phe-OH with H-Val-OMe (Anteunis test). In addition, epimerisation was low, BOMI **57** displaying 3.1% and BDMP **58** 2.3% of the DL-isomer. However, these reagents were not compared to classic reagents such as HATU **28a** or PyBOP **52b**. As an application, these reagents were used to carry out the total synthesis of Cyclosporine O, an immunosuppressive agent.[62]

2.4 Other reagents

DepOBt (originally called BDP) **62b** was reported by Kim (Fig. 9).[63] The reagent appeared to couple aniline to benzoic acid or phenylacetic acid in high yield, and also aminoacids (Phe, Val, Met, Ile) to other amino acids (Gly, Ser, Val) in high yield although *N*-Methylated substrates were not tested. Epimerisation was evaluated *via* Young's test and found to be low. The same group reported DpopOBt **63b** but epimerisation was high.[64]

Carpino reported DepOAt **62a**, DpopOAt **53a**, DmppOAt **64**, DtpOAt **65a** and DtpOBt **65b**.[65] Again, no real improvement was gained compared to HATU **33a**. For the synthesis of ACP(65-74), HATU **33a** outperformed any of these reagents. An epimerisation study for the coupling of Z-Phe-Val-OH and H-Pro-NH_2 showed that DmppOAt **64** (3.6% of LDL isomer) and DtpOAt **65a** (2.9%) gave less epimerisation than HATU **28a** (5.0%), while DtpOBt **65b** was worse (11.4%), but no explanation was given.

HAPyTU **66**, a thio-analogue of HAPyU **31**, was tested by Klose but proved to be unsuccessful as yields were lower and epimerisation higher than HAPyU **31**.[66]

Another type of reagent based on sulfonates was developed by Itoh.[67] These reagents **67–70** incorporated HOBt or HOCt (6-chloro-HOBt) with different substituents on the sulfonate. The best results were obtained with HCSCP **70**, the chlorine group enhancing the reactivity of the reagent. However, the reagents were not compared directly to each other. Compared to DCC **5** (without using HOBt), these reagents gave less side-reactions and the by-products were easily removed during aqueous workup. According to the authors, epimerisation was

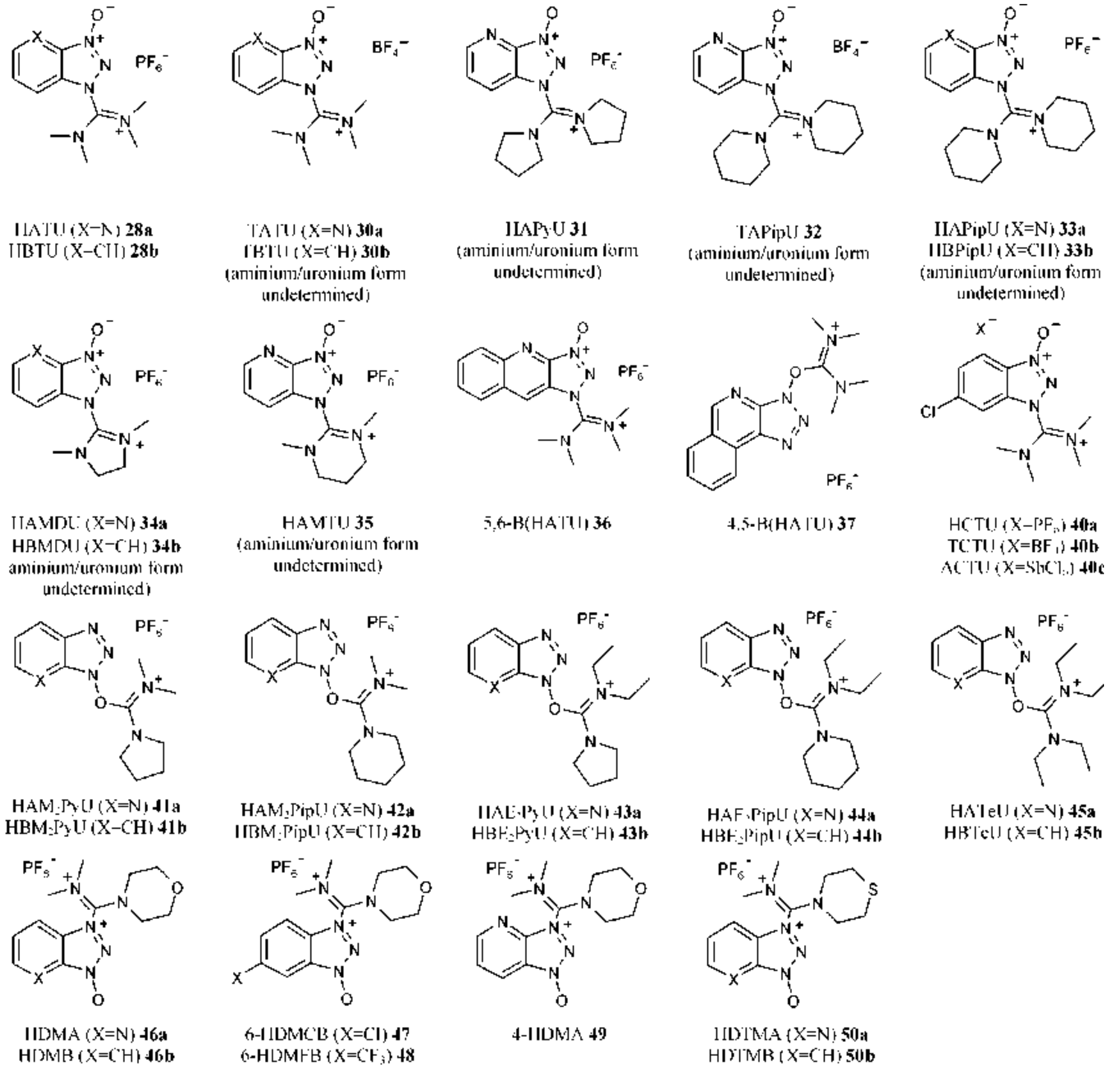


Fig. 6 Uronium/Aminium-based coupling reagents.

lower than with DCC **5**, but this was no surprise as DCC alone give very high levels of epimerisation.

2.5 Conclusion on 1*H*-benzotriazole-based reagents

1-*H*-benzotriazole-based reagents probably represent the widest class of coupling reagents. Although differences in reactivities have been reported by their authors, there is practically very little difference, as exemplified by Hachman,[68] and HBTU **28b** or TBTU **30b** are reagents which usually perform very well. Surprisingly, the potential explosive properties of these reagents is almost always disregarded.[30,31]

3. Reagents generating acid halides

3.1 General reagents used in organic chemistry and triazine-type reagents

Fischer reported the first synthesis of a dipeptide (Gly-Gly) in 1901 using acid chlorides for coupling.[69] The general approach consisted of using reagents such as thionyl chloride or phosphorus pentachloride to generate the acid chloride which reacted quickly with amines to form amides. This original method was quite harsh and not compatible with many protecting groups. It has however been adapted by Carpino to synthesise peptides *via* a Fmoc strategy.[70] Triphosgene has also been reported to generate amino-acid acid chlorides,[71] especially useful for hindered substrates.[72] Similarly, acid cyanides and azides have been used to synthesise amides.[73]

Cyanuric fluoride **71** can be used to synthesise acid fluorides,[74] which couple *N*-methylated amino-acids very efficiently. A variety of other reagents have been reported for the formation of acid fluorides, and include Deoxo-Fluor **72** and DAST **73** (Fig. 10).[75] However a side-reaction is observed when using Deoxo-Fluor **72** especially with hindered amines (Scheme 7), which limits the applicability of this reagent. In addition, Deoxo-Fluor **72** and DAST **73** are expensive and hazardous reagents, and purification by chromatography is required after reaction.

Part of this category of reagents is based on triazines (cyanuric fluoride, chloride and derivatives) and has been reviewed in details by Kaminski.[76] The mechanism of activation involves the generation of an acid halide moiety

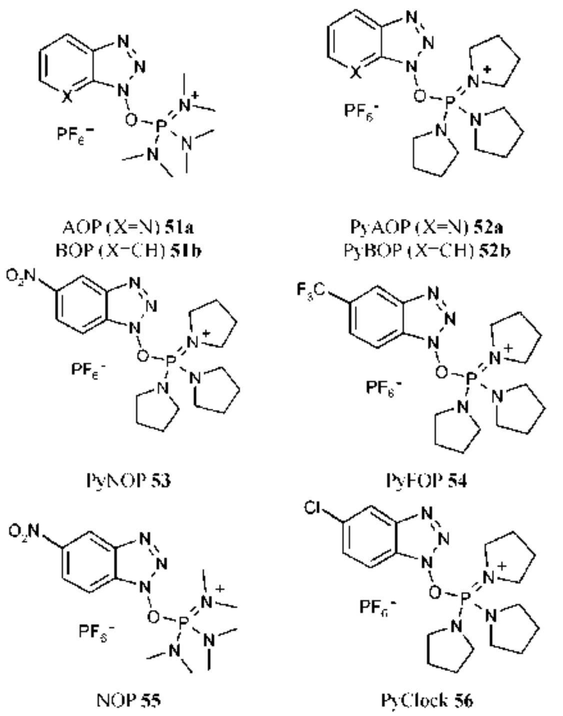


Fig. 7 Phosphonium type coupling reagents.

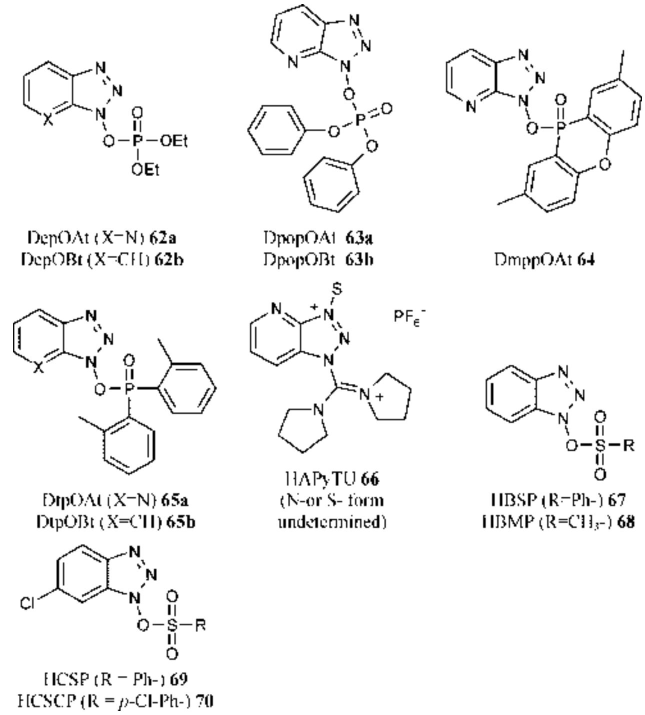


Fig. 9 Other coupling reagents based on 1-hydroxybenzotriazole and 1-hydroxy-7-azabenzotriazole.

Table 3 Comparison of pentapeptides yield when using PyClock **56** and PyBOP **52b**

		Yield (%)	
Entry	Amine	PyClock	PyBOP
1	H-Tyr-NMeVal-Phe-Leu-NH_2	11	0
2	H-Tyr-Aib-Aib-Phe-Leu-NH_2	97	83
3	H-Tyr-Arg-Arg-Phe-Leu-NH_2	85	75

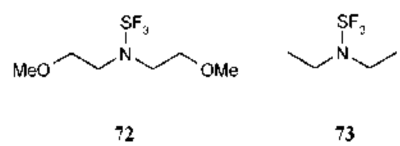


Fig. 10 Structure of Deoxo-Fluor **72** and DAST **73**.

