

DECEMBER 4, 2023

THE CONTROLLER OF PATENT
THE PATENT OFFICE
DELHI, MUMBAI, KOLKATA, CHENNAI

KIND ATTENTION: MR. SOUMEN GHOSH
[DEPUTY CONTROLLER OF PATENTS & DESIGNS]

Re: REPRESENTATION U/S 25(1) OF THE PATENT ACT – BY BALAJI R.
AGAINST INDIAN PATENT APPLICATION NO. 201737015848 DATED
05/05/2017

TITLE: MODULATORS OF CYSTIC FIBROSIS TRANSMEMBRANE
CONDUCTANCE REGULATOR

APPLICANT: VERTEX PHARMACEUTICALS INCORPORATED

R&A REF.: OPP0431

Respected Sir,

We are filing this representation by way of Pre-Grant Opposition along with annexures u/s 25 (1) of the Patents Act, 1970 and Rule 55 of the Patent Rules, 2003 in Form 7A.

The Learned Controller is requested to take said opposition along with annexures on record and proceed further in the matter and keep the Opponent advised of each and every step taken in the matter.

We crave the leave of the Learned Controller to submit additional documents and/or evidence to support any of the averments in the representation as may be necessitated during the future proceeding.

Lastly, we request the Learned Controller to grant an opportunity of being heard before the present Opposition is finally decided.

Thanking you,

Yours faithfully,

A handwritten signature in blue ink, appearing to read 'Pragya Singh', is written over a light yellow rectangular background.

PRAGYA SINGH THAKUR (IN/PA – 3329)
FOR RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

Encl.: As stated

C.C: ANAND AND ANAND

EMAIL: email@anandandanand.com;

BEFORE THE CONTROLER OF PATENTS, THE PATENT OFFICE,
KOLKATA

IN THE MATTER OF:

The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005, and The Patents Rules, 2003, as amended by The Patents (Amendment) Rules, 2006

AND

IN THE MATTER of Pre-Grant Opposition under Section 25(1)

AND

IN THE MATTER of Indian Patent Application No. 201737015848

IN THE MATTER OF:

BALAJI R.

.....OPPONENT

VS.

VERTEX PHARMACEUTICALS INCORPORATED

.....APPLICANT

PRE-GRANT OPPOSITION BY BALAJI R.

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7.	Annexure – 5: Copy of WO2010123822A1 (WO'822) published 28 October 2010.	507-610

8.	Power of Attorney	Will follow
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Dated this 04th day of December, 2023



PRAGYA SINGH THAKUR (IN /PA – 3329)
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, KOLKATA

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

I, Balaji R., having address at No. 428, 3rd Cross, Chikkarmarana Halli, New BEL Road, Devesandra, MSRIT PO, Bangalore – 560054, India, hereby give Notice of opposition to the grant of patent in respect of Indian Patent Application No. 201737015848 dated 05/05/2017 made by **VERTEX PHARMACEUTICALS INCORPORATED** on the grounds.

- (a) Section 25(1)(e): Lack of inventive step
- (b) Section 25(1)(f): Invention is not patentable under section 3(d) and 3(e)
- (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)(h): Failure to disclose the information required by section 8 of the Patents Act.

(Detailed grounds are set out in the Opposition)

Our address for service in India is:

RAJESHWARI & ASSOCIATES

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NEAR HDFC BANK

PANCHSHEEL PARK

MALVIYA NAGAR

NEW DELHI – 110017, INDIA

Tel: + 91-11-41038911

Mobile No. 8368982401; Email: pragya@ralegal.co.in

Dated this 04th day of December, 2023

A handwritten signature in blue ink, appearing to read 'Pragya Singh', is placed over a light yellow rectangular background.

PRAGYA SINGH THAKUR (IN /PA – 3329)
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO
THE CONTROLLER OF PATENTS
PATENT OFFICE, KOLKATA

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE,
KOLKATA

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 Patents (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application 201737015848 dated 05/05/2017, in the name of **VERTEX PHARMACEUTICALS INCORPORATED**

REPRESENTATION BY:

BALAJI R.

.....OPPONENT

VS.

VERTEX PHARMACEUTICALS INCORPORATED

.....APPLICANT

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

I, Balaji R. an Indian citizen, hereby submit my representation by way of opposition to the grant of patent in respect of Indian Patent Application 201737015848 dated 05/05/2017 in the name of VERTEX PHARMACEUTICALS INCORPORATED titled “Modulators of Cystic Fibrosis Transmembrane conductance Regulator”.

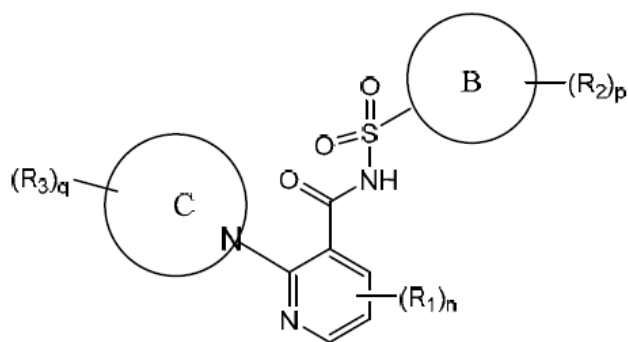
STATEMENT OF CASE OF OPPONENT

1. The Opponent has learnt that the Applicant has filed an Indian Patent Application 201737015848 (hereinafter “the Impugned Patent Application”) on 02/09/2020. The impugned patent application was published in the official journal of the patent office on 25/08/2017, which is currently pending before the Patent Office. The Impugned Patent

Application is the national phase application of PCT/US2015/054316 and draws its priority from US application 62/060,182 dated 06th Oct 2014, US application 62/114,767 dated 11th Feb 2015 and 62/153,120 dated 27th April 2015.

2. The Impugned Patent Application is entitled “Modulators of Cystic Fibrosis Transmembrane conductance Regulator”.
3. 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-1** and the representative claim 1 is reproduced herein below for ready reference:

1. A compound of formula Ib-iii:



Ib-iii

or a pharmaceutically acceptable salt thereof, wherein:

Ring B is a C6-C10 aryl ring or C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

Ring C is a C3-C14 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently N, O, or S, and wherein one nitrogen on Ring C is the point of attachment to the pyridine ring;

and wherein, independently for each occurrence:

R₁ is halo; CN; F₅S; SiR₃; OH; NRR; C1-C6 alkyl or fluoroalkyl; C1-C6 alkoxy or fluoroalkoxy; C2-C6 alkenyl; C2-C6 alkynyl; (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR; C6-C10 aryl; C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; or C3-C10 cycloalkyl;

R₂ is halo; OH; NRR; azide; CN; CO₂R; C1-C6 alkyl or fluoroalkyl; C1-C6 alkoxy or fluoroalkoxy; C2-C6 alkenyl; C2-C6 alkynyl; C6-C10 aryl; C3-C13 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;

or two R₂ groups taken together may form a =CH₂ or =O group;

R₃ is halo; CN; CO₂R; C1-C6 alkyl or fluoroalkyl; C2-C6 alkenyl; C2-C6 alkynyl; C1-C6 alkoxy or fluoroalkoxy; or C6-C10 aryl; C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;

or two R₃ groups taken together may form a =CH₂ or =O group;

R₄ is H; azide; CF₃; CHF₂; OR; CCH; CO₂R; OH; C₆-C₁₀ aryl, C₃-C₁₀ heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C₃-C₁₀ cycloalkyl; NRR, NRCOR, CONRR, CN, halo, or SO₂R;

R is independently H; OH; CO₂H; CO₂C₁-C₆ alkyl; C₁-C₆ alkyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₆-C₁₀ aryl; C₃-C₁₀ heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; or C₃-C₁₀ cycloalkyl; n is 0, 1, 2 or 3;

p is 0, 1, 2, or 3; and

q is 0, 1, 2, 3, 4, or 5.

wherein each of the specific groups for the variables R₁-R₄ can be optionally substituted with one or more group selected from halo, phospho, OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, fluoroalkyl, alkyl, alkenyl, alkynyl, nitro, CN, hydroxyl, and (C₁-C₉alkylene)-E wherein up to 4 CH₂ units are independently replaced with O, S, SO₂, SO, CO, NH, *N*-alkyl, *N*-alkenyl, or *N*-alkynyl, and E is H, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, CN, or CF₃, further wherein each of the aryl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with one or more group selected from halo, alkyl, amino, CN, alkenyl, alkynyl, and alkoxy; and

when two alkoxy groups are bound to the same atom or adjacent atoms, the two alkoxy groups can form a ring together with the atom(s) to which they are bound; and

wherein the term “amino” refers to NH₂ which is optionally substituted with one or two groups independently selected from alkyl, cycloalkyl, and heterocycloalkyl.

4. Impugned Patent Application: The present pre-grant opposition is against Indian Patent Application 201737015848 dated 05/05/2017 in the name of “MODULATORS OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR”. The impugned patent application is drawn towards compounds that are modulators of CFTR channel. The claims of the impugned application are also drawn towards pharmaceutical compositions comprising compounds of the invention with pharmaceutical acceptable carrier(s). The pending claims are also drawn towards compositions of compounds of the invention with pharmaceutical acceptable carrier(s) and one or more additional

therapeutic agent(s) comprising a CFTR modulator which include combination with tezacaftor and ivacaftor.

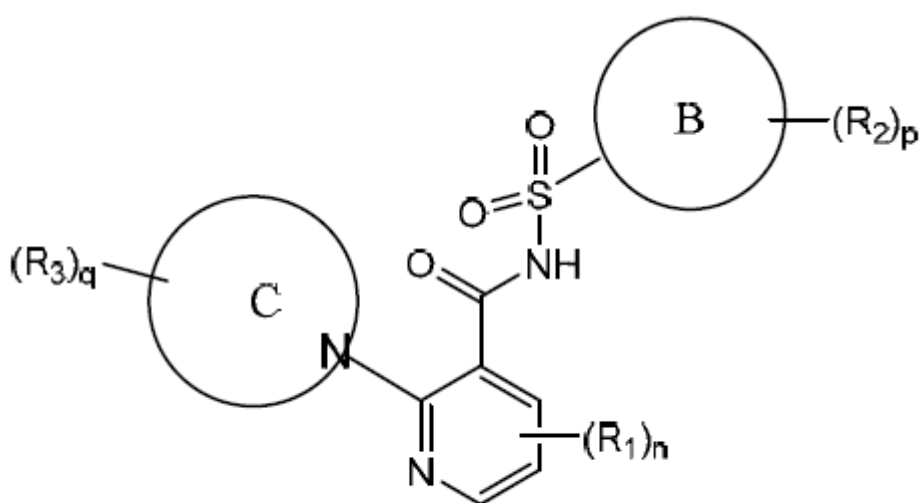
BRIEF BACKGROUND ABOUT CYSTIC FIBROSIS (CF) AND TREATMENT

5. This impugned patent application concerns with compounds aimed at treating the genetic disease cystic fibrosis. Cystic fibrosis (CF) is a genetic disorder that primarily affects the lungs and digestive system. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which regulates the movement of salt and water in and out of cells. These mutations lead to the production of a faulty CFTR protein, resulting in the buildup of thick, sticky mucus in various organs.
6. In the lungs, the thick mucus obstructs the airways, making it difficult to breathe and leading to frequent lung infections and inflammation. Over time, this can cause progressive lung damage and respiratory failure. The symptoms of cystic fibrosis can vary widely, but they often include persistent cough, recurrent lung infections, wheezing, poor weight gain despite a good appetite, greasy and bulky stools, and salty-tasting skin.
7. Advancements in research and medical treatments have improved the prognosis and life expectancy of individuals with cystic fibrosis. Therapies targeting specific CFTR mutations, known as CFTR modulators (caftors), have shown promising results in improving lung function and reducing disease progression.
8. In the context of treating cystic fibrosis (CF), CFTR (cystic fibrosis transmembrane conductance regulator) modulators, i.e., caftors have emerged as a significant advancement in therapy. (reference ~ De Boeck, Kris, and Margarida D. Amaral. "Progress in therapies for cystic fibrosis." *The Lancet Respiratory Medicine* 4, no. 8 (2016): 662-674.) These are carboxamide molecules synthesized in the laboratory following routine total synthesis protocols (reference ~ WO2013038390 (WO'390), 21 March 2013, discloses N-substituted heterocyclyl carboxamides along with their preparation and use in treatment.) These drugs work by targeting and modulating the function of the CFTR protein. By enhancing CFTR activity, carboxamide drugs aim to restore chloride ion transport and reduce the buildup of thick mucus in the lungs and other affected organs.