(Scheme 8). Thus CDMT **74** and DCMT **75** (2,4-dichloro-6-methoxy-1,3,5-triazine) have been successfully applied in the synthesis of acid anhydrides (Fig. 11).[77]

3.2 Halo-uronium and halo-phosphonium type reagents (Fig. 12)

TFFH **76a**,[78] BTFFH **77**,[78,79] and DFIH[78] **78a** have been used to generate acid fluorides with amino acids such as histidine and arginine since the activated form of Fmoc-Arg-OH underwent deactivation *via* lactam formation when using cyanuric fluoride.[78] PyFloP **79a** did not yield any acid fluoride.[78] Interestingly, TFFH **76a** (100% coupling after 10 min) gave better results than the analogues TCFH **76b** (86%) and TBFH **76c** (79%), for the coupling of Fmoc-Val-OH to H-Ile-PEG-PS,[78] but overall, BTFFH **77** gave the best conversions.[79]

El-Faham synthesised three acid fluoride generating reagents: DMFFH **80**, DEFFH **81** and TEFFH **82**,[48] but these were poorly stable to hydrolysis in the presence of a base (most of the reagent hydrolysed within 1 h). The reactivity of these reagents was studied by monitoring acid fluoride formation for various hindered and unhindered amino acids, and all three reagents were shown to be less reactive than TFFH **76a** or BTFFH **77**.

Reagents aimed at generating acid chlorides or bromides under milder conditions than thionyl chloride have been targeted. BroP **83a** was first synthesised by Coste,[80] followed by PyBroP **79b** and PyCloP **79c**.[81] These reagents were shown

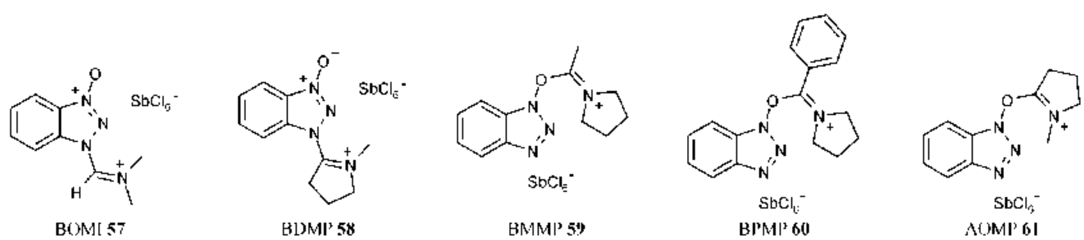
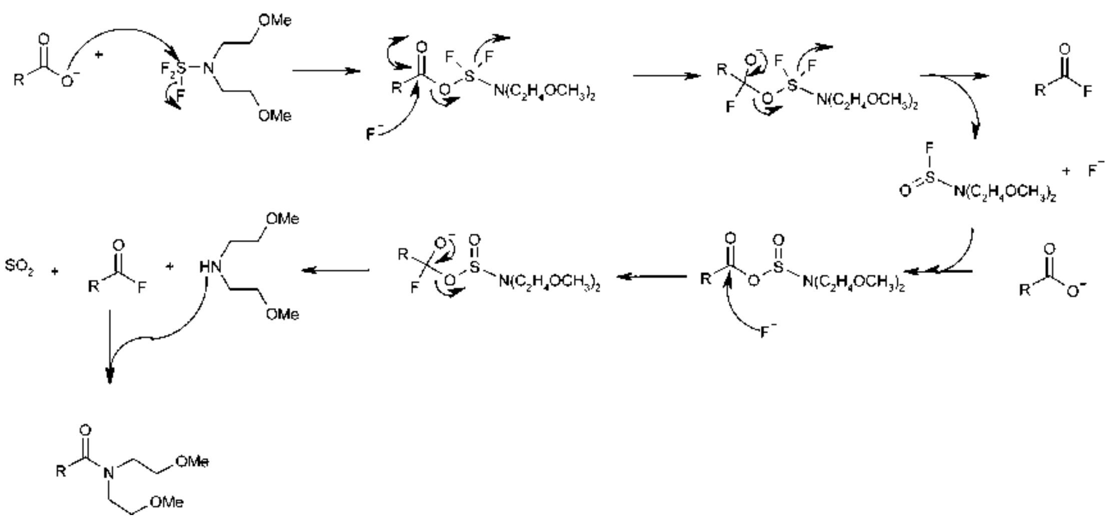
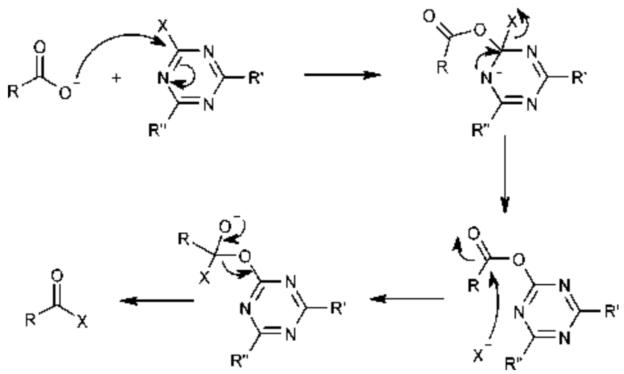


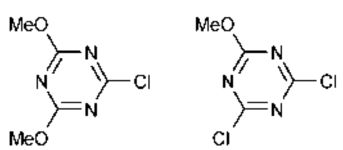
Fig. 8 Immonium type coupling reagents.



Scheme 7 Side-reaction observed during the activation process when using Deoxo-Fluor.



Scheme 8 Formation of acid halides when using triazines as coupling reagents.



CDMT 74 DCMT 75

Fig. 11 Coupling reagents based on triazines.

to be more efficient that PyBOP **52b** in coupling *N*-methylamino acids. PyClU **84**, also synthesised by Coste, gave high yields when coupling hindered amino acids,[81] while DCIH **78b** (named CIP originally) gave comparable results to PyBroP **79b** and PyCloP **79c**.[82] One of the drawbacks of PyBroP **79b**, PyCloP **79c** and DCIH **78b** is the established formation oxazolones. CloP **83b** was reported by Castro and shown to give low levels of epimerisation *via* Young's test.[83]

PyClopP **85**, an analogue of PyCloP **79c**, was reported by Li in an attempt to increase reactivity by replacing a pyrrolidine ring with a phenyl group. The reagent was reported as being efficient for hindered peptide synthesis, but no results were given to illustrate this fact.[57]

BOP-Cl **86** is a reagent that has been widely used in peptide synthesis,[84] and was in particular reported as being suitable for coupling hindered substrates,[85] but it has the major drawback of capping primary amines.[86]

Other reagents include CDTP[87] **87** and CMMM[84] **88**, but these reagents, like PyBroP **79b** and PyCloP **79c**, usually give high epimerisation during coupling. CMMM **88** was also compared to other reagents such as FEP **96b**, and gave poor results with coupling times of over 2 h and epimerisation of over 30% (Anteunis test).[57]

DMC **89**, has been investigated as a coupling reagent.[88] It proved to be successful in the generation of some amides but questions of functional group compatibility are raised when considering its high reactivity. Recently, El-Faham tested DMFH **90a** and DMCH **90b**. DMFH **90a** was really efficient for coupling the hindered Aib amino acid to a tripeptide Aib-Phe-Leu. The tetrapeptide was synthesised on solid phase in 99% yield compared to 68% for HATU **28a**,[50] but complete scope of this reagent was not investigated. DMCH **90b** on the other hand performed poorly.

3.3 Halo-sulfonium, halo-dioxolium and halo-dithiolium coupling reagents

Li synthesised other types of coupling reagents, including CDMS **91**, CBDO **92** and CPDT **93** (Fig. 13).[57] However these reagents were far too reactive and decomposed in solution before activation could take place.

3.4 Halo-thiaziolium and halo-pyridinium type reagents

Li designed reagents based on thiazolium and 2-halopyridinium salts. Their design was based on the fact that, in halouronium type coupling reagents, the carbocation is well stabilised *via* the electron pairs on the amine groups. Therefore, the carbocation shares a relatively high electron density and the uronium salt demonstrates relatively low reactivity in the addition of the carboxylic acid. For this reason Li attempted to replace one nitrogen group with other groups without lone pairs or more electronegative groups with lone pairs to enhance the reactivity of the reaction-mediated carbocations. The first attempt to replace nitrogen with sulfur yielded thiazolium reagent, BEMT **94**.[89] The same type of

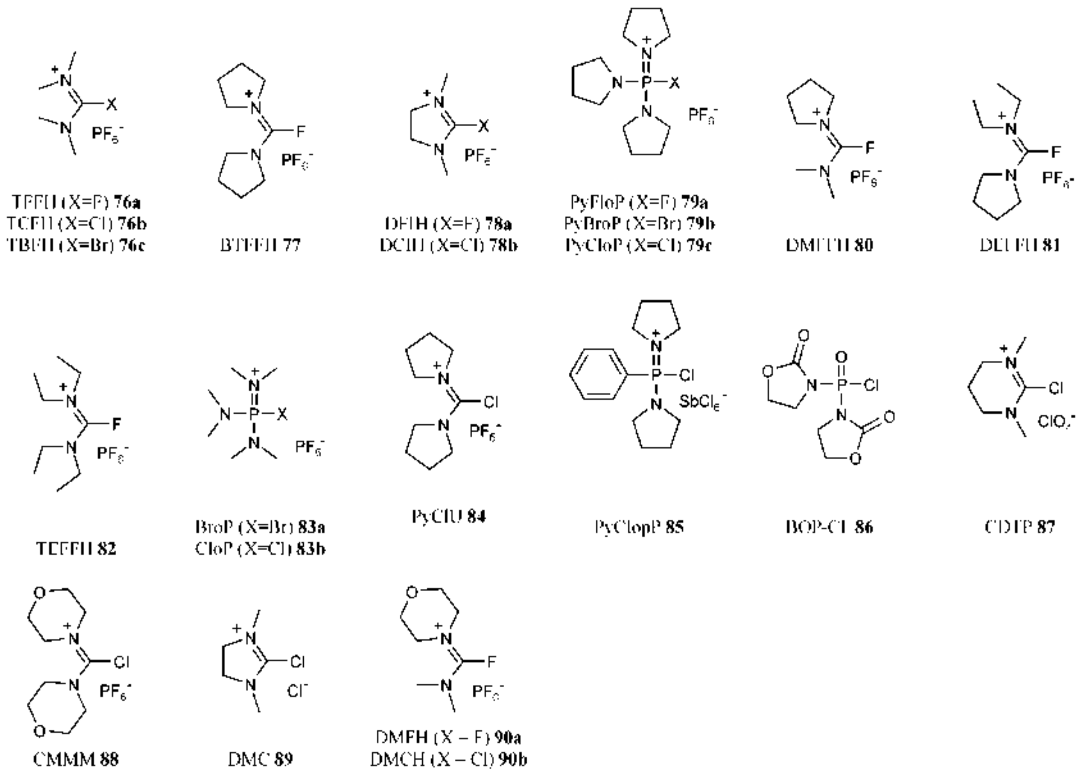


Fig. 12 Halo-uronium and halo-phosphonium type reagents.

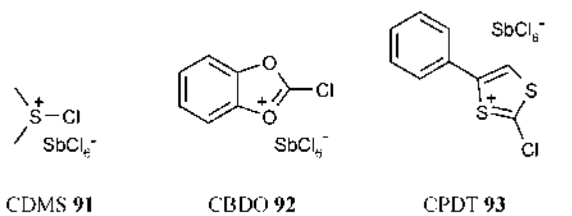
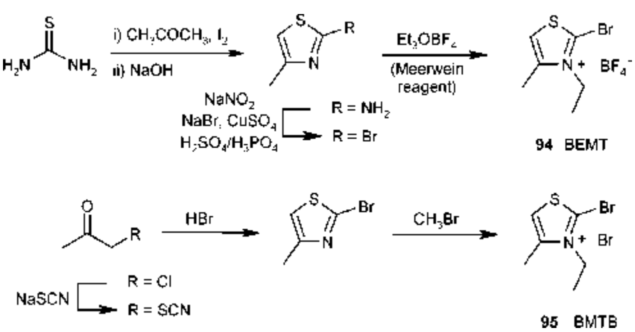


Fig. 13 Halo-sulfonium, halo-dioxolium and halo-dithiolium type reagents.



Scheme 9 Synthesis of BEMT and BMTB.

reagent, BMTB **95**, was proposed by Wischnat (Scheme 9).[90] BMTB **95** performed better than HATU **28a** in coupling Boc-*N*(Me)-Ile to *N*(Me)-Ile-OBn. However BMTB **95** was not compared to BEMT **94**.

Li reported 2-halopyridinium salts such as BEP **96a**, FEP **96b**, BEPH **97a** and FEPH **97b** (Fig. 14).[91] Mukaiyama has extensively used 2-chloro- and 2-bromo-pyridinium iodide **98**

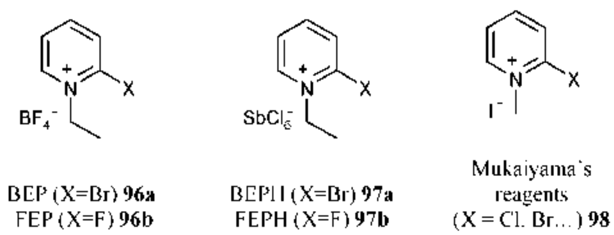


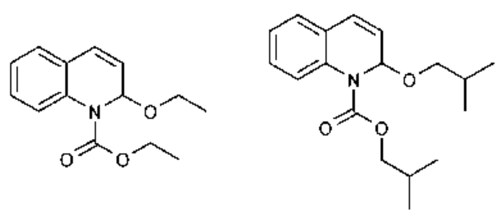
Fig. 14 Halo-pyridinium type reagents.

to synthesise esters, lactones and amides,[92] but the conditions used were not ideal for peptide synthesis, as reactions had to be performed at reflux in DCM due to the poor solubility of the reagents. For this reason Li used tetrafluoroborate and hexachloroantimonate counter anions to improve solubility, and chose the fluoro-analogues for higher reactivity. The efficiency of these reagents proved to be higher than BTFFH **77**, PyBrop **79b**, PyClU **84** or BOP-Cl **86**. However these reagents might be a bit too reactive as the base used during the coupling had to be added very slowly to avoid the coupling reagents reacting too violently. Thus side-reactions may be expected for some substrates.

4. Other coupling reagents

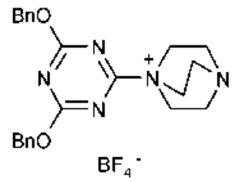
4.1 Reagents generating carbonic anhydrides (Fig. 15)

EEDQ **99**, was originally developed in 1967.[93] EEDQ **99** offers several advantages over most coupling reagents, as the reaction with an amine cannot yield a guanidinium salt, a typical side reaction observed with uronium type coupling



EEDQ **99**   IIDQ **100**

Fig. 15 Structure of EEDQ and IIDQ.



103

Fig. 16 Structure of dibenzyloxytriazine **103**.

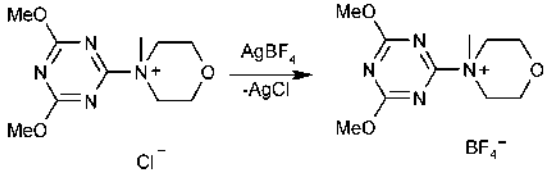
Table 4 Comparison of EEDQ and IIDQ

Entry	Amine	Acid	IIDQ yield	EEDQ yield
1	4-*tert*-Butylaniline	Phenylacetic acid	96	94
2	Benzylamine	Phenylacetic acid	91	87
3	Morpholine	Phenylacetic acid	38	32
4	4-*tert*-Butylaniline	Benzoic acid	88	85
5	Benzylamine	Benzoic acid	85	66
6	Morpholine	Benzoic acid	50	41
		Average	76	67

reagents. In addition, the carbonic anhydride is formed slowly but consumed rapidly, which avoids its accumulation and therefore minimises the possibility of side-reactions such as epimerisation, and it can also be used with unprotected hydroxy residues.[93] EEDQ **99** has thus been used for the synthesis of various amide derivatives.[94,95] Analogues of EEDQ **99** have also been successfully investigated such as IIDQ **100**, and a number of unsymmetrical reagents.[96] Not many comparison studies have been published, but IIDQ **100** proved, over a few examples, to perform slightly better than EEDQ **99** (Table 4).[97] Interestingly, when compared to other coupling reagents without activation, IIDQ **100** outperformed HATU **28a**, PyAOP **52a** and BOP-Cl **86**.[97]

4.2 Triazine-based reagents (not generating acid halides)

DMTMM **101** is a triazine derivative, which has the particular advantage of promoting amide synthesis in alcohols or aqueous media, without ester formation and with selectivity comparable to DCC **5** and EDC **20**.[98] Recently, a series of reagents based on DMTMM **101** was developed by Kaminski (Scheme 10).[99] *N*-Triazinylammonium salts were synthesised using different tertiary bases and the derivative incorporating



101
DMTMM   **102**

Scheme 10 Exchange of counter anion on DMTMM **101**.

DABCO proved to give the best yield. However a full study was carried out on the *N*-methylmorpholine derivative **102**, because of its lower production cost. The reagent proved to be particularly efficient with high yields and low epimerisation levels. For the synthesis of the 65–74 segment of ACP, each coupling went faster (15 min.) than with TBTU **30b** (45 min) or HATU **28a** (30 min) and gave better purities (84%) than TBTU **30b** (69%).[99] Sulfonates of *N*-triazinylammonium salts were also synthesised, but a complete evaluation of these reagents was not reported.[100] The reagents were further optimised by replacing the methoxy groups by benzyloxy groups (Fig. 16).[101]

Remarkably, reagents such as triazine **103** proved to be stable in DMF with only 2.5% decomposition after 48 h. Comparison between the parent methoxy compounds (*e.g.* **97**) and the benzyloxy derivatives (*e.g.* **103**) showed that the later were more efficient for the synthesis of the 65–74 segment of ACP.

4.3 Pentafluorophenol (HOPfp)-based coupling reagents (Fig. 17)

These types of reagents are based on the traditional pentafluorophenol leaving group and the generation of active esters. They usually require the addition of HOAt as the level of epimerisation is quite high: when coupling Z-Phe-Val-OH to H-Pro-NH_2, 33.7% of the LDL isomer was observed in solution phase when using HPyOPfp **104a**, while epimerisation dropped to 1.7% when adding HOAt to the reaction mixture. The use of a thiophenol-analogue, HPySPfp **104b** did not change the outcome of the coupling reactions.[66] Like most reagents based on HOAt/HOBt, these reagents are not ideal for solution-phase chemistry as the use of an additive means that this has to be removed from the reaction mixture after coupling.

Li described a pentafluorophenyl immonium type reagent FOMP **105**,[56] but this reagent was not as efficient as the other immonium type reagents, based on HOBt/HOAt.

A reagent, PFNB **106**, was reported by Pudhom, but Boc-Gly-OH reacted slowly and incompletely and it was necessary to add HOBt to get good conversion.[102] In order to synthesise thioamides, Hoeg-Jensen synthesised PyPOP **107**, but this reagent was not as efficient as PyNOP **53** or PyFOP **54**.[54] Other reagents include FDPP **108**, which gave lower epimerisation levels than HBTU **28b**, BOP **51b** and DCC **5**.[103]

Recently, HDMPfp **109** was synthesised by El-Faham but the reagent proved to be outperformed by HATU **28a**.[50]

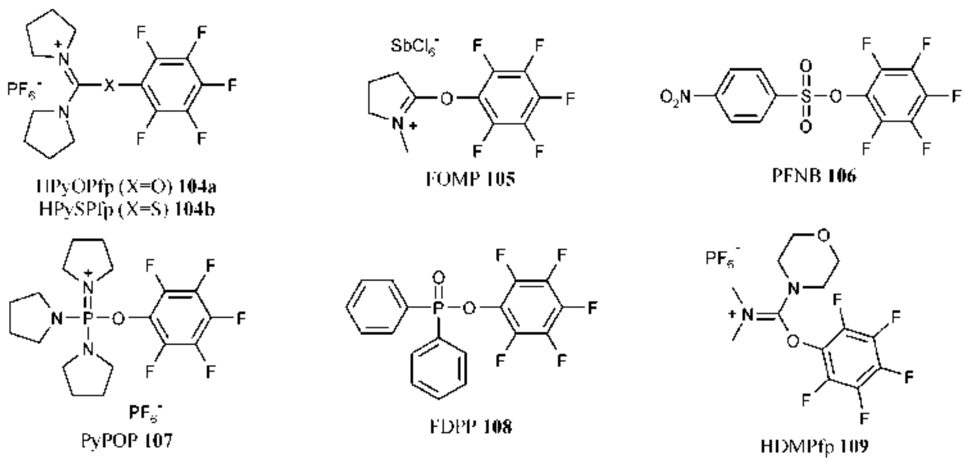
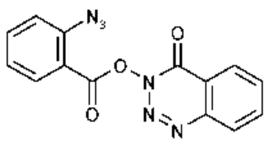


Fig. 17 Coupling reagents based on pentafluorophenol.



110

Fig. 18 Side-product formed when using HODhbt as additive.

4.4 Reagents based on 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HODhbt)

HODhbt was first mentioned in 1970 by Koenig who investigated over 30 *N*-hydroxy compounds as additives for peptide synthesis.[25] HOBt gave excellent results but HODhbt proved to be generally superior. However Koenig pointed out that the potential of HODhbt is limited due to inherent side reactions, in particular the formation of an azido-benzoyl derivative **110** (Fig. 18).

Knorr proposed the generation of a HODhbt based coupling reagent, synthesising TDBTU **111** (Fig. 19).[40] Although TDBTU **111** gave little epimerisation, its use was recommended only in critical cases because of the risk of side reactions. Indeed, ring opening of the 3,4-dihydro-4-oxo-1,2,3-benzotriazine ring can occur to form **110**, which can then react with amines. Another reagent, HDTU **112b**, where the counter ion of TDBTU **111** was replaced by hexafluorophosphate had similar efficiency to TBTU **30b**.[104] The disadvantage of HDTU **112b** has ever being its poor stability in DMF compared to classic reagents such as HATU **28a** as after 5 h HDTU **112b** had totally decomposed compared to less than 1% for HATU **28a**.[37]

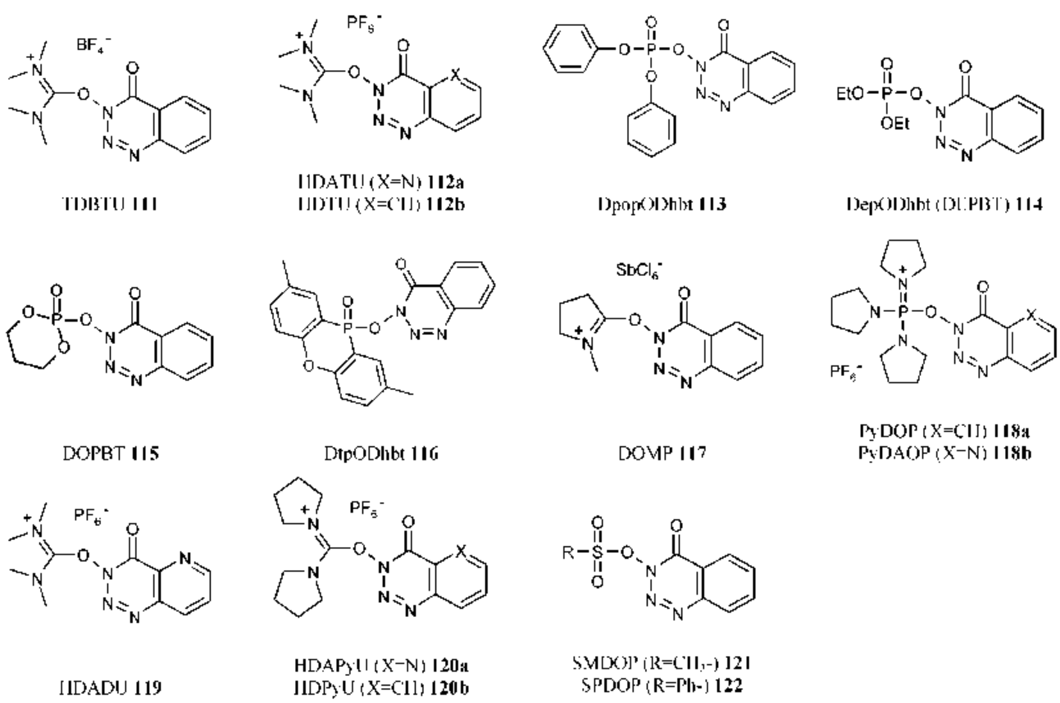


Fig. 19 Coupling reagents based on HODhbt.