PRELIMINARY: LACK OF UNITY OF INVENTION

9. It is submitted that the claims of impugned application relate to multiple inventions that are being claimed in a single application as shown:

- a) Claim 1 is independent claim which is directed to modulators of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), or a pharmaceutically acceptable salt. The claimed compounds purportedly possess activity as CFTR modulators. Claim 1 is representative and encompasses structures claimed in claims 1-24. The Markush structure of claim 1 is represented below



Ib-iii

- b) Claims 2-12 are dependent on claim 1, and claim modulators of CFTR or salt of those compounds. These claims describe specifications for the Markush claimed in claim 1.
- c) Claim 13 – 16 are dependent on claim 1, and are also Markush claims with specifications. Claims 13 – 16 are Markush claims which are derived by modifying the Markush of claim 1.
- d) Claim 17 is dependent on claim 1, and it specifically claims a large number of compounds.
- e) Claim 18 and claim 19 are dependent on claim 17, wherein compound numbers 368 and 1356 are claimed from the list of already claimed compounds under claim 17.
- f) Claim 20 claims pharmaceutical composition comprising the compound or salt as claimed in any one of claims 1 to 19 and a pharmaceutically acceptable carrier,

which is a distinct invention separate from the purported invention claimed in claims 1-19.

- g) Claim 21 claims pharmaceutical composition as claimed in claim 20, further comprising one or more additional therapeutic agent(s). This claim represents a separate aspect and invention different from the aforementioned claims 1-19 and claim 20.
- h) Claim 22 is dependent on claim 21, and claims pharmaceutical composition as claimed in claim 21, wherein the one or more additional therapeutic agent(s) comprises a CFTR modulator
- i) Claim 23 is dependent on claim 21 or 22, and claims pharmaceutical composition as claimed in claims 21 or 22, wherein the one or more additional therapeutic agent(s) comprises tezacaftor (or pharmaceutically acceptable salt thereof).
- j) Claim 24 claims pharmaceutical composition as claimed in any one of claims 21 to 23, wherein the one or more additional therapeutic agent(s) comprises Ivacaftor (or pharmaceutically acceptable salt thereof).

10. **PRIOR ARTS:** The opponent wishes to rely on the following prior arts as evidence in support of the grounds of opposition.

- i. WO2013038373A1 (WO'373) published 21 March 2013 (**Annexed herewith as Annexure 2**)
- ii. WO2007056341A1 (WO'341) published 18 May 2007 (**Annexed herewith as Annexure 3**)
- iii. Pedemonte et al., "Phenylglycine and Sulfonamide Correctors of Defective $\Delta F508$ and G551D Cystic Fibrosis Transmembrane Conductance Regulator Chloride-Channel Gating"; Molecular Pharmacology May 2005, 67 (5) 1797-1807 (**Annexed herewith as Annexure 4**)
- iv. WO2010123822A1 (WO'822) published 28 October 2010 (**Annexed herewith as Annexure 5**)

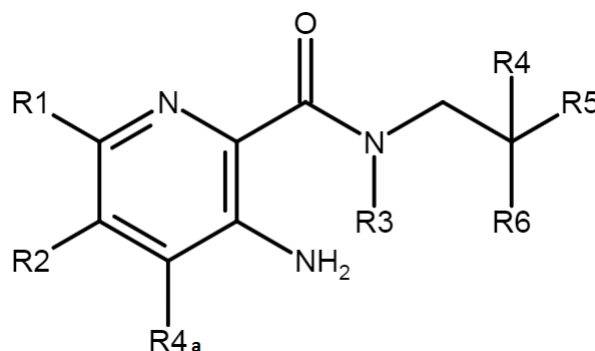
11. It is submitted that the claims of impugned patent application are liable to be refused on following grounds as below, which are without prejudice to each other:

- (a) Section 25(1)(e): Lack of inventive step
- (b) Section 25(1)(f): Invention is not patentable under section 3(d) and 3(e)

- (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)(h): Failure to disclose the information required by section 8 of the Patents Act.

GROUND 1: Lack of inventive step under Section 25(1)(e)

12. It is submitted that WO'373 discloses compounds which restore or enhance the function of mutant and/or wild type CFTR to treat cystic fibrosis (lines 15-16, internal page 1). The compounds disclosed in WO'373 are represented by the Markush formula as depicted below:



13. From the above it can be seen that, the R3 substituent in the above structure may be a hydrogen (line 11, internal page 2). Further, the R1 substituent may be-(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S (lines 3-4, internal page 2). Thus, the compounds encompassed by the above Markush structure represent compounds that include pyridine carboxamide compounds. These compounds can, by way of the substituent R1, have a heterocyclic group with a nitrogen heteroatom attached to the pyridine ring, since the R1 substituent includes 3 to 14 membered heterocyclic groups with the heterocyclic group incorporating at least one heteroatom selected from N, O and S. Further, the R2 substituent is defined to be R2 C1-C4 haloalkyl. Thus, the pyridine ring can have a haloalkyl substituted upon it e.g. fluoroalkyl.
14. Further, it is submitted that the structures in WO'373 are disclosed to be suitable CFTR activity modulators (Line 4, internal page 41). The

15. Some compounds that fall within the Markush disclosed in WO'373 are shown below:

Structure	Name
	5-Amino-4-chloro-2'-methoxy-3-trifluoromethyl-[2,3']bipyridinyl-6-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide
	5-Amino-4-vinyl-2'-methoxy-3-trifluoromethyl-[2,3']bipyridinyl-6-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide
	5'-Amino-2''-methoxy-3'-trifluoromethyl-[2,4';2',3'']terpyridine-6'-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide

16. Further, the compounds of the invention demonstrate activity as CFTR potentiator in CFTR potentiator assay as shown below:

Table 1.

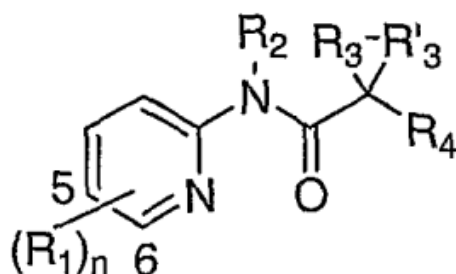
Example No	EC ₅₀ μ M
1.0	0.0035

17. The activity demonstrated in the impugned specification is expressed in EC₃₀ (μ M). The activity of compounds is specified as “+++” indicating $< 3 \mu$ M; “++” indicating activity between 3μ M and 10μ M and “+” indicating activity greater than 10μ M. The activity of all compounds is thus inferior to that shown above in WO'373.

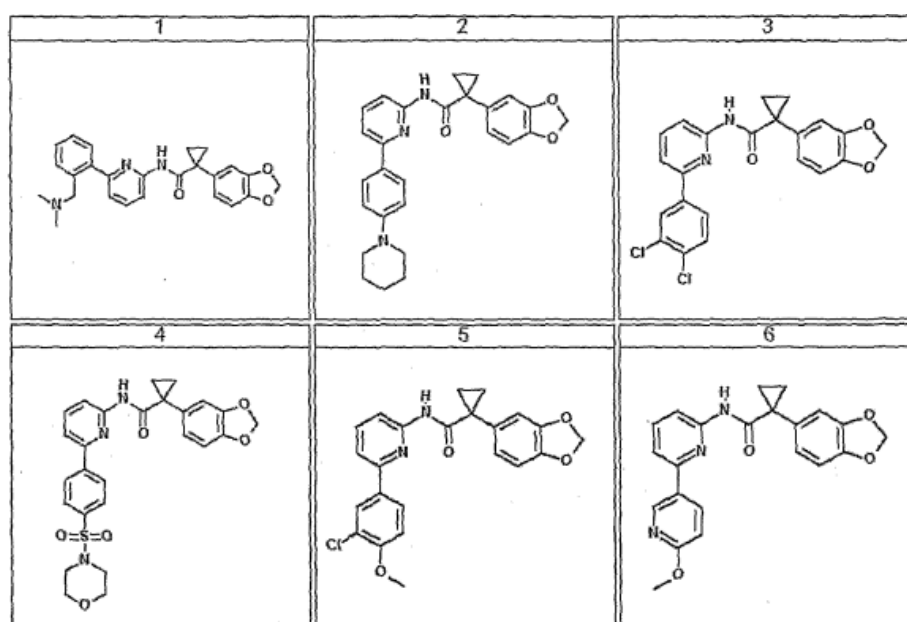
18. It is submitted that WO'341 discloses compounds which are modulators of ABC transporter activity (para [00127], internal page 7). WO'341 discloses that compounds that modulate ABC Transporter activity, such as CFTR activity, by increasing the activity of the ABC Transporter, e.g., a CFTR anion channel, are called agonists (para [00132], internal page 8). It is further disclosed that an agonist interacts with an ABC Transporter, such as CFTR anion channel, to increase the ability of the receptor to

transduce an intracellular signal in response to endogenous ligand binding (para [00132], internal page 8).

19. The compounds disclosed in WO'341 are represented by the Markush formula as depicted below:



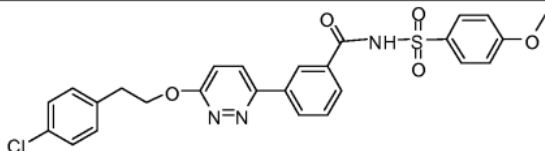
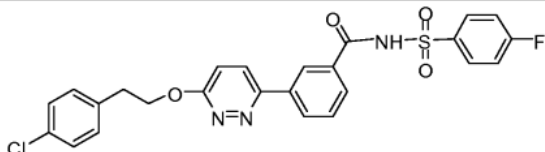
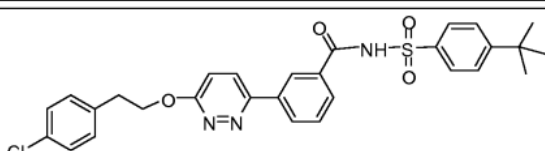
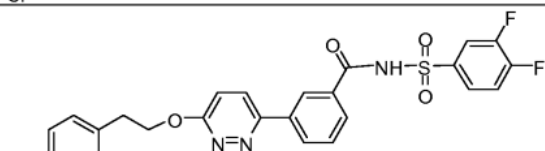
20. Some compounds that fall within the above Markush are shown below

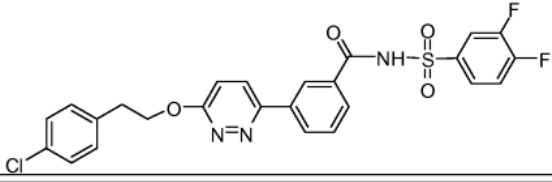
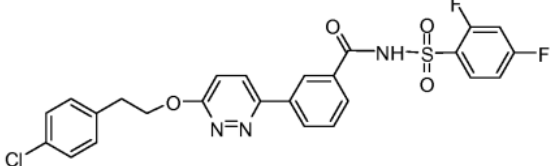


21. From the above, it can be seen that the substituent R₂ can be a hydrogen (para [00199], internal page 22). Further, the substituent R₁ includes an optionally substituted heteroaryl (para [00199], internal page 22). The optionally substituted heteroaryl can thus be a nitrogen-containing ring attached to the pyridine ring. It is further disclosed that the substituent R₁ is attached to the 5 or 6 position of the pyridyl ring. A nitrogen-containing heterocyclic ring can thus be attached to the 6th position of the pyridyl ring, adjacent to the nitrogen of the pyridyl ring. WO'341 thus discloses pyridine carboxamide compounds that are active as modulators of CFTR activity that include compounds with a nitrogen-containing heteroaryl ring adjacent to the nitrogen on the pyridine ring. Thus, it is clear that such pyridine carboxamide compounds were already known in the art.

22. The above disclosures are to be read with Pedemonte et al. (Annexure 4). Pedemonte et al. discloses the results of screening efforts to identify compounds that would be active as correctors of gating. It is disclosed that a large screening of diverse compounds yielded two novel classes of correctors of defective F508-CFTR gating (“potentiators”) with nanomolar potency that were active in human F508 and G551D cells (Abstract, internal page 1797).
23. It is further disclosed that one of the classes of said compounds is sulfonamides may be useful for monotherapy of cystic fibrosis caused by gating mutants and possibly for a subset of Δ F508 subjects with significant Δ F508-CFTR plasma-membrane expression (Abstract, internal page 1797).
24. Pedemonte et al. further discloses that Measurement of transepithelial chloride current in FRT cells confirmed the correction of defective Δ F508-CFTR gating by the sulfonamide compounds (left hand last paragraph, internal page 1806).
25. Thus, Pedemonte et al. teaches that sulfonamides are an entire class of compounds that possess activity as correctors of defective Δ F508-CFTR gating. It would be advantageous to investigate and incorporate the sulfonamide moiety in a molecule to arrive at effective and potent modulators of CFTR channel activity.
26. Thus, the prior arts Annexures 2-3 teach that compounds possessing pyridine carboxamide scaffold are CFTR modulators. A person skilled in the art would thus be motivated to investigate this scaffold for developing further compounds that possess activity as CFTR modulators. Further, the compounds disclosed in Annexure 4 having sulfonamide moiety possess activity as correctors of defective Δ F508-CFTR gating. Thus, a person skilled in the art would be motivated to consider attaching this moiety to pyridine carboxamide moiety to obtain better CFTR modulator activity. Thus, these prior arts teach that compounds possessing both pyridine carboxamide moiety and the sulfonamide moiety would be effective as CFTR modulators, and hence it would be obvious to a person skilled in the art to screen compounds having both pyridine carboxamide moieties and sulfonamide moieties to act as CFTR modulators. Therefore, these chemical modifications are obvious.