Carpino compared some organophosphorus reagents to commonly used coupling reagents,[65] and showed that DpopODhbt **113** was comparable to HATU **28a** in terms of reaction times for the formation of the active ester of Z-Aib-OH (<2 min) but DepODhbt **114** (also named DEPBT by Ye[105,106]) was not as efficient (7–8 min). Similarly DOPBT **115** was poorer than DepODhbt **114**.[107] Another reagent, DtpODhbt **116** gave more epimerisation (4.3% of LDL isomer) than DepODhbt **114** (3.5%) but less than HATU **28a** (5.0%) when carrying out the coupling of Z-Phe-Val-OH and H-Pro-NH_2. The synthesis of the ACP decapeptide (H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-NH_2) was used to show that DepODhbt **114** gave poor results (<1% yield) compared to HATU **28a** (85%).

Li also based immonium type reagents on HODhbt, but DOMP **117** showed very poor results for the coupling between Z-Gly-Phe-OH and H-Val-OMe with only 5.6% yield after 2 h compared to 95% for BDMP for example.[56] PyDOP **118a** was targeted for the synthesis of thioamides, but proved to be surpassed by PyNOP **53** or PyFOP **54**.[54]

More recently, Carpino developed coupling reagents based on aza-analogues of HODhbt,[65] and successfully synthesised HDATU **112a**, PyDAOP **118b**, HDADU **119**, HDAPyU **120a**, and HDPyU **120b**. As expected, derivatives of HODAhbt were more reactive than their HODhbt analogue. Thus, HDATU **112a** gave better results than HDTU **112b**, but was still less reactive than HATU **28a**. Moreover, results were more random for segment coupling as they depended on the system studied. However, in many cases, HDATU **112a** proved to be better than HATU **28a** for the solid-phase synthesis of ACP.

Itoh developed sulfonate reagents based on HODhbt.[67] The two reagents synthesised, SMDOP **121** and SPDOP **122** were however not as efficient as the other sulfonate reagents that this group synthesised, such as HCSCP **70**.

Overall, reagents based on 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HODhbt) do not appear to be more efficient that classical reagents like DIC **13**. Moreover, a critical issue regarding the safety of these materials has to be addressed due to the presence of the azide moiety.

4.5 Reagents based on 2-hydroxysuccinimide (HOSu) and 2-(5-norbornene–2,3-dicarboximide) (HONB) (Fig. 20)

Only a few reagents incorporating the hydroxysuccinimide leaving group have been synthesised. Knorr developed TSTU **123a** and its norbornene–dicarboximide analogue TNTU **124**, which showed high epimerisation levels without the use of additives.[40] Gruber reported HSTU (also called SbTMU) **123b**, but the reagent was not studied in detail as it was directly used for the preparation of thiol-reactive Cy5 derivatives.[108]

Other examples are SOMP[56] **125** and SOMI[57] **126** developed by Li, and similar other immonium type reagents, but they gave poor results.

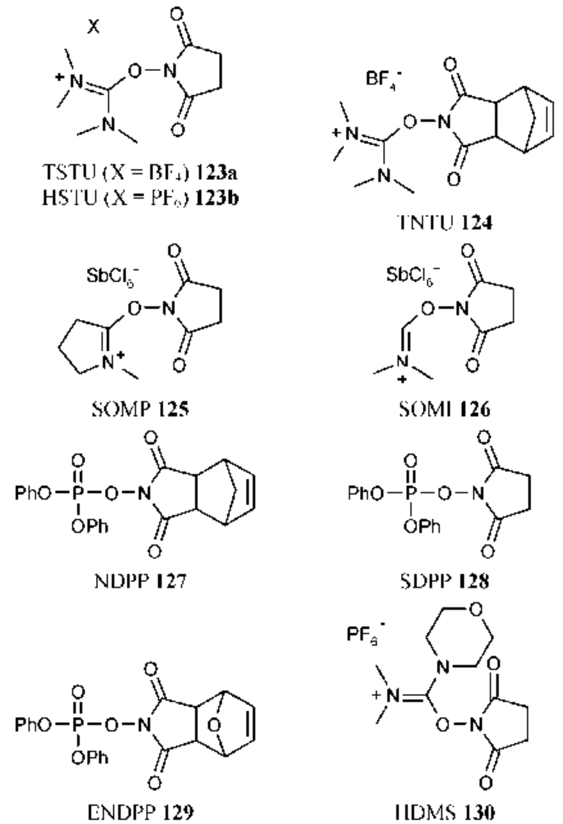


Fig. 20 Coupling reagents based on HOSu and HONB.

Phosphate-based succinimide coupling reagents such as NDPP[109] **127** and SDPP[110] **128** have also been developed. The use of ENDPP **129** proved to be a better method than the isobutylchloroformate method because it could be performed at room temperature, but no other comparison was reported. Similarly, SDPP **128** was only reported as being a "more convenient method" to use than DCC **5**.

El-Faham reported the use of HDMS **130**, which was based on a morpholino uronium salt.[50] The reagent proved to be less efficient than the HOAt/HOBt based analogues HDMA **46a** and HDMB **46b**.

4.6 Phosphorus-type reagents (not based on HOAt, HOBt, –OPfP, –OSu, and –ODhbt) (Fig. 21)

PyTOP **131** was developed by Hoeg-Jensen for the formation of thioamides but the reagent gave poorer selectivities than PyNOP **53** or PyFOP **54**.[54]

The possibility of using DPP-Cl **132** was first investigated with success by Jackson,[111] who claimed that NMR proved that no epimerisation was observed,[112] although this result is quite surprising, as epimerisation is usually high when acid chlorides are generated.

Other derivatives have also been synthesised and include the azide analogue DPPA **133a**,[113] and cyano analogue DECP **134**, which gave good coupling yields but with many side-reactions *via* the cyanide.[114] Dpop-Cl **133b** was also tested but poor results were observed without the use of an additive.[65] Similarly DEPC[115] **135a** and DEPB[116] **135b** typically give side reactions due to the release of the reactive halogen atom.

Reagents based on the same principle, Cpt-Cl[117] **136**, MPTA[118] **137a**, Mpt-Cl[119] **137b**, MPTO[118] **138**, and BMP-Cl[120] **139**, appeared overall to have similar efficiencies to reagents such as DPP-Cl **132**.

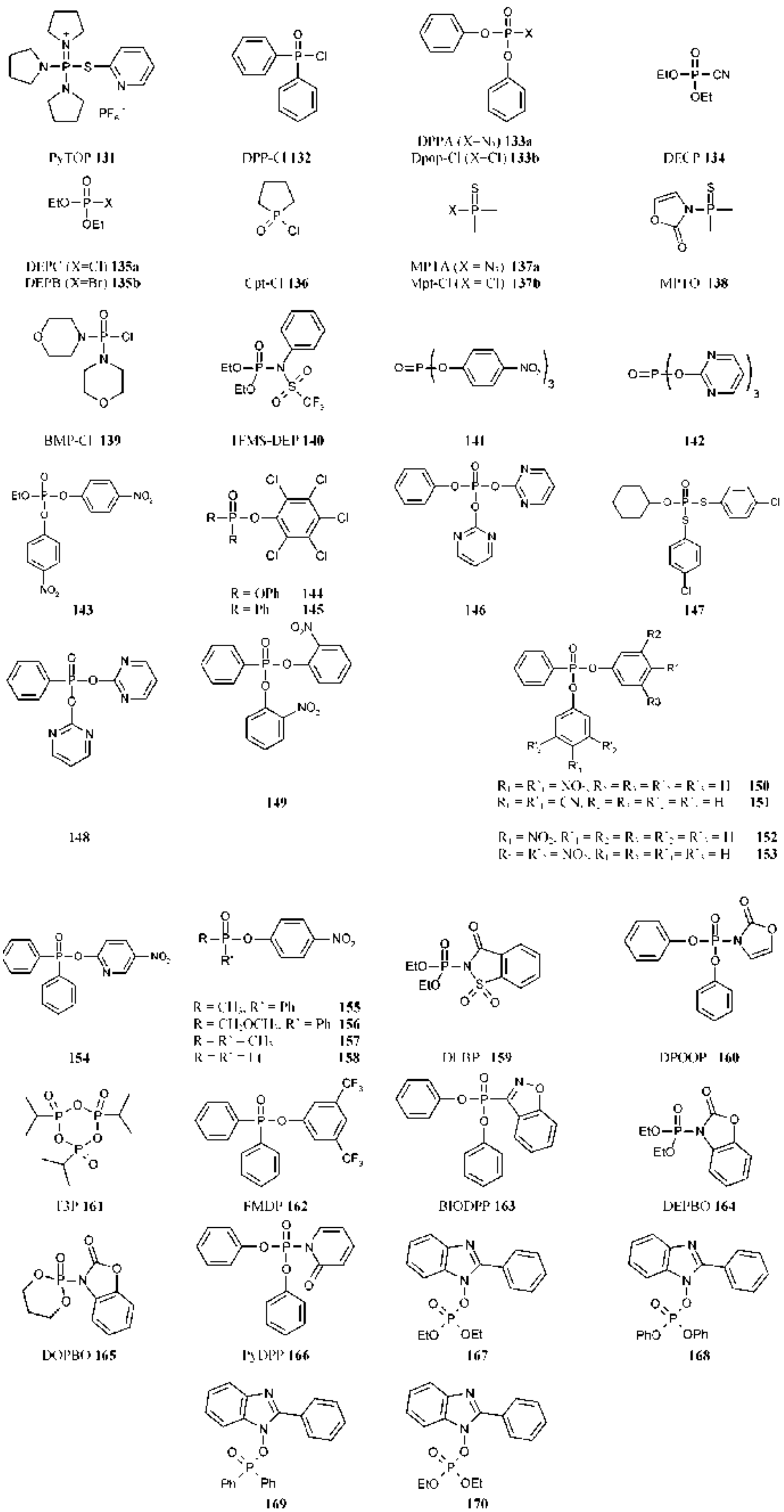


Fig. 21 Other phosphorus-based reagents.

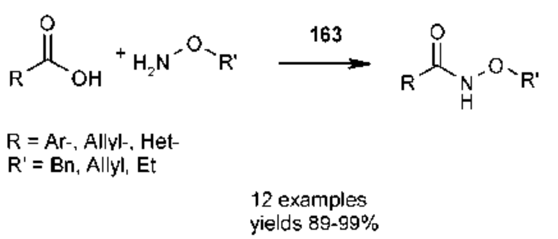
Another coupling reagent TFMS-DEP **140** was produced by activating diethylphosphate with trifluoromethanesulfonalide.[121] Using 1.2 equiv. of coupling reagent, hindered *tert*-butylamine was coupled in 89% yield to acetic acid. Other examples showed goods yields, typically over 80% yield, including a secondary amine (*N*-methylbenzylamine) and two anilines (*N*-methylaniline and aniline). Application for peptide synthesis was studied by carrying out Young's test, which showed 2% epimerisation. Also, the difficult synthesis of Z-Aib-Aib-OMe proved to be successful affording the product in a satisfactory 70% yield.

A wide range of phosphorus-based coupling reagents **141–153** were investigated by Mukaiyama.[122] Using Young's test as model reaction, it was concluded that the bis(nitrophenyl) phenylphosphonates **149** and **150** gave the best results. Further studies, using this time phosphinic esters **154–158** showed that (5-nitropyridyl)diphenylphosphinate **154** was an efficient coupling reagent, giving 92% of the expected dipeptide in Young's test, with less than 2% epimerisation.[123]

DEBP[124] **159** and DPOOP[125] **160** have been proposed as coupling reagents, but for both reagents, examples were limited to a few dipeptides and were not compared to any classical methods. T3P **161** was claimed to be more efficient than HAPyU **31** for head-to-tail cyclisation of hindered peptides.[126] However, the use of T3P may be limited as yields were lower and epimerisation higher than HAPyU when segment coupling studies were carried out.

Other reagents include FDMP **162**, which gave poor results (2% yield compared to 84% yield for BEMT when coupling Z-Gly-Phe-OH to H-Val-OMe),[57] BIODPP **163**, which gave amides in good yields but was not compared to any other coupling reagent,[127] and DEPBO **164** and DOPBO **165**, which proved to be not as efficient as DepODhbt **114**.[107] PyDPP **166** was reported as giving low epimerisation rates, but was not compared to other coupling reagents.[128]

Kokare reported three new reagents **166–169** based on phosphate derivatives of 1-hydroxy-2-phenylbenzimidazole.[129] The reagents gave in most cases similar results and yields over a wide range of substrates (*e.g.* 4-nitrobenzoic acid, cinnamic acid, anisic acid, piperidine, *tert*-butylamine) were excellent. However, one can wonder at the purity of the isolated products. The synthesis of the three reagents were reported (63–71% yields), but when used for amide bond formation, the reagents were generated *in situ* through the reaction of 2-phenylbenzimidazole with a chlorophosphate or phosphinic chloride. The acid and then amine were added to this mixture, and side-reactions were thus likely to occur. Kokare also used the diethylphosphate derivative **170** as a coupling reagent for the synthesis of *O*-alkyl hydroxamic acids (Scheme 11).[130] Yields were excellent for the 12 amides synthesised but comparison with other coupling reagents was not carried out.



Scheme 11 Synthesis of *O*-alkyl hydroxamic acids.

4.7 Miscellaneous reagents

CPMA **171**, a reagent based on a chloroimmonium salt (Fig. 22), mediated the esterification of carboxylic acids,[131] and in terms of amide bond formation, the reagent performed well (complete conversion) but only two examples were reported.

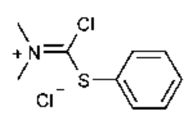
2-Mercaptopyridone-1-oxide **172** was used as a starting material to generate a cheaper and new type of uronium coupling reagent TOTT **173** and HOTT **174** (Scheme 12).[132] Both reagents gave better results that DCIH **78b** or PyBrop **79b** and were comparable to HATU **28a**, and the dipeptide Z-MeVal-Aib-OMe was obtained in 80% yield (89% for HATU **28a**). The epimerisation level was evaluated *via* Young's test and the use of TOTT **173** resulted in only 3.7% epimerisation compared to BOP **51b** (20%), PyBOP **52b** (15%), or HATU **28a** (20%). TOTT **173** and HOTT **174** have also been successfully used to synthesise primary amides from carboxylic acids and ammonium chloride.[133]

Najera synthesised two analogues of HOTT/TOTT, HODT **175** and TODT **176** (Fig. 23).[134] These two reagents gave higher yields in solid phase peptide synthesis, but associated with more epimerisation.

A reagent similar to the ones based on 2-mercaptopyridine oxide was proposed by Knorr but TPTU **177** (Fig. 24), based on 2-hydroxypyridine-*N*-oxide, gave high epimerisation level when used without an additive.[40]

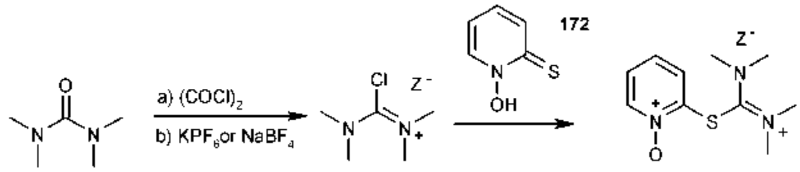
The possibility of using a 2-pyridinone based reagent, DPTC **178** (Fig. 25), for amide synthesis was investigated by Shiina.[135] Carboxylic acids were activated as 2-pyridyl esters using DPTC **178** and a catalytic amount of DMAP. However, a long pre-activation time was required (over 25 min) to limit the formation of an isothiocyanate specie (and probably a thiourea) upon addition of an amine. Thus the application of DPTC **178** is limited although simple amides can be obtained in good yield at room temperature. More hindered substrates imply carrying out the synthesis at higher temperature.

An original coupling reagent based on the rearrangement of carboxylic–sulfonic mixed anhydrides has been reported. Substituted *O*-hydroxybenzenesulfonyl chlorides **179** were used as condensation reagents *via* the mechanism suggested in Scheme 13.[136] Using this method various peptides were obtained in good yields. The epimerisation level was assessed through optical purity, but no comparison was made with any common coupling reagent. Itoh investigated the possibility of using sulfonate-based coupling reagents, and developed 2-methanesulfonyloximino-2-cyanoacetate **180** (Fig. 26), which proved however to be outperformed by HCSCP **69**.[67]



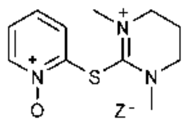
171

Fig. 22 Structure of CPMA.



TOTT (Z=BF_4) **173**
HOTT (Z=PF_6) **174**

Scheme 12 Synthesis of HOTT and TOTT from 2-mercaptopyridone.



HODT (Z=PF_6) **175**
TODT (Z=BF_4) **176**

Fig. 23 Structure of HODT and TODT.

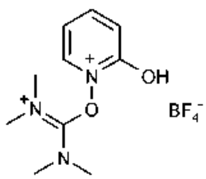


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Fig. 24 Structure of TPTU.

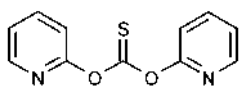

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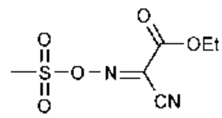
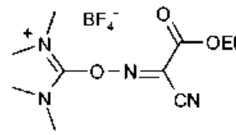
Fig. 25 Structure of DTPC.

A related reagent, also based on a cyanoacetate moiety, TOTU **181** was reported by König.[137]

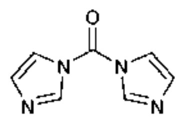
Carbonyl-diimidazole (CDI **182**) has been used to generate amide bonds.[138] Interestingly, Sharma showed that CDI **182**



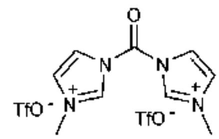
180



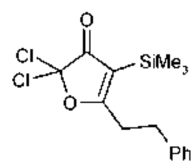
TOTU **181**



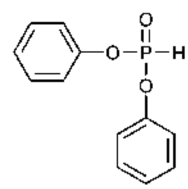
CDI **182**



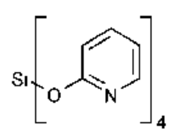
CBMIT **183**



DPTF **184**

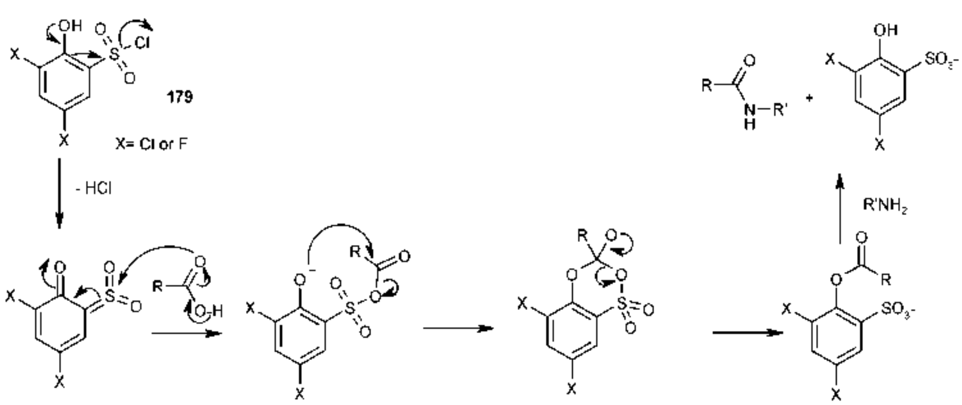


DPP **186**

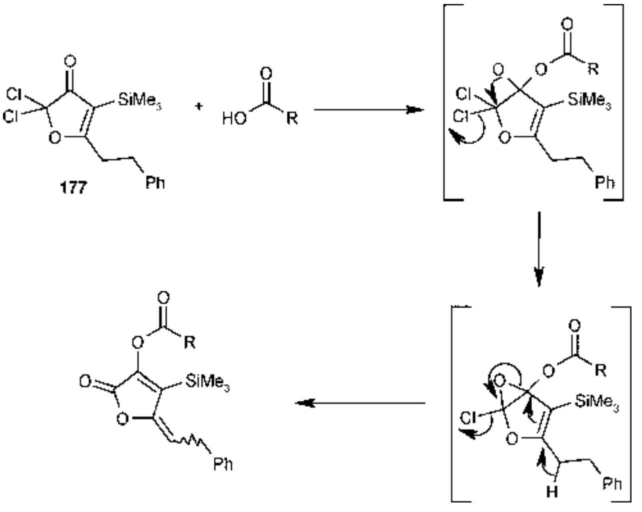


$Si(OPy)_4$ **187**

Fig. 26 Structure of other miscellaneous reagents.



Scheme 13 Mechanism of the coupling reagents using substituted *O*-hydroxybenzenesulfonyl chlorides.



Scheme 14 Suggested mechanism of DPTF.[141]

could be used to couple unprotected amino acids to amines in water.[139] The strategy however offers limited applicability as only primary amines were successfully coupled, while yields were moderate.

More recently, Saha proposed the use of an analogue, CBMIT **183**.[140] He obtained good yields and low epimerisation but these were not evaluated on standard tests and are therefore difficult to compare to classical reagents.

DPTF **184** was reported by Ito as a dehydrating reagent.[141] Its mechanism of action follows the active ester pathway to generate amides in good yields (Scheme 14). However hindered building blocks were not evaluated. One of the main advantages of DPTF **184** is its ability to activate a carboxylic acid in aqueous media.

In order to avoid the use of expensive reagents, Campagne suggested the use of ethyl propiolate **185** as coupling reagent, as described in Scheme 15.[142] Although being original, this route required a long pre-activation time (12 h) and the use of an additive (sodium bisulfite) was necessary to give good yields. Moreover, yields were typically lower than standard coupling reagents such as PyBOP **52b**.

Recently, diphenyl phosphite (DPP **186**),[143] and tetrakis-(pyridine-2-yloxy)silane **187**,[144] have been used to synthesise amides. DPP **186** forms a phosphonic-carboxylic mixed anhydride, while tetrakis(pyridine-2-yloxy)silane gives silyl esters **188** (Scheme 16). These reagents afforded amides in good yields but were not compared to other coupling reagents.

Phenylsilane $PhSiH_3$ **189** has been used in amide library formation.[145] The reagent was tested on seven carboxylic acids and 11 amines. Although amides were sometimes obtained in good yield, it was necessary to use reverse phase HPLC to purify the products, making the phenylsilane method unattractive for library generation. In addition, anilines and some secondary amines failed to couple with this reagent resulting in poor scope.

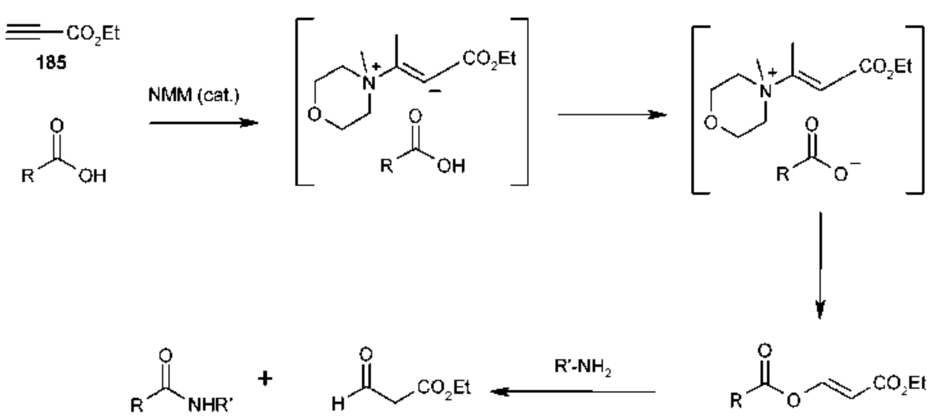
5. Other methods of *N*-acylation

5.1 Mixed anhydrides

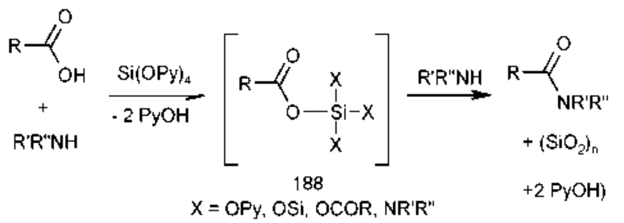
The formation of mixed anhydrides is a classic method of amide bond formation. It is important to note that many mixed anhydrides can be generated using some of the coupling reagents reported so far in this review. The mixed anhydride method was first reported by Vaughan,[146] who tested many acid chloride derivatives and concluded that the success of the amide-bond formation was governed by steric and inductive effects. Isovaleryl chloride proved to give the best results. However, as reported by many research groups, this method has a tendency to generate symmetrical anhydrides by reaction of a second carboxylic acid molecule on the mixed anhydride (Scheme 17). In addition regioselectivity is a major issue, as the amine can potentially react at either carbonyl group although this can be biased by using a bulky acid group. These drawbacks can sometimes be minimised by carrying out the coupling reactions at low temperature.