27. With regard to the technical advancement of the impugned application, the Applicant submitted in the specification as well as in FER response that the technical problem addressed by impugned invention is provision of novel treatments of CFTR mediated diseases.
28. However, it is submitted that at the time of the invention novel treatments of CFTR mediated diseases were already known in the field of the invention such as in document WO'822.
29. It is submitted that WO'822 relates to compounds for the treatment of cystic fibrosis (claim 44). The compounds disclosed for the treatment of cystic fibrosis shown in WO'822 are as shown below:
30. It is submitted that WO'822 relates to compounds for the treatment of cystic fibrosis (claim 44). The compounds disclosed for the treatment of cystic fibrosis shown in WO'822 are as shown below:

11		3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(4-methoxyphenylsulfonyl)benzamide
12		3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(4-fluorophenylsulfonyl)benzamide
14		N-(4-tert-butylphenylsulfonyl)-3-(6-(4-chlorophenethoxy)pyridazin-3-yl)benzamide
15		3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(3,4-difluorophenylsulfonyl)benzamide

19		3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(3,4-difluorophenylsulfonyl)benzamide
21		3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(2,4-difluorophenylsulfonyl)benzamide

31. It is further submitted that there are minor structural differences between the compounds disclosed in WO'822 and the compounds claimed in impugned application. Even in these minor differences the alternate structural features are merely isosteres of each other.
32. Since the effect of a compound is by virtue of pharmacophore of a compound, the compounds of WO'822 and compounds claimed in impugned application have same effect unless otherwise proven by the Applicant. However, the Applicant has failed to provide any such improvement in effect of the claimed compounds over the effect obtained by the compounds of WO'822, and/or obtained by compounds of WO'373.
33. In view of the above, the claimed subject matter of the impugned application lacks technical advancement in view of the knowledge which was already available in the field at the time of the invention.
34. In view of the above, the subject matter claimed in the impugned application is obvious and lacks technical advancement. Therefore, the subject matter claimed in impugned application lacks inventive step and the impugned application ought to be rejected on this ground alone.
35. Further, since the claim 1 is directed to a Markush formula covering compounds purported to be effective as CFTR modulators, it follows that all claimed compounds should possess that activity.
36. The Applicant has claimed a very large number of compounds, but has failed to provide data that establishes CFTR modulation activity over the entire breadth of the claim. In the absence of such activity, the alleged "invention" is nothing but the provision of novel compounds. Furthermore, since activity over entire claimed range is not established,

there is nothing inventive about the compounds claimed in the impugned application. Thus, the Applicant has failed to establish inventive step of the purported invention claimed in the impugned Application.

37. Thus, the prior arts (Annexure 2-5) taken together, amply disclose and teach the alleged invention claimed in the impugned application. The pending claims 1-24 are clearly obvious and do not involve any inventive step in light of Annexure 2-5. Therefore, the impugned application ought to be rejected in its entirety on this ground alone.

The claimed compounds represent an arbitrary selection from those in the Application

38. The amended claims of the impugned application claim a large number of compounds. The complete specification of the impugned application demonstrates the purported CFTR modulator activity of the compounds disclosed therein, in the form of EC30 (μM) and relative efficacy data (Table 3, internal page 1392-1426). The activity is shown symbolically with “+++” indicating $< 3 \mu\text{M}$; “++” indicating activity between $3 \mu\text{M}$ and $10 \mu\text{M}$ and “+” indicating activity greater than $10 \mu\text{M}$.
39. From the aforementioned data, it can be seen that there are several claimed compounds that have significantly inferior activity as compared to several unclaimed compounds. The aforementioned claimed compounds, with significantly inferior activity, are shown below. From the said data, it can be seen that there are several unclaimed compounds with identical activity to those being claimed in the currently amended claims. It can also be seen that there are claimed compounds that have inferior activity than several unclaimed compounds. The relevant data is shown below:

Claimed compounds having significantly inferior activity:

Claimed compounds	EC30 (μM)
445	+
556	+
565	+
660	+
781	+
1073	+
1245	+

1323	+
1382	+
1538	+
1882	+
2110	+
2131	+
2157	+
2636	+

40. Further, several claimed compounds have inferior activity compared to several unclaimed compounds. Some of such aforementioned claimed compounds are shown below:

Claimed compounds	EC30 (μ M)
373	++
373	++
400	++
403	++
431	++
476	++
486	++
487	++
495	++
519	++

41. Further, several claimed compounds have identical activity compared to several unclaimed compounds. Some of such aforementioned claimed compounds are shown below:

Claimed compounds	EC30 (μ M)
114	+++
171	+++
233	+++
353	+++
307	+++
321	+++

337	+++
361	+++
368	+++
371	+++

42. Thus, it is clear that several compounds claimed in impugned application are inferior or simply equivalent in terms of activity compared to a number of unclaimed compounds.

GROUND 2: Claims not patentable under Section 25(1)(f)

The claimed subject matter is not patentable under Section 3(d) of the Act

43. It is submitted that the impugned patent application falls within the purview of section 3(d) of the Patents Act, 1970 which states that *“the mere discovery of a new form of a known substance which does not result in the enhancement of the 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, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

*Explanation -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other **derivatives of known substance** shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.”*

44. It is humbly submitted that the compounds claimed in impugned application are derivatives of compounds already known in prior art that possess CFTR activity as disclosed in Annexure 2-5. The compounds claimed in the application are therefore derivatives of such known substances that are active as CFTR modulators.
45. Opponent submits that the compounds disclosed in WO'373 demonstrate activity as CFTR potentiator in CFTR potentiator assay as shown below:

Table 1.

Example No	EC ₅₀ μ M
1.0	0.0035

46. Further, the amended claims of the impugned application claim a large number of compounds. The complete specification of the impugned application demonstrates the purported CFTR modulator activity of the compounds disclosed therein, in the form of

EC30 (μM) and relative efficacy data (Table 3, internal page 1392-1426). The activity is shown symbolically with “+++” indicating $< 3 \mu\text{M}$; “++” indicating activity between $3 \mu\text{M}$ and $10 \mu\text{M}$ and “+” indicating activity greater than $10 \mu\text{M}$.

47. From the aforementioned data, it can be seen that there are several claimed compounds that have significantly inferior activity as compared to several unclaimed compounds. The aforementioned claimed compounds, with significantly inferior activity, are shown below. From the said data, it can be seen that there are several unclaimed compounds with identical activity to those being claimed in the currently amended claims. It can also be seen that there are claimed compounds that have inferior activity than several unclaimed compounds. The relevant data is shown below:

Claimed compounds having significantly inferior activity:

Claimed compounds	EC30 (μM)
445	+
556	+
565	+
660	+
781	+
1073	+
1245	+
1323	+
1382	+
1538	+
1882	+
2110	+
2131	+
2157	+
2636	+

48. Further, several claimed compounds have inferior activity compared to several unclaimed compounds. Some of such aforementioned claimed compounds are shown below:

Claimed compounds	EC30 (μM)
373	++

373	++
400	++
403	++
431	++
476	++
486	++
487	++
495	++
519	++

49. Further, several claimed compounds have identical activity compared to several unclaimed compounds. Some of such aforementioned claimed compounds are shown below:

Claimed compounds	EC30 (μ M)
114	+++
171	+++
233	+++
353	+++
307	+++
321	+++
337	+++
361	+++
368	+++
371	+++

50. Thus, it is clear that several compounds claimed in impugned application are inferior or simply equivalent in terms of activity compared to a number of unclaimed compounds.
51. The activity demonstrated in the impugned specification is expressed in EC30 (μ M). The activity of compounds is specified as “+++” indicating $< 3 \mu$ M; “++” indicating activity between 3μ M and 10μ M and “+” indicating activity greater than 10μ M. The activity of all compounds is thus inferior to that shown above in WO’373. Thus, no enhanced therapeutic efficacy of compounds of the impugned application has been established with respect to compounds in the prior art.

52. It is submitted that the complete specification fails to demonstrate enhanced therapeutic efficacy of the compounds of the invention in comparison to other pyridine carboxamide derivatives already known to possess CFTR modulation activity. The claimed compounds thus attract the provisions of section 3(d) of the Act and the impugned application ought to be rejected on this ground alone.

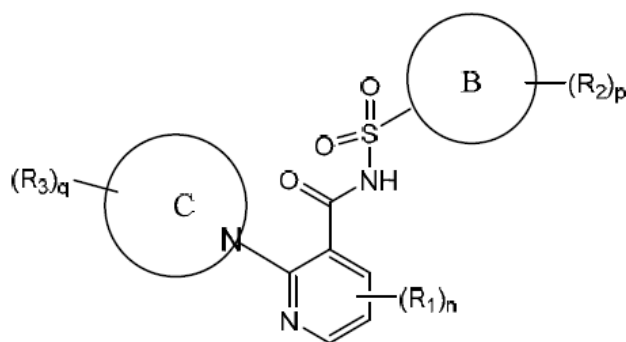
The claimed subject matter is not patentable under Section 3(e) of the Act

53. It is submitted that the impugned patent application falls within the purview of section 3(e) of the Patents Act, 1970 which states that “*a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance*”.
54. Claims 20 claims a pharmaceutical composition comprising the compound or salt as claimed in any one of claims 1 to 19 and a pharmaceutically acceptable carrier. It is submitted that no data is presented showing any synergistic effect resulting from formulating the compounds claimed in impugned application with a pharmaceutically acceptable carrier. Thus, said pharmaceutical composition merely represents an admixture and attracts the provisions of section 3(e) of the Act.
55. Further, claims 21-24 claim pharmaceutical composition as claimed in claim 20, further comprising one or more additional therapeutic agent(s). It is submitted that no data is presented showing any synergistic effect resulting from a combination of any of the compounds claimed in the impugned application with any additional therapeutic agent(s). Such combinations thus represent mere admixtures and attract the provisions of section 3(e) of the Act and should be refused on the said ground.

GROUND 4: INSUFFICIENCY OF DISCLOSURE

56. It is submitted that claim 1 claims a compound of formula Ib-iii as shown below:

1. A compound of formula Ib-iii:



Ib-iii

57. In the reply to the FER dated 3rd December, 2020, the Applicant has contended that support from claim 1 can be found in Paragraph [00227] of the PCT publication WO2016/057572 (Annexure A, Claim Support Table, response to FER). However, this passage does not include the definition of the substituents on R₁-R₄, and therefore does not provide basis for claim 1.

58. Further, the support for dependent claims 2 to 7 and 10 to 15 was shown as follows in the response to the FER:

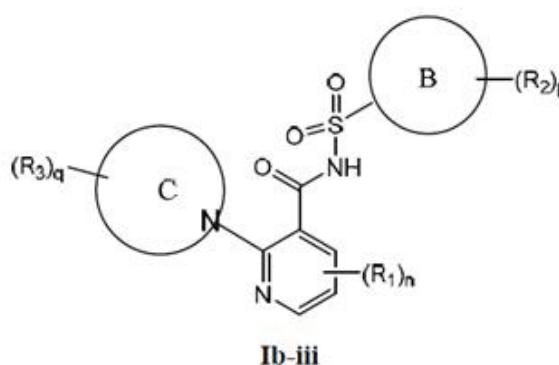
Claim Number	Support for Amendments in WO 2016/057572	Support for amendment from the PCT claims
1	Paragraph [00227]	PCT claims 1 and 56
2	Paragraphs [00229], [00230]	PCT claims 4 and 5
3	Paragraph [00231]	PCT claim 6
4	Paragraph [00232]	PCT claim 7
5	Paragraphs [00233], [00234]	PCT claims 15 and 16
6	Paragraphs [00235], [00236]	PCT claims 17 and 18
7	Paragraphs [00237], [00238]	PCT claims 19 and 20
8	Paragraph [00239]	PCT claims 24-26
9	Paragraph [00240]	PCT claims 27-29
10	Paragraph [00241]	Dependent claims
11	Paragraph [00241]	Dependent claims
12	Paragraph [00241]	Dependent claims
13	Paragraph [00271]	PCT claims 1 and 56
14	Paragraph [00312]	PCT claims 1 and 56
15	Paragraph [00350]	PCT claims 1 and 56

59. However, the aforementioned claims disclose new combinations of features, by virtue of their multiple dependencies, that are not disclosed in the application as-filed, because each relevant paragraph in the description identified above is a separate paragraph that is not linked to the other paragraphs. The options defined at paragraph [00232] are incompatible with the options defined at paragraph [00231]. Paragraph [00232] includes the option that ring C is morpholinyl, which is not covered by the options at paragraph [00231]. It can be seen that the options at paragraph [00232] cannot be read in combination with the options at paragraph [00231], because they are incompatible.

Therefore, the impugned application does not provide basis for the dependent claims 2 to 7 and 8 to 15, as these claims, by virtue of their multiple dependencies claim combinations that have no support in the specification.