5.2 Chloroformates

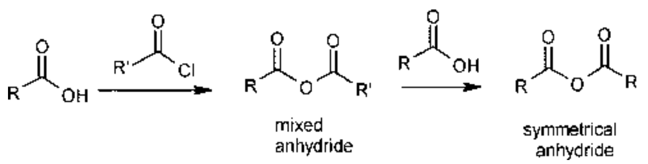
The use of chloroformates for amide-bond formation was first reported by Vaughan,[147] and was based on the mixed anhydride method. In the presence of a base, the reaction between a carboxylate and a chloroformate yields a mixed carbonic anhydride, which reacts quickly with amines to form amides. Vaughan's study highlighted slightly better results when using *sec*-butylchloroformate compared to isobutylchloroformate.[148] The method was "reinvestigated" by Anderson,[149] who tested several different chloroformates, and whose conclusions suggested that isobutylchloroformate was the most efficient reagent.



Scheme 15 Activation process when using ethyl propiolate as coupling reagent.



Scheme 16 Mechanism proposed by Tozawa for tetrakis(pyridine-2-yloxy)silane.



Scheme 17 Disproportionation issue with the mixed anhydride method.

5.3 Direct preparation of active esters

The direct formation of active esters has often attracted a lot of attention due to the stability of many of them, which allows storage. Many example of active esters have therefore been reported and include –*O*-succinimides,[150] –OBt and derivatives,[24] *p*-nitrophenol,[151] –OPfP,[152] –ODhbt,[153] and PTOC.[154] As this review focuses directly on coupling reagents, this useful method of amide-bond formation will not be discussed herein, but the reader is referred to Montalbetti's review for further details.[13]

5.4 Newer approaches to amide bond formation

Several alternatives to the use of coupling reagents have been reported. These interesting new methods were reviewed by Bode,[155] and include the so-called native chemical ligation and the Staudinger ligation (Scheme 18). Recently, Milstein reported another approach based on the ligation of amines to alcohols using a ruthenium complex as catalyst.[156] Molecular hydrogen was formed during the reaction and amides were obtained in high yield.

6. Polymer-supported coupling reagents

6.1 Immobilised carbodiimides

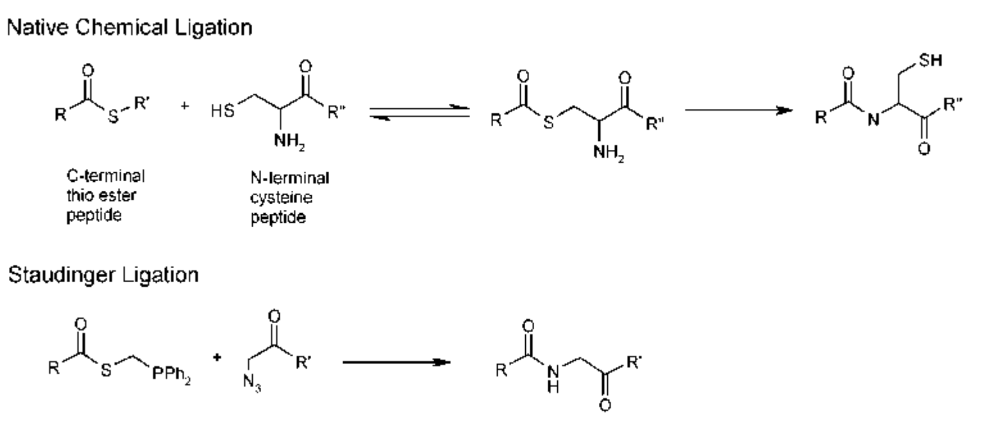
Only a few polymer-supported coupling reagents are available, probably because coupling reagents are mainly used in peptide synthesis, which is usually carried out on solid phase, the coupling reagent being in solution. Nevertheless, DCC **5**,[157] DIC **13**,[158] and EDC[159] **20** have been successfully immobilised and applied to the synthesis of amides.[160] However these carbodiimides maintain the same drawbacks as their solution-phase equivalents, in particular in terms of epimerisation in the absence of an additive. Furthermore, one can wonder at the interest of PS-EDC **190** (Fig. 27) in comparison to PS-DCC **191** as EDC **20** was originally designed and synthesised to be water soluble. Having the "extractable" moiety on a polystyrene support appears to be odd, especially as the ionic part of EDC **20** in solution-phase has proven to be counterproductive regarding the coupling reaction rate compared to DIC **13**.[34] A polyhexamethylene-carbodiimide has also been reported.[161]

Charette "attached" carbodiimides to tetraarylphosphonium salts as a means of "tagging" the reagent.[162] Reaction was carried out in solution phase, before precipitation of the salt with apolar solvents. Several carbodiimides derivatives **192** were synthesised (Fig. 28), and the ethyl and isopropyl derivatives based on a hexafluorophosphate salt were the most efficient, both in terms of yields and purities.

6.2 Immobilised additives and reagents based on HOBt

Some coupling reagents in solution can in rare cases be extracted after reaction (*e.g.* EDC **20**). However, the use of an additive is often required to limit epimerisation, and this additive has also to be separated from the reaction mixture. Therefore polymer-supported HOBt has been reported in different guises.[163,164] PS-HOBt **193** has also been used as a core for synthesising supported reagents for the preparation of *N*-hydroxysuccinimide active esters.[165]

The idea of using PS-HOBt **193** to form an immobilised HOBt-based coupling reagent was first exploited by Chinchilla, who synthesised polymer-supported TBTU **194**.[166] This idea was also applied by Filip for the synthesis of polymer-supported BOP **195**.[167] These reagents offer however the same



Scheme 18 Examples of newer methodologies for amide bond formation.

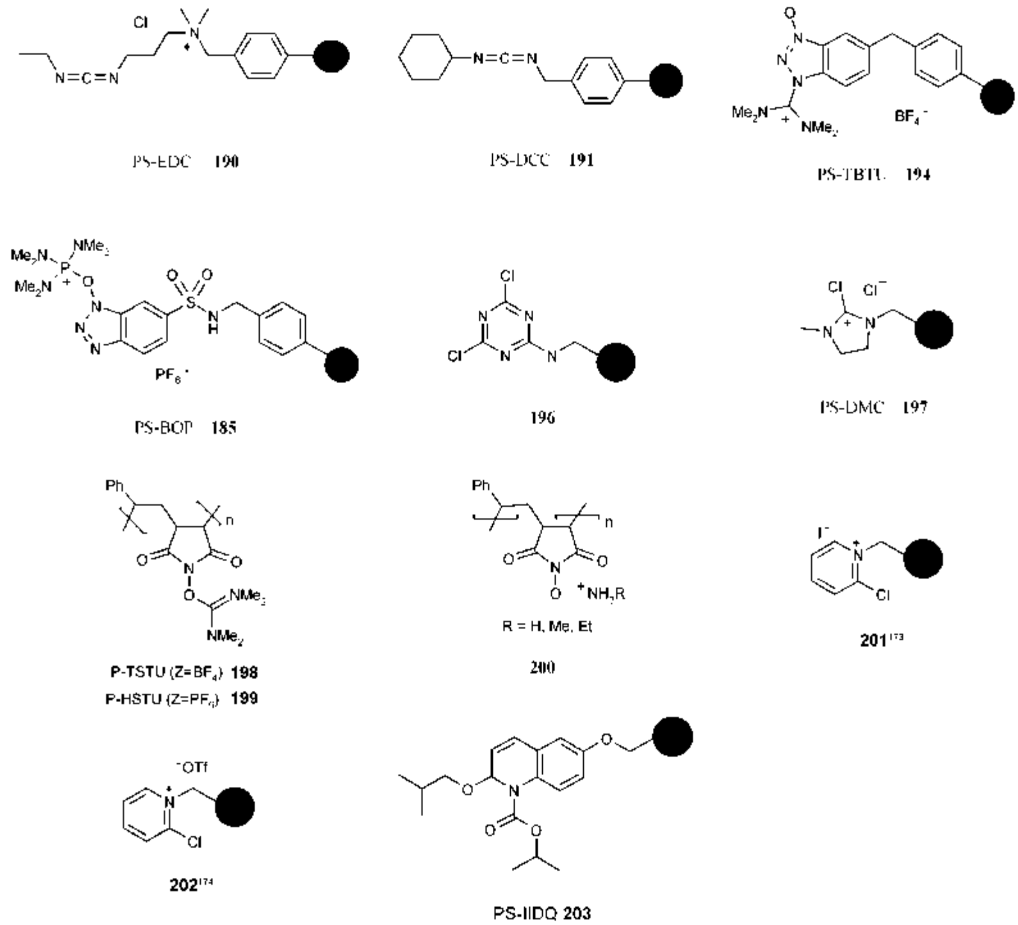


Fig. 27 Structure of polymer-supported reagents.

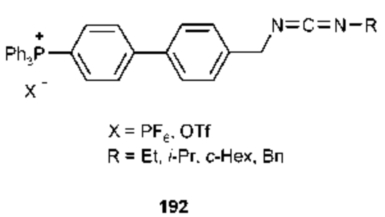


Fig. 28 Tetraarylphosphonium-supported carbodiimides.

drawbacks as TBTU **30b** and BOP **51b** in solution, while the structure of the reagent means that part of it will end up in solution after the coupling, clearly an undesirable occurrence for a supported reagent.

6.3 Other immobilised reagents

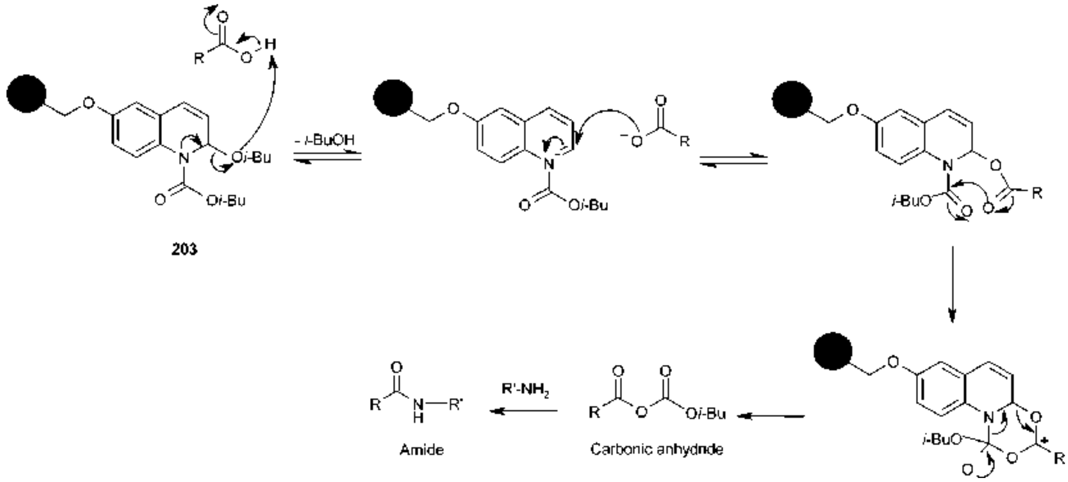
Triazine-based coupling reagents have been widely used in solution-phase. In 1999, Taddei reported polymer-supported chlorotriazine **196**.[168] Although amides were synthesised in moderate to good yield using this reagent, the ^{1}H NMR of the crude compounds revealed the presence of 5 to 10% of by-products. Hioki used another strategy to obtain polymeric triazine-type reagents.[169] Using a norbornene-derivatised triazine, they synthesised *via* ROMP an immobilised mono-methoxychlorotriazine, which was tested on anilines and primary amines. Yields were good (nine examples, 80–98%), but no secondary amine was tested while the reagent was not compared to other classical amide bond formation methods.