60. It is submitted that impugned application claims a large number of compounds. However, the synthesis of only a few of these compounds is disclosed. Moreover, a number of compounds covered by claim 1, are such that they would not be stable, and rapidly degrade to form different byproducts. This is elaborated in detail below

The representative structure of claim 1 is shown below



or a pharmaceutically acceptable salt thereof, wherein:

Ring B is a ... C₃-C₁₀ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

Ring C is a C₃-C₁₄ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently N, O, or S, and wherein one nitrogen on Ring C is the point of attachment to the pyridine ring;

... R₁ is ... C₃-C₁₀ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

... R₂ is ... C₃-C₁₀ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

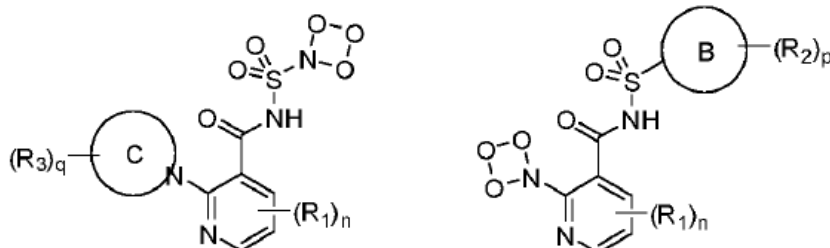
... R₃ is ... C₃-C₁₀ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

... R₄ is ... C₃-C₁₀ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

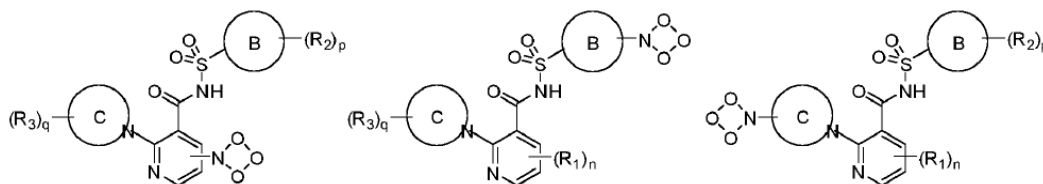
... R is ... C₃-C₁₀ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

...wherein each of the specific groups for the variables R_1 - R_4 can be optionally substituted with one or more group selected from ... (C₁-C₉alkylene)-E wherein up to 4 CH₂ units are independently replaced with O, S, SO₂, SO, CO, NH, N-alkyl, N- alkenyl, or N-alkynyl,

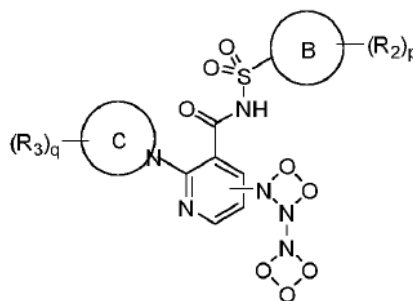
61. Therefore, it can be seen from the above that two definitions are emphasised. The first permeates the entire claim, insofar as it applies to each generically defined substituent. It is that ring B, ring C, R_1 , R_2 , R_3 , R_4 , and R can each be a C₃-C₁₀ (C₃-C₁₄ in the case of ring C) heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR.
62. The second relates to the further substitution of substituents R_1 - R_4 . It is that in addition to the first definition, each of R_1 - R_4 may further be optionally substituted with (C₁-C₉alkylene)-E wherein up to 4 CH₂ units are independently replaced with O, S, SO₂, SO, CO, NH, N-alkyl, N- alkenyl, or N-alkynyl.
63. It is submitted that the chemical space covered by the first definition of compounds—C₃-C₁₀ or C₃-C₁₄ heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR, is not commensurate with the disclosure contained in the specification of the impugned application, as illustrated below:
64. Ring B, ring C, R_1 , R_2 , R_3 , R_4 , and R can, for example, each be a C₃, C₄ or C₅ heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently selected from O, S, N, or NR. Therefore, if using a C₄ heterocyclic ring wherein 4 ring atoms are independently selected from O and N, we apply the first definition to ring B and ring C, the following structures are obtained:



65. Further, if using a C₄ heterocyclic ring wherein 4 ring atoms are independently selected from O and N, we apply the first definition to R₁, R₂ and R₃, the following structures are obtained:

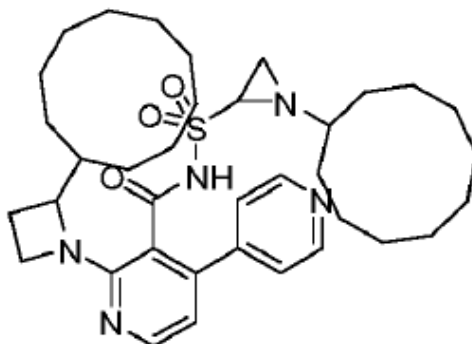


66. Furthermore, if using a C₄ heterocyclic ring wherein 4 ring atoms are independently selected from O and NR we apply the first definition to R₁ and R the following structure is obtained:

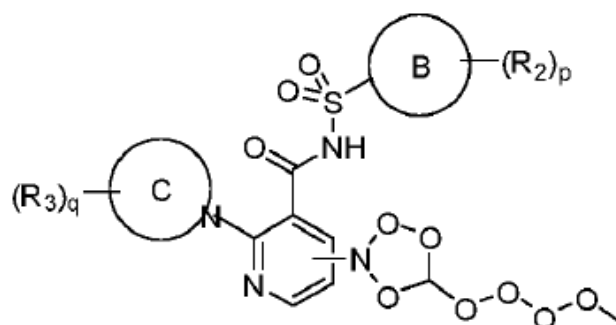


67. It is submitted that it would be readily apparent to a skilled person that these compounds could not be obtained or would be unstable. Indeed, four-membered rings containing three oxygen atoms and a nitrogen atom are inherently unstable, and even if they could be synthesised (of which we have found no evidence) they would presumably rapidly degrade to form gaseous by-products. For these reasons, the skilled person could not obtain compounds containing one such group, let alone two, three, four or five groups, which are all contemplated by the claim. Thus, owing to the presence of the first definition, and that it applies to each generically defined substituent, claim 1 is insufficiently disclosed.
68. Further, structures with three- and five-membered rings would suffer from similar issues, for example, any sized ring (C₃-C₁₄) with three or more ring atoms (independently selected from O, S, N, or NR) wherein the atoms are one after the other e.g. O-O-O, N-S-S, N-N-N etc.
69. Moreover, a further issue to consider is the one of steric hindrance. This is because, one or more (or all) of ring B, ring C, R₁, R₂, R₃, R₄ and R can at least be a C₃-C₁₀ heterocyclic ring. This issue is compounded by the fact that the substitution pattern of R₁

R₂ and R₃ are not defined in the Markush formula. For example, the following compound falls within the scope of the claim 1, but would not be accessible to the skilled person because it could not be synthesised owing to steric hindrance:

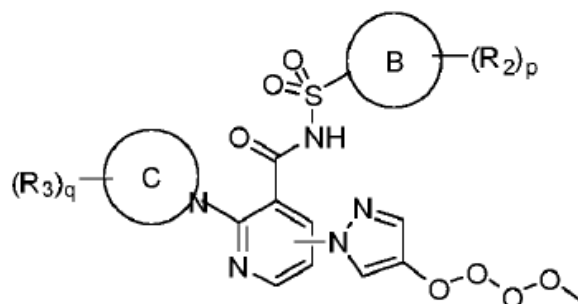


70. In this definition, ring B is a C₃ heterocyclic ring wherein one ring atom is nitrogen, and R₂ is C₁₀ cycloalkyl; ring C is a C₄ heterocyclic ring and R₃ is C₁₀ cycloalkyl; and R₁ is C₆ heteroaryl.
71. It also is worth pointing out that the above example does not go to the extremes of the substituent definitions provided by the claim. For example, it does not account for substitution of R₁, R₂ or R₃ with further large substituents (substituted upon any atom) nor does it consider the largest group definitions for ring C (C₁₁-C₁₄) or substitution of R₁ and R₂ with planar aromatic substituents, which would likely pose a greater steric barrier than cycloalkyl substituents (particularly in combination with further substitution of R₁, R₂ or R₃ with aromatic substituents).
72. Compounds covered by the first and second definitions — C₃-C₁₀ or C₃-C₁₄ heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR and (C₁-C₉alkylene)-E wherein up to 4 CH₂ units are independently replaced with O, S, SO₂, SO, CO, NH, N-alkyl, N- alkenyl, or N-alkynyl.
73. If using a C₅ heterocyclic ring wherein 4 ring atoms are independently selected from O and NR we apply the first definition to R₁ (the same would apply equally to R₂ and R₃), and using (C₁- C₉alkylene)-E wherein up to 4 CH₂ units are independently replaced with O, S, or NH we apply the second definition to R₁ (optional substitution of R₁) the following structure is obtained:



74. For the same reasons discussed hereinabove, the skilled person would not be able to obtain such a compound. Thus, the second definition relating to R₁-R₄ provides even more compounds that fall within the scope of the claim that the skilled person could not obtain.

75. Equally, if we define R₁ as follows (C₅ heteroaryl) and using (C₁-C₉alkylene)-E wherein up to 4 CH₂ units are independently replaced with O, S, or NH we apply the second definition to R₁ (optional substitution of R₁) the following structure is obtained:



76. It is submitted that this compound also could not be obtained by the skilled person owing to the four consecutive oxygen atoms present in the sidechain.

77. In conclusion, it can be seen that the permeation of a definition to each generic substituent (namely ring B, ring C, R₁, R₂, R₃, R₄, and R can each be a C₃-C₁₀ (C₃-C₁₄ in the case of ring C) heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR) renders the skilled person unable to obtain a vast number of compounds falling within the scope of the claims.

78. Thus, the specification does not clear does not sufficiently and clearly describe the invention or the method by which it is to be performed and is liable to be rejected on said ground.

**GROUND 5: INFORMATION RELATING TO CORRESPONDING APPLICATIONS
UNDER SECTION 8 [SECTION 25(1)(H)]**

79. The Applicant has failed to disclose to the Patent Office the information required under Section 8. The Applicant is required to provide all the information regarding the prosecution of the equivalent applications till the grant of the Indian application to the Patent Office in writing from time to time and also within the prescribed time.
80. It is observed that Applicant has not provided information about updated the status of corresponding application in the Form-3 which information has not been provided to the learned Controller.
81. Therefore, the applicant has failed to comply with the requirements of the section 8 of the act and the opponent demands rejection on this ground also.
82. It is submitted that the Applicant has failed to disclose the details of corresponding foreign applications and impugned patent application to be refused.
83. The opponents crave leave to file further submissions and evidence with respect to this ground.

CONCLUSION

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

HEARING REQUESTED

85. The Opponent hereby requests a hearing under section 25(1) of the Patents Act, 1970 (hereinafter referred to as “the Patents Act”) and Rule 55 of the Patents Rules (hereinafter referred to as “the Rules”).

P R A Y E R

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

- i. that the Controller take the present Opposition on record; that the Indian application 201737015848, be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;
- ii. that the Opponent may be allowed to file further documents and evidence if necessary to support their averments;
- iii. that the Opponent may be allowed to file rejoinder and affidavit 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 04th day of December, 2023



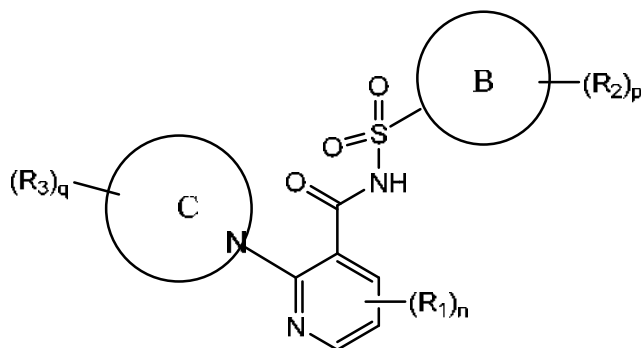
PRAGYA SINGH THAKUR (IN /PA – 3329)
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO
THE CONTROLLER OF PATENTS
PATENT OFFICE, KOLKATA

Annexure - 1

Clean copy03.12.2020We Claim:

1. A compound of formula Ib-iii:

**Ib-iii**

or a pharmaceutically acceptable salt thereof, wherein:

Ring B is a C6-C10 aryl ring or C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

Ring C is a C3-C14 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently N, O, or S, and wherein one nitrogen on Ring C is the point of attachment to the pyridine ring;

and wherein, independently for each occurrence:

R₁ is halo; CN; F₅S; SiR₃; OH; NRR; C1-C6 alkyl or fluoroalkyl; C1-C6 alkoxy or fluoroalkoxy; C2-C6 alkenyl; C2-C6 alkynyl; (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR; C6-C10 aryl; C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; or C3-C10 cycloalkyl;

R₂ is halo; OH; NRR; azide; CN; CO₂R; C1-C6 alkyl or fluoroalkyl; C1-C6 alkoxy or fluoroalkoxy; C2-C6 alkenyl; C2-C6 alkynyl; C6-C10 aryl; C3-C13 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;

or two R₂ groups taken together may form a =CH₂ or =O group;

R₃ is halo; CN; CO₂R; C1-C6 alkyl or fluoroalkyl; C2-C6 alkenyl; C2-C6 alkynyl; C1-C6 alkoxy or fluoroalkoxy; or C6-C10 aryl; C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;

or two R₃ groups taken together may form a =CH₂ or =O group;

R₄ is H; azide; CF₃; CHF₂; OR; CCH; CO₂R; OH; C6-C10 aryl, C3-C10 heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; NRR, NRCOR, CONRR, CN, halo, or SO₂R;

R is independently H; OH; CO₂H; CO₂C1-C6 alkyl; C1-C6 alkyl; C2-C6 alkenyl; C2-C6 alkynyl; C6-C10 aryl; C3-C10 heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; or C3-C10 cycloalkyl;

n is 0, 1, 2 or 3;

p is 0, 1, 2, or 3; and

q is 0, 1, 2, 3, 4, or 5.

wherein each of the specific groups for the variables R₁-R₄ can be optionally substituted with one or more group selected from halo, phospho, OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, fluoroalkyl, alkyl, alkenyl, alkynyl, nitro, CN, hydroxyl, and (C1-C9alkylene)-E wherein up to 4 CH₂ units are independently replaced with O, S, SO₂, SO, CO, NH, *N*-alkyl, *N*-alkenyl, or *N*-alkynyl, and E is H, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, CN, or CF₃, further wherein each of the aryl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with one or more group selected from halo, alkyl, amino, CN, alkenyl, alkynyl, and alkoxy; and

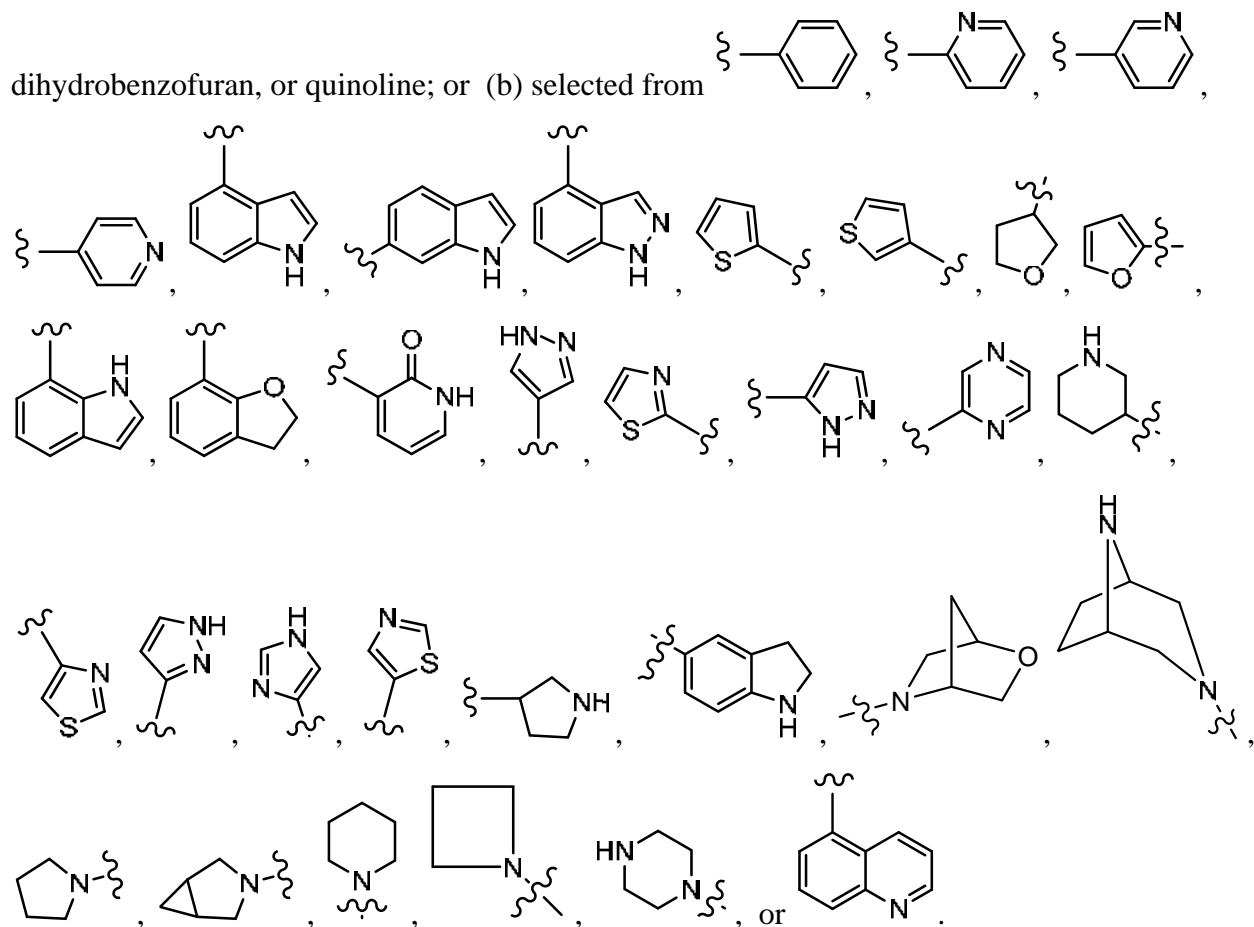
when two alkoxy groups are bound to the same atom or adjacent atoms, the two alkoxy groups can form a ring together with the atom(s) to which they are bound; and

wherein the term “amino” refers to NH₂ which is optionally substituted with one or two groups independently selected from alkyl, cycloalkyl, and heterocycloalkyl.

2. The compound or salt as claimed in claim 1, wherein ring B is:

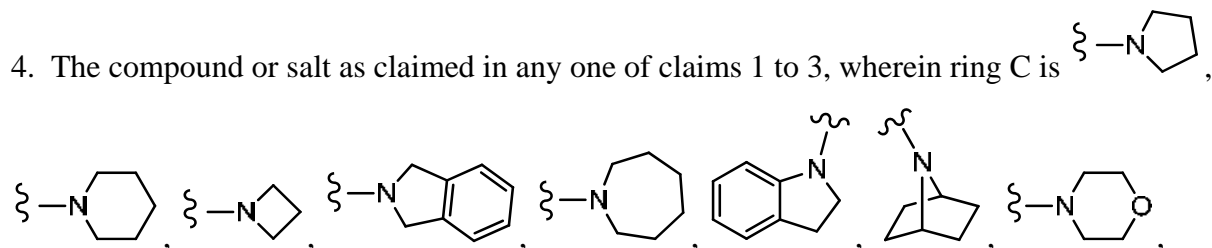
(a) phenyl, pyridyl, pyridine-2(1*H*)-one, pyrazole, indole, aza-indole, thiophene,

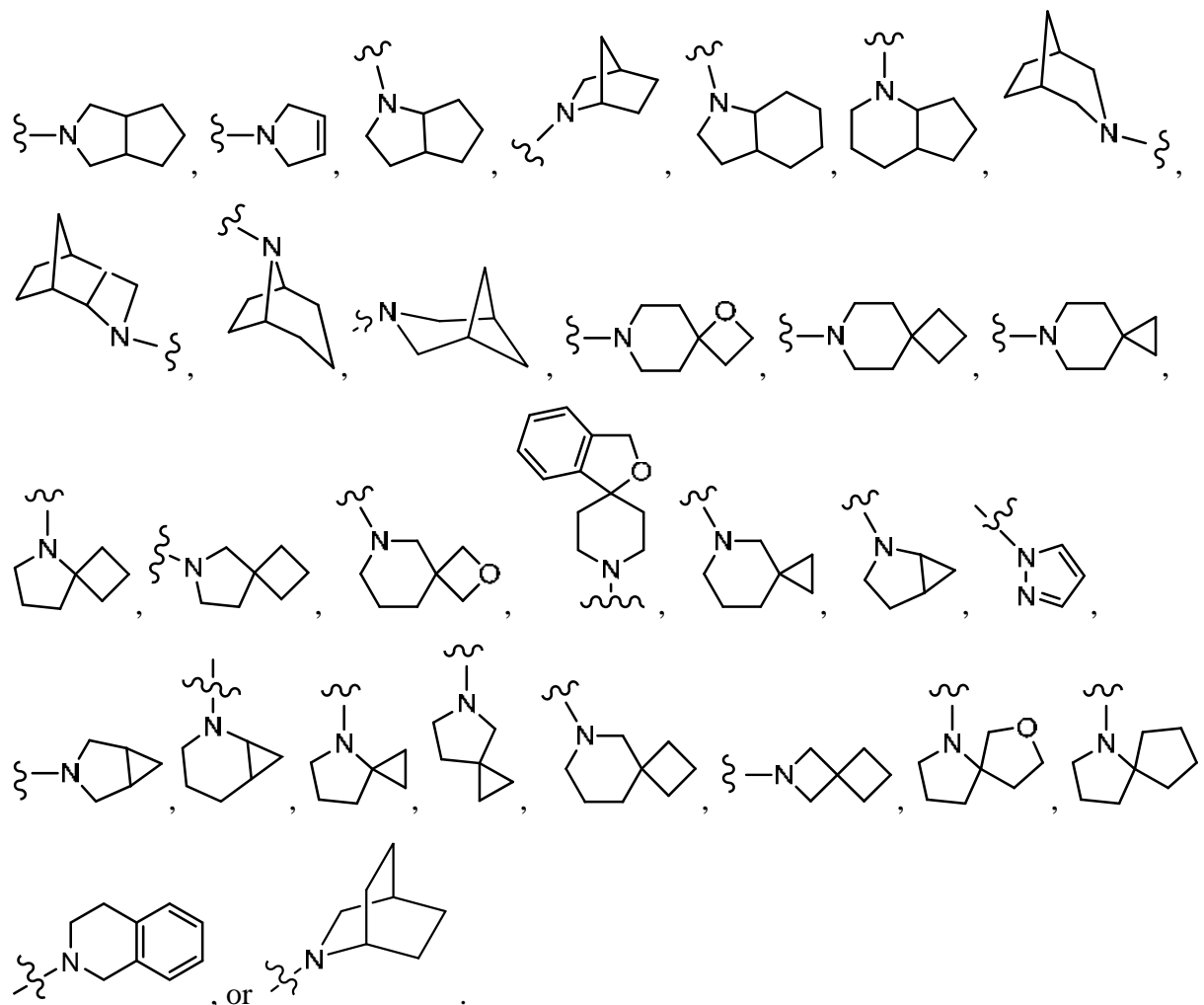
dihydrobenzofuran, or quinoline; or (b) selected from



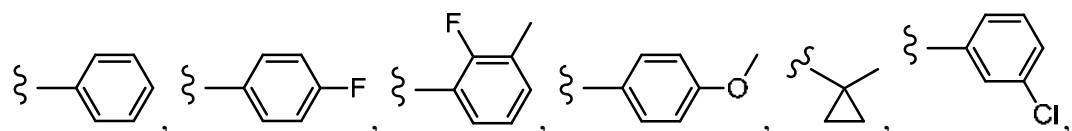
3. The compound or salt as claimed in claim 1 or claim 2, wherein ring C is selected from indole, piperidine, azepane, azetadine, indoline, isoindoline, or pyrrolidine.

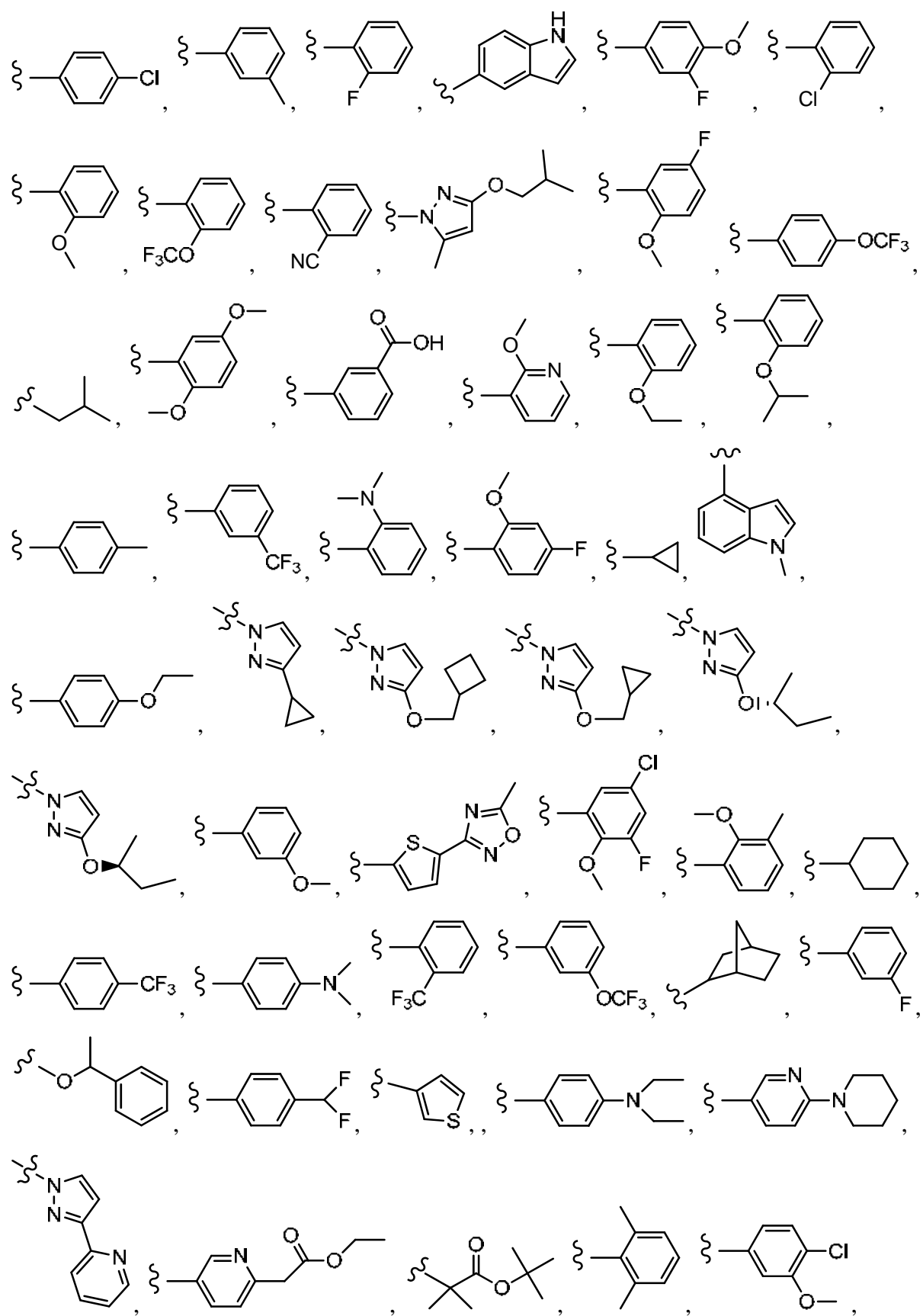
4. The compound or salt as claimed in any one of claims 1 to 3, wherein ring C is