PS-DMC **197**, a supported equivalent of DMC **89**, was reported by Ishikawa.[170] Yields over five examples were slightly lower for the polymer-supported version of the reagent, and the examples provided did no allow a full display of the scope and limitations of the reagent.

Chinchilla developed some reagents based on polymeric succinimides such as P-TSTU **198** and P-HSTU **199**,[171] and **200** (Fig. 27).[172] The results were good for classic amino acids but the yields were moderate to low when coupling hindered amino acids. Globally these reagents did not really add any benefit to the range of coupling reagents available, and, like PS-TBTU **194** and PS-BOP **195**, part of the reagent ended up in solution.

More recently, Convers reported an immobilised Mukaiyama reagent **201**.[173] However, Crosignani investigated this new reagent and concluded that the synthesis was poorly reproducible, and developed another route.[174] This reagent **202** appeared to work very efficiently for the synthesis of esters and amides including hindered substrates, secondary amines and anilines.[174,175]

Polymer-supported IIDQ **203** is an immobilised version of the solution-phase IIDQ **100** reagent.[97,176] It was synthesised in three steps from Merrifield resin and 6-hydroquinoline to provide a high loading reagent (>1.68 mmol/g). The main



Scheme 19 Activation process when using PS-IIDQ.

advantages of PS-IIDQ **203** are that no base is required during coupling, while the order of addition of amine, carboxylic acid and reagent do not influence the outcome of the reaction (Scheme 19).

This reagent was compared to other classically used and commercially available coupling reagents such as Polymer-supported EDC **190** and DCC **191**, as well as HATU **28a**. Interestingly, PS-IIDQ **203** performed better than any of these reagents on a set of three amines and three carboxylic acids, including anilines and bulky substrates (Table 5). Furthermore, PS-IIDQ **203** was evaluated on 9 amines and 5 carboxylic acids and gave an average yield of 73%. Epimerisation was low as Anteuni's test did not reveal any trace of the diastereoisomer by NMR. PS-IIDQ **203** was stable under standard laboratory storage conditions and it was shown that the reagent could be advantageously recycled after any coupling reaction. Thus PS-IIDQ **203** appears to be a very versatile coupling reagent for the parallel synthesis of amides.

Very recently, Kakarla duplicated these studies to make PS-EEDQ **204**.[177] It was obtained using identical conditions for the transformation of PS-Quinoline into PS-EEDQ **204**, the only variation being the use of a Wang resin. However the loading of the so-called "high-loading" PS-EEDQ **204** was erroneous (starting from a 1.7 mmol/g Wang resin, the maximum physical loading of PS-EEDQ **204** would be 1.19 mmol/g assuming total conversion during synthesis, while the authors claimed 1.36 mmol/g loading), while a Wang linker was clearly of no use. When looking at the efficiency of EEDQ **99** and IIDQ **100** (Table 4),[97] the choice appears evident.

Table 5 Comparison of the yields and purities obtained over three amines (4-*tert*-butylaniline, benzylamine, H-PhG-OMe) and three carboxylic acids (Boc-Aib-OH, phenylacetic acid, benzoic acid)

Entry	Coupling reagent	Average yield (%)	Average purity (%)
1	PS-IIDQ	72	100
2	HATU	55	98
3	PS-EDC	41	96
4	PS-DCC	26	97

7. Conclusion on available coupling reagents

Although hundreds of coupling reagents have been reported, conclusions on their efficiency are in fact quick and simple. Most of these reagents are simply not efficient for a broad range of amide bond formation. Some reagents do perform well in general, but differences are typically small. Solid-phase peptide chemists may find useful reagents which display fast kinetics for coupling as the synthesis of long peptides has ideally to be rapid. However, for the general organic chemist, simple reagents are often the most appropriate allowing coupling reagents to be used on a large selection of substrates with varying reactivities.

This summary can be illustrated by the comparison of coupling reagents carried out by Hachman.[68] Very few comparisons of reagents have been published and the work by Hachman displayed the importance of a comparison system. Hachman compared classical reagents such as phosphonium salts, uronium salts, reagents generating acid halides and carbodiimides. During the synthesis of decapeptides, HBTU **28b** was the "fastest" reagent after 2 min while almost none of the expected amide was formed by DIC after this time. However, after 8 min, DIC **13** was comparable to HBTU **28b**. In addition very few side-reactions were observed with DIC **13** (in particular deletion) compared to BOP **51b** or HATU **28a**. This demonstrated that a simple reagent like DIC **13** (using HOBt as additive) performs well in many cases, and a compromise of speed/purity/by-products needs to be sought.

An important point is the way new coupling reagents are reported. As stated and demonstrated by Hachman: "the use of only one model sequence for evaluation of synthetic reagents [. . .] can be misleading." As such, unless new reagents are systematically tested against commonly considered "top coupling reagents", such as HATU **28a**, and traditional methods such as DIC/HOBt, it is likely that most new coupling reagents will have an application limited to the original publication by their authors.

Overall, keeping in mind all possible issues (side-reactions), HATU **28a** and HBTU **28b** offer generally excellent reactivity.

If quick coupling times are required, HATU **28a** probably represents the reagent of choice, providing the substrates are not hindered. Otherwise, the traditional method DCC **5** (or DIC **13**) /HOBt remains an excellent choice for many substrates. One has nevertheless to keep in mind potential hazards when using reagents based on 1*H*-benzotriazole due to the potential explosive properties of HOBt.[30,31]

For difficult couplings (*e.g.* secondary amines), our experience tells us that PyBrop **79b** is generally reliable.[178] Triazines can be an alternative for difficult coupling, although the most reactive reagents tend to give side-products. However, the recent developments by Kaminski are bringing new applications to this class of coupling reagents.

Finally, for library synthesis either the PS-Mukaiyama reagent **202** or polymer-supported IIDQ **203** are clearly the most suitable reagents,[179] and their efficiency has been confirmed by many groups. These reagents have the advantage of simplifying purification as the reagent is separated *via* simple filtration after reaction.

In conclusion, selecting suitable coupling reagents could be summarised by "keep it simple" as most reagents appear to be merely fancy and costly alternatives. Finding a universal coupling reagent remains elusive considering the wide portfolio of potential substrates and it is generally wise to avoid "exotic" reagents and not be mislead by "fast" coupling reagents. Efficiency is the key, with high conversions, low levels of epimerisation and limited by-products all being essential criteria.

List of abbreviations

General

ACP	acyl carrier protein decapeptide 65–74
DABCO	bicyclo[2,2,2]-1,4-diazaoctane
DCU	dicyclohexylurea
DMAP	4-dimethylaminopyridine
DMPU	dimethylpropyleneurea
HMPA	hexamethylphosphoramide
LHRH	Luteinising Hormone Releasing Hormone
NMM	*N*-methylmorpholine
ROMP	Ring Opening Metathesis Polymerisation

Coupling reagents and additives

ACTU	(2-(6-chloro-1-*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium) hexachloroantimonate
AOMP	5-(7-azabenzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
AOP	(7-azabenzotriazol-1-yl)oxytris(dimethylamino)phosphonium hexafluorophosphate
BBC	benzotriazoloxy-bis(pyrrolidino)carbonium hexafluorophosphate
BDDC	bis[[4-(2,2-dimethyl-1,3-dioxolyl)]methyl]-carbodiimide
BDMP	5-(1*H*-benzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
BDP	benzotriazol-1-yl diethylphosphate
BEC	*N*-*tert*-butyl-*N*′-ethylcarbodiimide
BEMT	2-bromo-3-ethyl-4-methylthiazolium tetrafluoroborate
BEP	2-bromo-1-ethylpyridinium tetrafluoroborate
BEPH	2-bromo-1-ethylpyridinium hexachloroantimonate
4,5-B(HATU)	*N*-[(dimethylamino)(3*H*-1,2,3-triazolo[4,5-*c*]-isoquinolin-3-yloxy)-*N*-methylmethanaminium hexafluorophosphate
5,6-B(HATU)	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]quinolinium hexafluorophosphate-3-oxide
BIODPP	diphenyl benzo[*d*]isoxazol-3-ylphosphonate
BMC	*N*-*tert*-butyl-*N*′-methylcarbodiimide
BMMP	1-(1-(1*H*-benzo[*d*][1,2,3]triazol-1-yloxy)ethylidene)pyrrolidinium hexachloroantimonate
BMP-Cl	*N,N*′-bismorpholinophosphonic chloride
BMTB	2-bromo-3-methyl-4-methylthiazolium bromide
BOI	2-(benzotriazol-1-yl)oxy-1,3-dimethylimidazolidinium hexafluorophosphate
BOMI	benzotriazol-1-yloxy-*N*,*N*-dimethylmethaniminium hexachloroantimonate
BOP	benzotriazolyl-*N*-oxytrisdimethylaminophosphonium hexafluorophosphate
BOP-Cl	*N*,*N*′-bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BPMP	1-(1*H*-benzotriazol-1-yloxy)phenylmethylene pyrrolidinium hexachloroantimonate
BroP	bromotris(dimethylamino)phosphonium hexafluorophosphate
BTFFH	bis(tetramethylene)fluoroformamidinium hexafluorophosphate
CBDO	2-chlorobenzo[*d*][1,3]dioxol-1-ium hexachloroantimonate
CBMIT	1,10-carbonylbis(3-methylimidazolium) triflate
CDI	carbonyldiimidazole
CDMS	chlorodimethylsulfonium hexachloroantimonate
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
CDTP	2-chloro-1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-1-ium perchlorate
CIP	2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate
CloP	chlorotris(dimethylamino)phosphonium hexafluorophosphate
CMMM	chloro(4-morpholino)methylene morpholinium hexafluorophosphate
CPMA	(chlorophenylthiomethylene)dimethylammonium chloride
CPDT	2-chloro-5-phenyl-1,3-dithiol-1-ium hexachloroantimonate
Cpt-Cl	1-oxo-chlorophospholane
DAST	diethylaminosulfur trifluoride
DCC	dicyclohexylcarbodiimide
DCIH	1,3-dimethyl-2-chloro-4,5-dihydro-1*H*-imidazolium hexafluorophosphate
DCMT	2,4-dichloro-6-methoxy-1,3,5-triazine
DEBP	diethyl-2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl)phosphonate