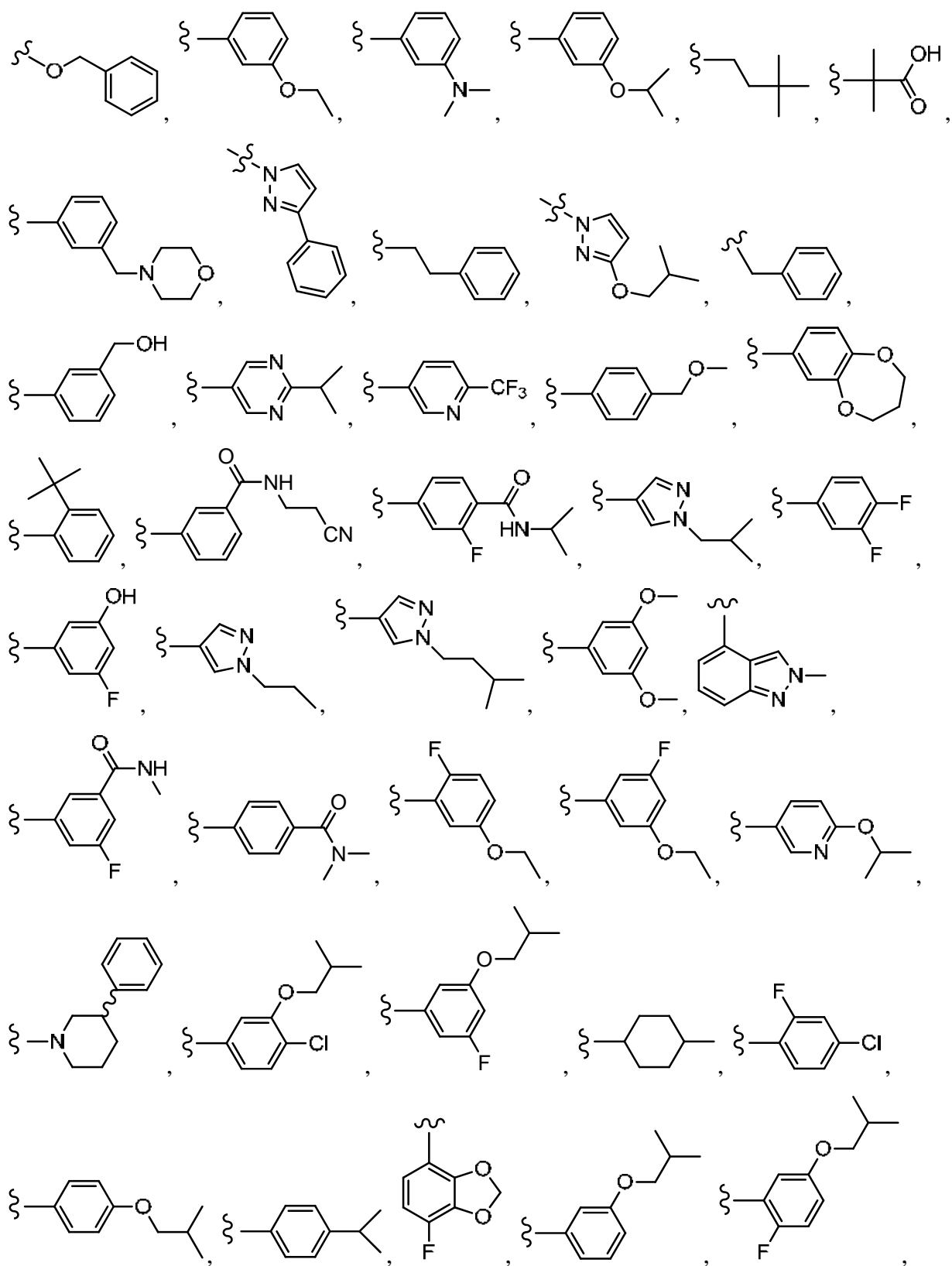




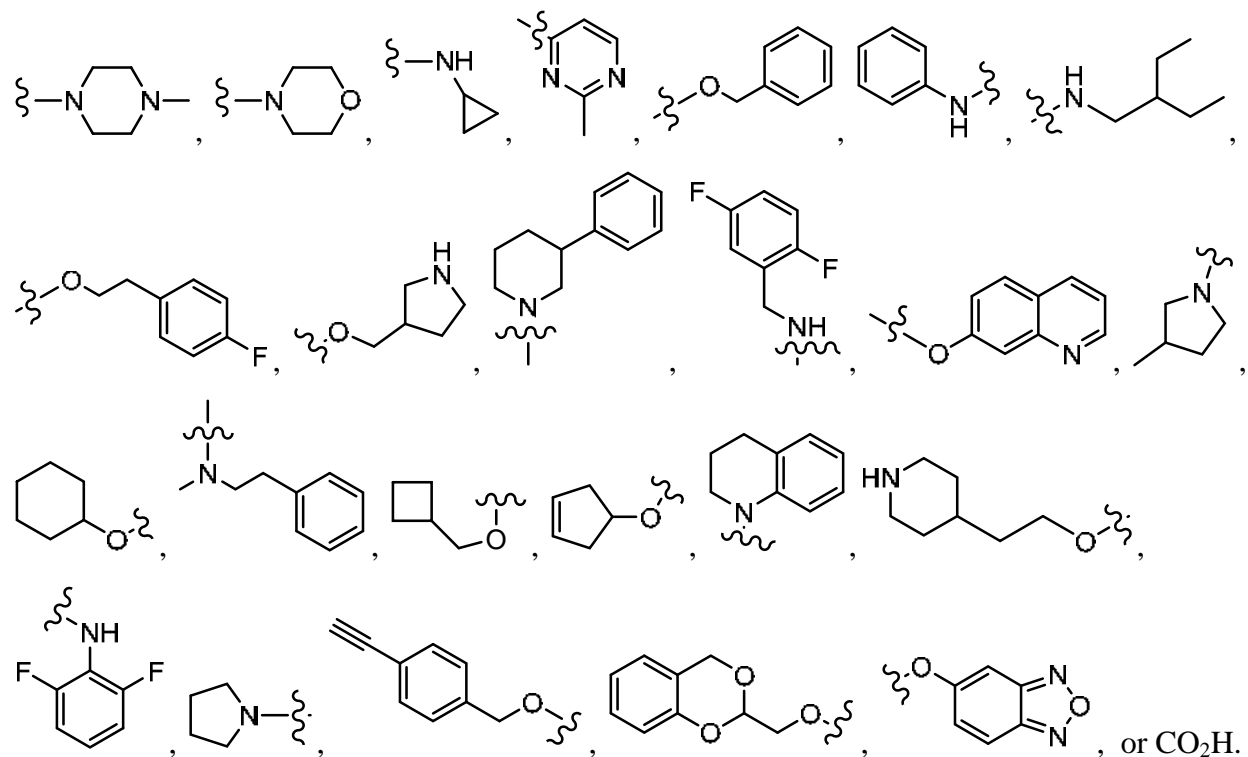
5. The compound or salt as claimed in any one of claims 1 to 4, wherein R_1 is: (a) halo, CN, C1-C6 alkyl, C1-C6 alkoxy, C3-C8 cycloalkyl, or a phenyl, pyridyl, pyrimidine, indole, aza-indole, pyrazole, or thiophene ring, or a (C1-C9 alkylene)- R_4 wherein up to four CH_2 units are independently replaced with O, CO, S, SO, SO_2 or NR, wherein all rings may be substituted with halo, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 fluoroalkyl, C1-C6 fluoroalkoxy, OH, CH_2OH , CH_2OCH_3 , CN, CO_2H , amino, amido, C3-C10 heteroaryl, or C3-C10 heterocycloalkyl; or (b) R_1 is selected from CH_3 , Cl, F, CN, OCH_3 , CF_3 , CH_2CH_3 , tBu, $CH(CH_3)_2$, $OCH_2CH_2OCH_2CH_3$,



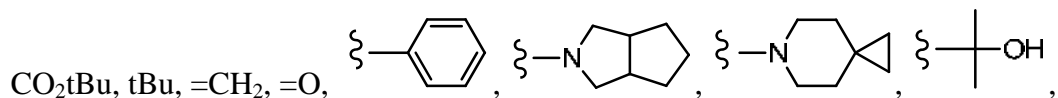


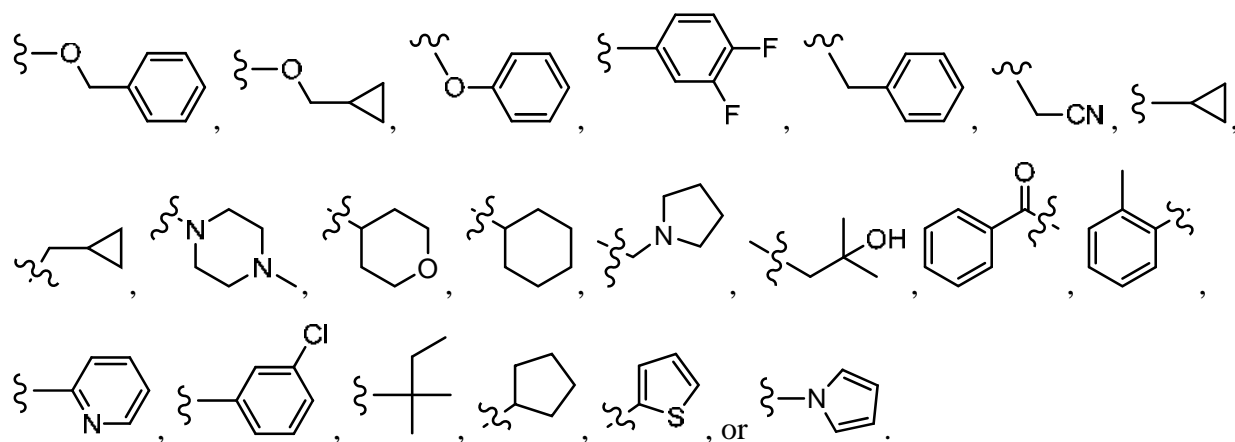


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7. The compound or salt as claimed in any one of claims 1 to 6, wherein R₃ is: (a) selected from halo, CN, C1-C6 alkyl or fluoroalkyl, C1-C6 alkoxy, or C3-C10 heteroaryl wherein up to 4 ring atoms may be replaced by O, S, N, or NR; or (b) selected from Cl, I, deuterium, F, CN, CH₃, OH, OCH₃, CF₃, CH₂CH₃, CH₂CF₃, CH₂CH₂CH₃, OCH₂CH(CH₃)₂, OCH(CH₃)₂, CO₂H, CO₂NH₂, OCH₂CH₃, CH₂OCH₃, CH(CH₃)₂, CCH, CH₂CONH₂, CO₂CH₃, -CH₂N(CH₃)₂,





8. The compound or salt as claimed in any one of claims 1 to 7, wherein n is:

- (a) 0; or
- (b) 1; or
- (c) 2.

9. The compound or salt as claimed in any one of claims 1 to 8, wherein p is:

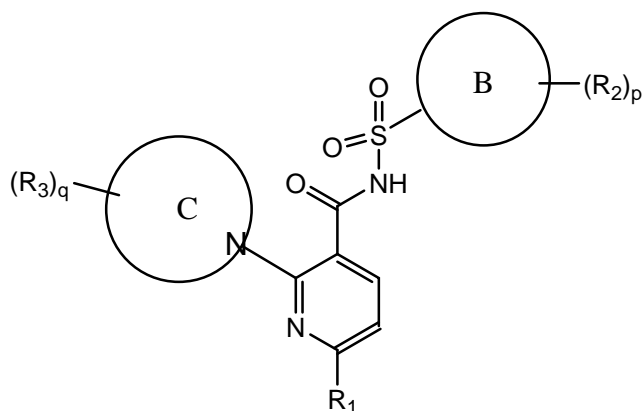
- (a) 0; or
- (b) 1; or
- (c) 2.

10. The compound or salt as claimed in claim 1, wherein R₁ is phenyl, pyridine, or pyrazole, and n is 1.

11. The compound or salt as claimed in claim 1, wherein R₁ is phenyl, pyridine, or pyrazole, n is 1, R₂ is amino or alkyl, and p is 0 or 1.

12. The compound or salt as claimed in claim 1, wherein R₁ is phenyl, pyridine, or pyrazole, n is 1, R₃ is alkyl, and q is 1, 2, 3, or 4.

13. The compound as claimed in claim 1, wherein the compound is a compound of formula Ib-iv:

**Ib-iv**

or a pharmaceutically acceptable salt thereof, wherein, independently for each occurrence:

Ring B is a C6-C10 aryl ring or C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

Ring C is a C3-C14 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently N, O, or S, and wherein one nitrogen on Ring C is the point of attachment to the pyridine ring;

R₁ is C6-C10 aryl or C3-C10 heteroaryl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

R₂ is halo; OH; NRR; azide; CN; CO₂R; C1-C6 alkyl or fluoroalkyl; C1-C6 alkoxy or fluoroalkoxy; C2-C6 alkenyl; C2-C6 alkynyl; C6-C10 aryl; C3-C13 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;

or two R₂ groups taken together may form a =CH₂ or =O group;

R₃ is halo; CN; CO₂R; C1-C6 alkyl or fluoroalkyl; C2-C6 alkenyl; C2-C6 alkynyl; C1-C6 alkoxy or fluoroalkoxy; or C6-C10 aryl; C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;

or two R₃ groups taken together may form a =CH₂ or =O group;

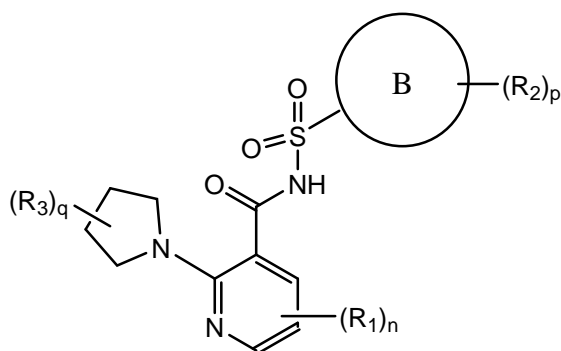
R₄ is H; azide; CF₃; CHF₂; OR; CCH; CO₂R; OH; C₆-C₁₀ aryl, C₃-C₁₀ heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C₃-C₁₀ cycloalkyl; NRR, NRCOR, CONRR, CN, halo, or SO₂R;

R is independently H; OH; CO₂H; CO₂C₁-C₆ alkyl; C₁-C₆ alkyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₆-C₁₀ aryl; C₃-C₁₀ heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; or C₃-C₁₀ cycloalkyl;

p is 0, 1, 2, or 3; and

q is 0, 1, 2, 3, 4, or 5.

14. The compound as claimed in claim 1, wherein the compound is a compound of formula Ib-v:



Ib-v

or a pharmaceutically acceptable salt thereof, wherein, independently for each occurrence:

Ring B is a C₆-C₁₀ aryl ring or C₃-C₁₀ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

R₁ is halo; CN; F₅S; SiR₃; OH; NRR; C₁-C₆ alkyl or fluoroalkyl; C₁-C₆ alkoxy or fluoroalkoxy; C₂-C₆ alkenyl; C₂-C₆ alkynyl; (C₁-C₉ alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR; C₆-C₁₀ aryl; C₃-C₁₀ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; or C₃-C₁₀ cycloalkyl;

R₂ is halo; OH; NRR; azide; CN; CO₂R; C₁-C₆ alkyl or fluoroalkyl; C₁-C₆ alkoxy or fluoroalkoxy; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₆-C₁₀ aryl; C₃-C₁₃ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C₃-C₁₀ cycloalkyl; or a (C₁-C₉ alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;

or two R_2 groups taken together may form a $=CH_2$ or $=O$ group;

R_3 is halo; CN; CO_2R ; C1-C6 alkyl or fluoroalkyl; C1-C6 alkenyl; C1-C6 alkynyl; C1-C6 alkoxy or fluoroalkoxy; or C6-C10 aryl; C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)- R_4 wherein up to four CH_2 units are independently replaced with O, CO, S, SO, SO_2 or NR;

or two R_3 groups taken together may form a $=CH_2$ or $=O$ group;

R_4 is H; azide; CF_3 ; CHF_2 ; OR; CCH; CO_2R ; OH; C6-C10 aryl, C3-C10 heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; NRR, NRCOR, CONRR, CN, halo, or SO_2R ;

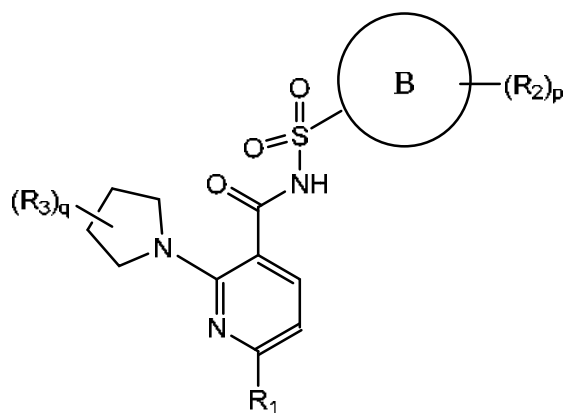
R is independently H; OH; CO_2H ; CO_2C1-C6 alkyl; C1-C6 alkyl; C2-C6 alkenyl; C2-C6 alkynyl; C6-C10 aryl; C3-C10 heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; or C3-C10 cycloalkyl;

n is 0, 1, 2 or 3;

p is 0, 1, 2, or 3; and

q is 0, 1, 2, 3, 4, or 5.

15. The compound as claimed in claim 1, wherein the compound is a compound of formula Ib-vi:



Ib-vi

or a pharmaceutically acceptable salt thereof, wherein, independently for each occurrence:

Ring B is a C6-C10 aryl ring or C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

R₁ is C6-C10 aryl or C3-C10 heteroaryl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

R₂ is halo; OH; NRR; azide; CN; CO₂R; C1-C6 alkyl or fluoroalkyl; C1-C6 alkoxy or fluoroalkoxy; C2-C6 alkenyl; C2-C6 alkynyl; C6-C10 aryl; C3-C13 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;
or two R₂ groups taken together may form a =CH₂ or =O group;

R₃ is halo; CN; CO₂R; C1-C6 alkyl or fluoroalkyl; C2-C6 alkenyl; C2-C6 alkynyl; C1-C6 alkoxy or fluoroalkoxy; or C6-C10 aryl; C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;
or two R₃ groups taken together may form a =CH₂ or =O group;

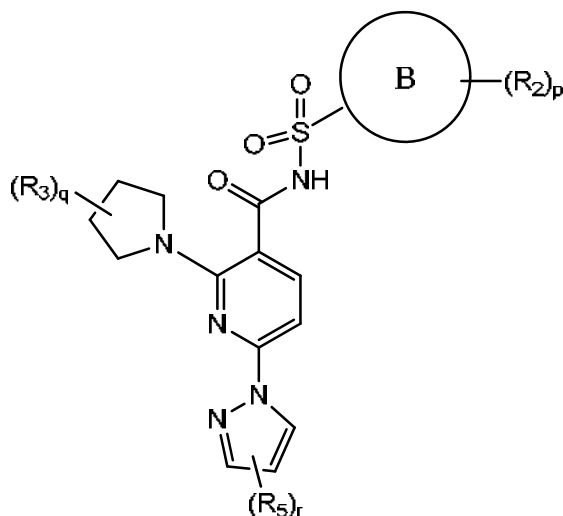
R₄ is H; azide; CF₃; CHF₂; OR; CCH; CO₂R; OH; C6-C10 aryl, C3-C10 heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; NRR, NRCOR, CONRR, CN, halo, or SO₂R;

R is independently H; OH; CO₂H; CO₂C1-C6 alkyl; C1-C6 alkyl; C2-C6 alkenyl; C2-C6 alkynyl; C6-C10 aryl; C3-C10 heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; or C3-C10 cycloalkyl;

p is 0, 1, 2, or 3; and

q is 0, 1, 2, 3, 4, or 5.

16. The compound as claimed in claim 1, wherein the compound is a compound of formula Ib-ix:

**Ib-ix**

or a pharmaceutically acceptable salt thereof, wherein, independently for each occurrence:

Ring B is a C6-C10 aryl ring or C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR;

R₂ is halo; OH; NRR; azide; CN; CO₂R; C1-C6 alkyl or fluoroalkyl; C1-C6 alkoxy or fluoroalkoxy; C2-C6 alkenyl; C2-C6 alkynyl; C6-C10 aryl; C3-C13 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;

or two R₂ groups taken together may form a =CH₂ or =O group;

R₃ is halo; CN; CO₂R; C1-C6 alkyl or fluoroalkyl; C2-C6 alkenyl; C2-C6 alkynyl; C1-C6 alkoxy or fluoroalkoxy; or C6-C10 aryl; C3-C10 heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; or a (C1-C9 alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;

or two R₃ groups taken together may form a =CH₂ or =O group;

R₄ is H; azide; CF₃; CHF₂; OR; CCH; CO₂R; OH; C6-C10 aryl, C3-C10 heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C3-C10 cycloalkyl; NRR, NRCOR, CONRR, CN, halo, or SO₂R;

R is independently H; OH; CO₂H; CO₂C₁-C₆ alkyl; C₁-C₆ alkyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₆-C₁₀ aryl; C₃-C₁₀ heteroaryl or heterocycloalkyl wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; or C₃-C₁₀ cycloalkyl;

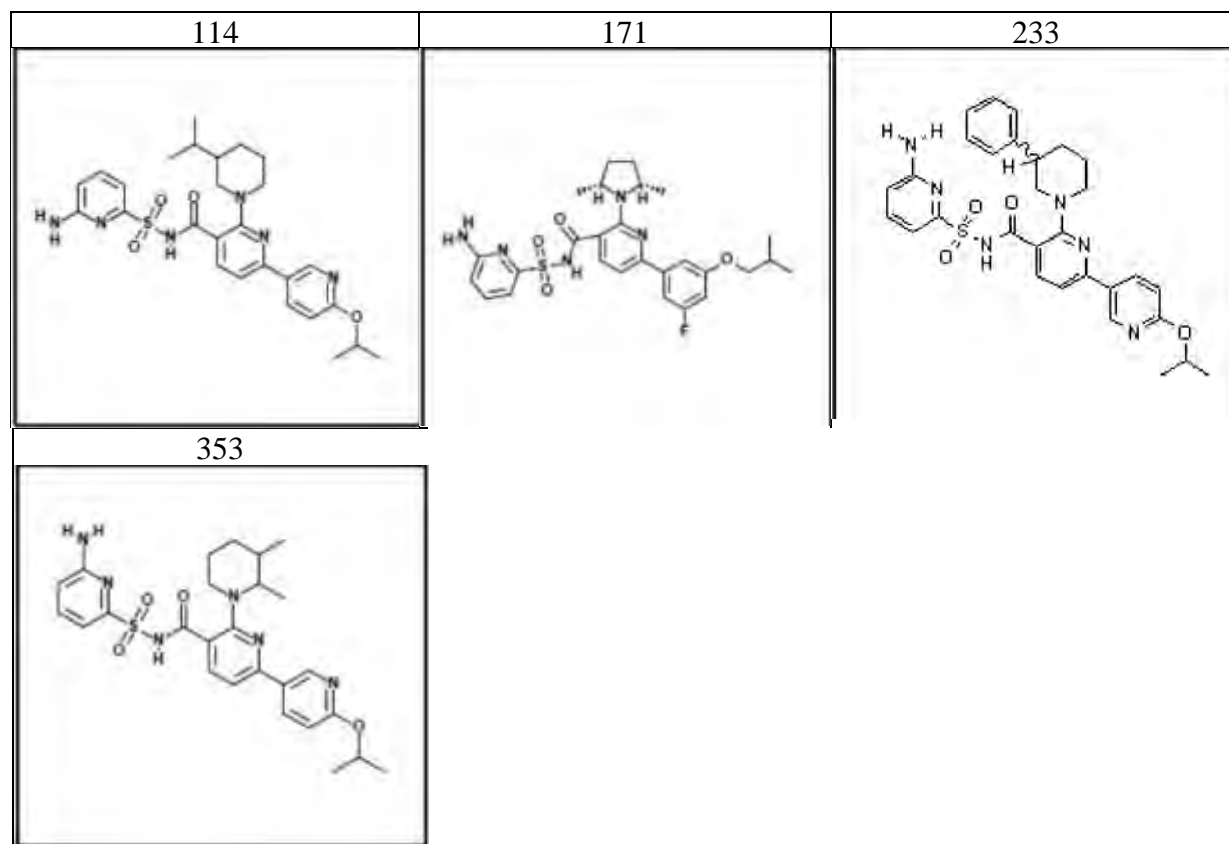
R₅ is halo; CN; CO₂R; C₁-C₆ alkyl or fluoroalkyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₁-C₆ alkoxy or fluoroalkoxy; or C₆-C₁₀ aryl; C₃-C₁₀ heteroaryl or heterocyclic ring wherein anywhere from 1 to 4 ring atoms are independently O, S, N, or NR; C₃-C₁₀ cycloalkyl; or a (C₁-C₉ alkylene)-R₄ wherein up to four CH₂ units are independently replaced with O, CO, S, SO, SO₂ or NR;