DEFFH 1,2-diethyl-3,3-tetramethylenefluoroformamidinium hexafluorophosphate
DECP diethylcyanophosphonate
DEPC diethyl phosphorochloridate
DEPB diethyl phosphorobromidate
DEPBO *N*-diethoxyphosphorylbenzoxazolone
DEPBT 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
DepOAt 3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yldiethyl phosphate
DepOBt diethoxyphosphinyloxybenzotriazole
DepODhbt diethyl 4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yl phosphate
DFIH 1,3-dimethyl-2-fluoro-4,5-dihydro-1*H*-imidazolium hexafluorophosphate
DIC diisopropylcarbodiimide
DMC 2-chloro-1,3-dimethylimidazolinium chloride
DMCH *N*-(chloro(morpholino)methylene)-*N*-methylmethanaminium hexafluorophosphate
DMFFH 1,2-dimethyl-3,3-tetramethylenefluoroformamidinium hexafluorophosphate
DMFH *N*-(fluoro(morpholino)methylene)-*N*-methylmethanaminium hexafluorophosphate
DmppOAt 1-(2,8-dimethylphenoxaphosphinyloxy)-7-azabenzotriazole
DMTMM 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride
DOMP 5-(3′,4′-dihydro-4′-oxo-1′,2′,3′-benzotriazin-3′-yloxy)-3,4-dihydro-1-methyl 2*H*-pyrrolium hexachloroantimonate
DOPBO *N*-(2-oxo-1,2,3-dioxaphosphorinanyl)benzoxazolone
DOPBT 3-[*O*-(2-oxo-1,2,3-dioxaphosphorinanyl)oxy]-1,2,3-benzotriazin-4(3*H*)-one
DPOOP diphenyl-2-oxo-3-oxazolinylphosphonate
Dpop-Cl diphenyl phosphorochloridate
DpopOAt 1-(diphenoxyphosphoryloxy)-7-azabenzotriazole
DpopOBt 1-(diphenoxyphosphoryloxy)benzotriazole
DpopODhbt 3-(diphenoxyphosphinyloxy)-3,4-dihydro-4-oxo-1,2,3-benzotriazene
DPP diphenylphosphite
DPPA diphenylphosphoryl azide
Dpp-Cl diphenylphosphinic chloride
DPTC *O*,*O*′-di(2-pyridyl)thiocarbonate
DPTF 2,2-dichloro-5-(2-phenylethyl)-4-(trimethylsilyl)-3-furanone
DtpOAt 1-[di(*O*-tolyl)phosphinyloxy]-7-azabenzotriazole
DtpOBt 1-[di(*O*-tolyl)phosphinyloxy]benzotriazole
DtpODhbt 3-di(*O*-tolyl)phosphinyloxy]-3,4-dihydro-4-oxo-1,2,3-benzotriazine
EDC 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EEDQ *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
ENDPP phosphoric acid 3,5-dioxo-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl ester diphenyl ester
FDMP 3,5-bis(trifluoromethyl)phenyl diphenylphosphinate
FDPP pentafluorophenyl diphenyl phosphinate
FEP 2-fluoro-1-ethylpyridinium tetrafluoroborate
FEPH 2-fluoro-1-ethylpyridinium hexachloroantimonate
FOMP 5-(pentafluorophenyloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
HAE$_2$PipU *O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-diethyl-3,3-pentamethyleneuronium hexafluorophosphate
HAE$_2$PyU *O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-diethyl-3,3-tetramethyleneuronium hexafluorophosphate
HAMDU *O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate
HAM$_2$PipU *O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-dimethyl-3,3-pentamethyleneuronium hexafluorophosphate
HAM$_2$PyU *O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-dimethyl-3,3-tetramethyleneuronium hexafluorophosphate
HAMTU *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate
HAPipU *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate
HAPyTU *S*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)thiouronium hexafluorophosphate
HAPyU 1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene)pyrrolidinium hexafluorophosphate *N*-oxide
HATeU *O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1,3,3-tetraethyluronium hexafluorophosphate
HATU *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBE$_2$PipU *O*-(1*H*-benzotriazol-1-yl)-1,1-diethyl-3,3-pentamethyleneuronium hexafluorophosphate
HBE$_2$PyU *O*-(1*H*-benzotriazol-1-yl)-1,1-diethyl-3,3-tetramethyleneuronium hexafluorophosphate
HBMDU *O*-(benzotriazol-l-yl)-l,3-dimethyl-l,3-dimethyleneuronium hexafluorophosphate
HBMP 1*H*-benzo[*d*][1,2,3]triazol-1-ylmethanesulfonate
HBM$_2$PipU *O*-(1*H*-benzotriazol-1-yl)-1,1-dimethyl-3,3-pentamethyleneuronium hexafluorophosphate
HBM$_2$PyU *O*-(1*H*-benzotriazol-1-yl)-1,1-dimethyl-3,3-tetramethyleneuronium hexafluorophosphate
HBPipU *O*-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate
HBSP 1*H*-benzo[*d*][1,2,3]triazol-1-ylbenzenesulfonate
HBTeU *O*-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetraethyluronium hexafluorophosphate
HBTU *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCTU (2-(6-chloro-1-*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium) hexafluorophosphate
HCSCP 6-chloro-1*H*-benzo[*d*][1,2,3]triazol-1-yl-4-chlorobenzenesulfonate
HCSP 6-chloro-1*H*-benzo[*d*][1,2,3]triazol-1-ylbenzenesulfonate

HDATU (bis(dimethylamino)methyl)(4-oxopyrido[3,2-*d*]-[1,2,3]triazin-3(4*H*)-yl)oxonium hexafluorophosphate
HDADU (bis(dimethylamino)methyl)(4-oxopyrido[3,2-*d*]-pyrimidin-3(4*H*)-yl)oxonium hexafluorophosphate
HDAPyU 1-((4-oxopyrido[3,2-*d*][1,2,3]triazin-3(4*H*)-yloxy)-(pyrrolidin-1-yl)methylene)pyrrolidinium hexafluorophosphate
HDMA 1-((dimethylamino)(morpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate 3-oxide
4-HDMA 3-((dimethylamino)(morpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate 1-oxide
HDMB 1-((dimethylamino)(morpholino)methylene)-1*H*-benzotriazolium hexafluorophosphate 3-oxide
HDMCB 6-chloro-1-((dimethylamino)(morpholino)-methylene)-1*H*-benzotriazolium hexafluorophosphate 3-oxide
HDMFB 6-trifluoromethyl-1-((dimethylamino)-(morpholino)methylene)-1*H*-benzotriazolium hexafluorophosphate 3-oxide
HDMPfp 1-((dimethyamino)(morpholino))oxypentafluorophenyl metheniminium hexafluorophosphate
HDMS 1-((dimethyamino)(morpholino))oxypyrrolidine-2,5-dione methanaminium hexafluorophosphate
HDPyU 1-((4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yloxy)-(pyrrolidin-1-yl)methylene)pyrrolidinium hexafluorophosphate
HDTMA 1-((dimethylamino)(thiomorpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate 3-oxide
HDTMB 1-((dimethylamino)(thiomorpholino)methylene)-1*H*-benzotriazolium hexafluorophosphate 3-oxide
HDTU *O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOAt 1-hydroxy-7-azabenzotriazole
HOBt 1-hydroxy-1*H*-benzotriazole
HODhat 3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazine
HODhbt 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine
HODT *S*-(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiouronium
HONB 2-(5-norbornene-2,3-dicarboximide)
HOPfp pentafluorophenol
HPyOPfp *N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate
HPySPfp 1-((perfluorophenylthio)(pyrrolidin-1-yl)-methylene)pyrrolidinium hexafluorophosphate
HOSu *N*-hydroxysuccinimide
HOTT *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate
HSTU *O*-(*N*-succimidyl)-*N*,*N*,*N*′,*N*′-bis(tetramethylene)-uronium hexafluorophosphate
IDDQ *N*-isobutoxycarbonyl-2-isobutoxy-1,2-dihydroquinoline
MPTA dimethylphosphinothioyl azide
MPT-Cl dimethylphosphinothioyl chloride
MPTO 3-dimethylphosphinothioyl-2(3*H*)-oxazolone
NDPP norborn-5-ene-2,3-dicarboximidodiphenylphosphate
NOP [(6-nitrobenzotriazol-1-yl)oxy]tris(dimethylaminop)phosphonium hexafluorophosphate
PEC phenylethylcarbodiimide
PFNB perfluorophenyl 4-nitrobenzenesulfonate
PIC phenylisopropylcarbodiimide
PTOC pyridine-2-thione-*N*-oxycarbonyl
PyAOP [(7-azabenzotriazol-1-yl)oxy]tris(pyrrolidino)-phosphonium hexafluorophosphate
PyBOP benzotriazol-1-yloxytri(pyrrolidino)-phosphonium hexafluorophosphate
PyBroP bromotri(pyrrolidino)phosphonium hexafluorophosphate
PyClock 6-chloro-1-hydroxybenzotriazol-1-yl-*N*-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate
PyCloP chlorotri(pyrrolidino)phosphonium hexafluorophosphate
PyClopP chlorobispyrrolidinophenylphosphonium hexachloroantimonate
PyFloP fluorotri(pyrrolidino)phosphonium hexafluorophosphate
PyClU chlorodipyrrolidinocarbenium hexafluorophosphate
PyDAOP (4-oxopyrido[3,2-*d*][1,2,3]triazin-3(4*H*)-yloxy)-tripyrrolidin-1-ylphosphonium hexafluorophosphate
PyDOP [(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-oxy]tris(pyrrolidino)phosphonium hexafluorophosphate
PyDPP diphenyl 2-oxopyridin-1(2*H*)-ylphosphonate
PyFOP [[6-(trifluoromethyl)benzotriazol-1-yl]oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate
PyNOP [(6-nitrobenzotriazol-1-yl)oxy]tris(pyrrolidino)-phosphonium hexafluorophosphate
PyPOP (perfluorophenoxy)tripyrrolidin-1-ylphosphonium
PyTOP (pyridyl-2-thio)tris(pyrrolidino)-phosphonium hexafluorophosphate
SbTMU *O*-(*N*-succimidyl)-*N*,*N*,*N*′,*N*′-bis-(tetramethylene)-uronium hexafluorophosphate
SDPP 2,5-dioxopyrrolidin-1-yl diphenyl phosphate
SMDOP 4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yl methanesulfonate
SPDOP 4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yl benzenesulfonate
SOMI 5-(succinimidyloxy)-*N*,*N*-dimethylmethaniminium hexachloroantimonate
SOMP 5-(succinimidyloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
T3P 2-propanephosphonic acid anhydride
TATU *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate

TAPipU	1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene)pyrrolidinium tetrafluoroborate *N*-oxide
TBFH	*N*,*N*,*N*′,*N*′-tetramethylbromoformamidinium hexafluorophosphate
TBTU	*O*-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate
TCFH	*N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate
TCTU	(2-(6-chloro-1-*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium) tetrafluoroborate
TDBTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEFFH	tetraethylfluoroformamidinium hexafluorophosphate
TFMS-DEP	diethylphenyl(trifluoromethylsulfonyl)-phosphoramidate
TFFH	tetramethylfluoroformamidinium hexafluorophosphate
TNTU	2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate
TOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetra-methylthiouronium tetrafluoroborate
TODT	*S*-(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-tri-methylenethiouronium tetrafluoroborate
TOTU	*O*-(cyano(ethoxycarbonyl)methylenamino)-1,1,3,3-tetramethyluronium tetrafluoroborate
TPTU	1-((dimethylamino)(dimethyliminio)methoxy)-2-hydroxypyridinium tetrafluoroborate
TSTU	2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate

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FORM 26
THE PATENTS ACT, 1970
(39 of 1970)
&
The Patent Rules, 2003

FORM OF AUTHORISATION OF A PATENT AGENT/OR ANY PERSON IN A MATTER OR PROCEEDING UNDER THE ACT
[See sections 127 and 132 and rule 135]

We, **SANKALP REHABILITATION TRUST**, having its office at, SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002; hereby authorize Rajeshwari H., Gopalan Deepak Sriniwas, Sweety Sharma and Pragya Singh Thakur, all Indian citizens, Advocates / Patent Agents of RAJESHWARI & ASSOCIATES, A – 202, FIRST FLOOR, SHIVALIK COLONY, ,MALVIYA NAGAR, NEW DELHI - 110017, India, jointly or severally to act on our behalf for filing an opposition and/or representation by the way of opposition against an invention entitled: **"ANTI-INFECTIVE COMPOUNDS"** Indian Application No: **8533/DELNP/2012** filed on 28th September, 2012 by **INSTITUT PASTEUR KOREA and INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST)** is a National Phase of PCT Application No. PCT/EP2011/001345 dated 08th March, 2011 under the above mentioned Act and in all matters and proceedings relating to the patent applications before the Controller of Patents or the Government of India in connection therewith or incidental thereto and in general to do all acts or things including filing of representation, statements, replies, extensions, fees, evidence and any or all documents or pleadings, attending hearings and appointment of a substitute or substitutes as the said Agent(s) may deem necessary or expedient and request that all notices, requisitions and communication relating thereto may be sent to such Agent(s) at Rajeshwari & Associates, India.

We hereby revoke all previous authorization, if any made, in respect of same matter or proceeding.

We hereby assent to the action already taken by the said person in the above matter.

Dated this 29 day of June, 2020

For SANKALP Rehabilitation Trust

Signature:

ELDRED TELLIS
(Director)

To
The Controller of Patents
The Patent Office,