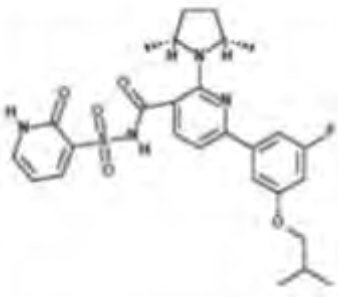
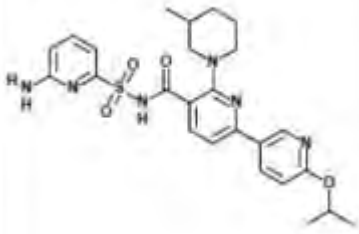
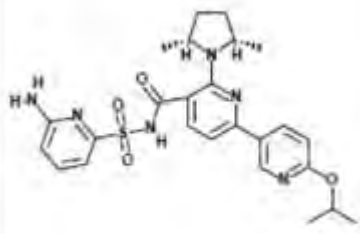
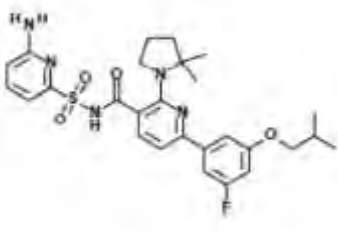
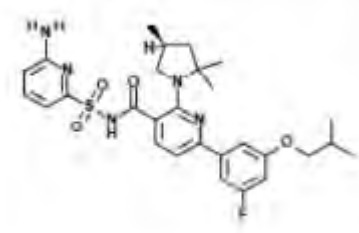
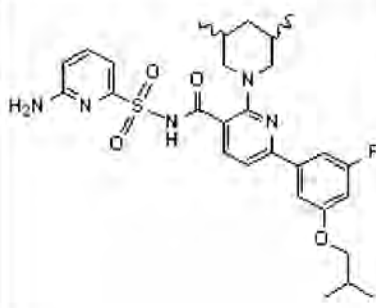
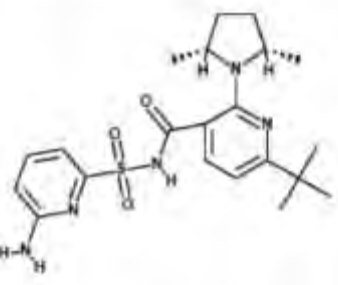
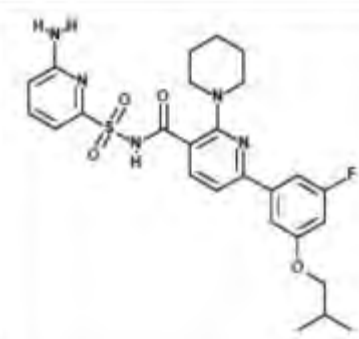
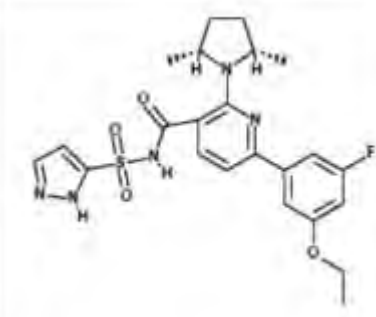
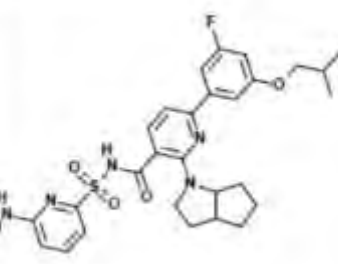
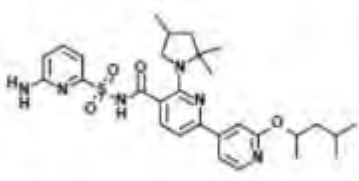
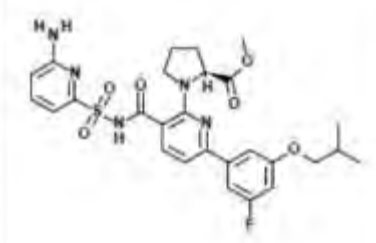
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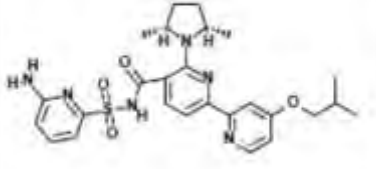
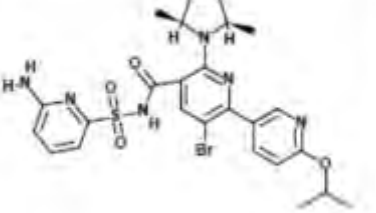
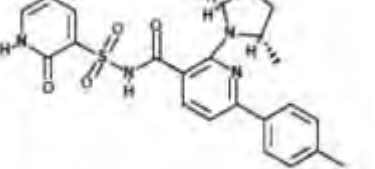
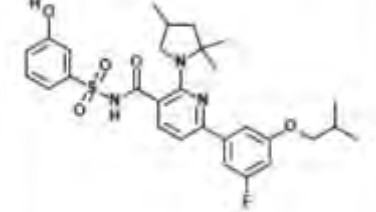
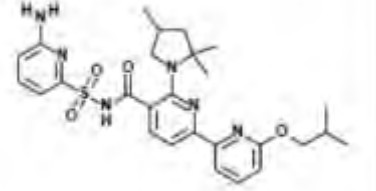
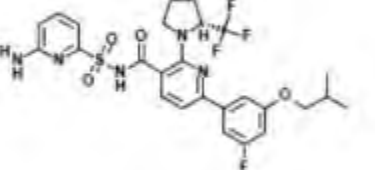
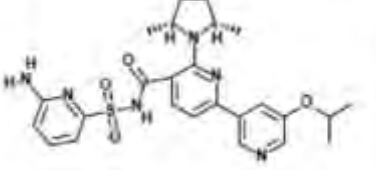
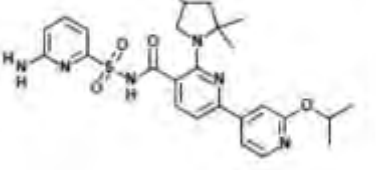
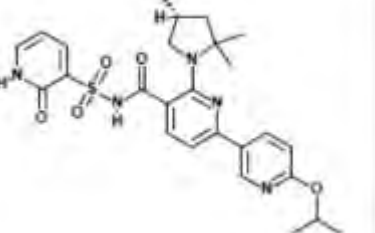
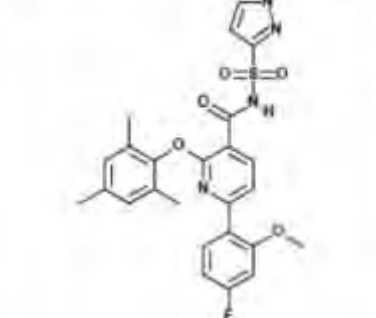
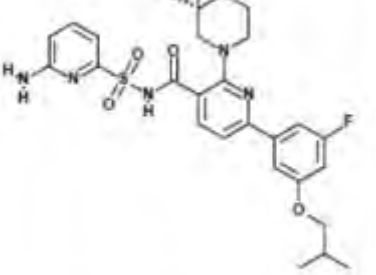
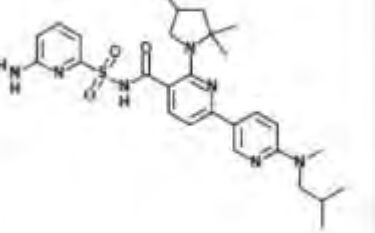
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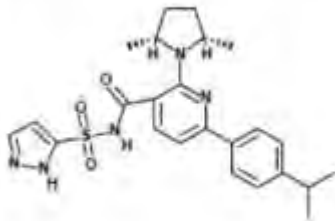
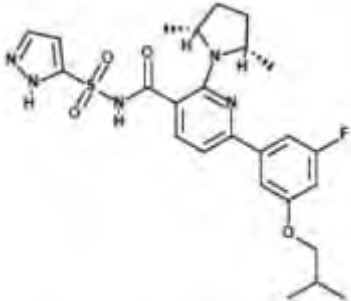
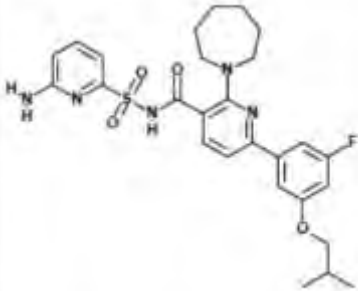
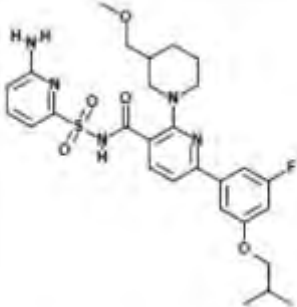
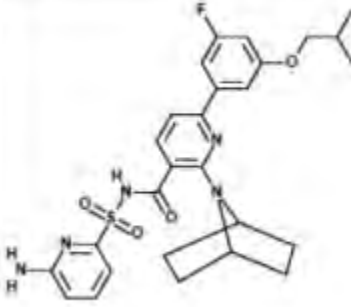
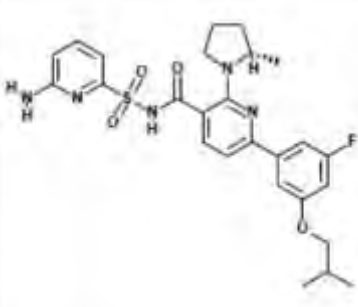
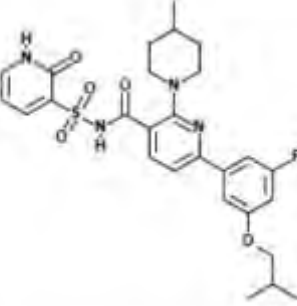
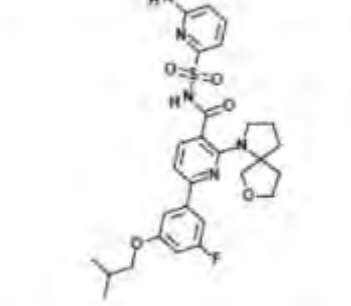
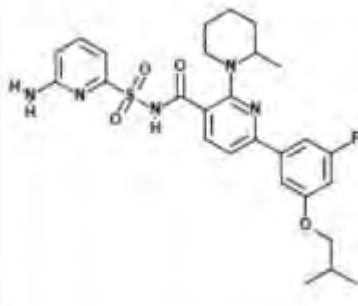
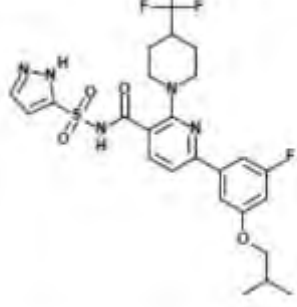
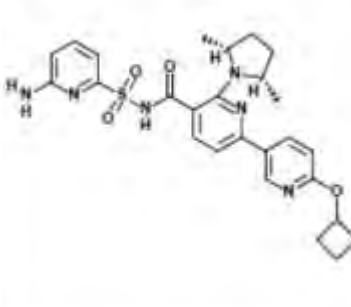
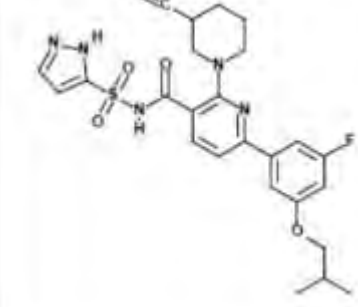
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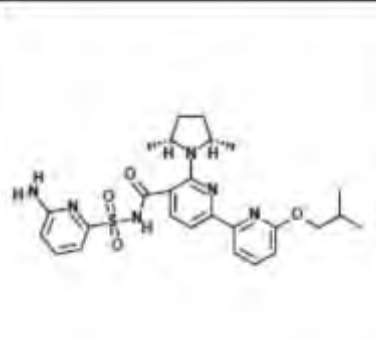
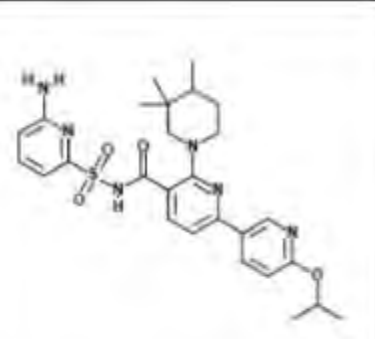
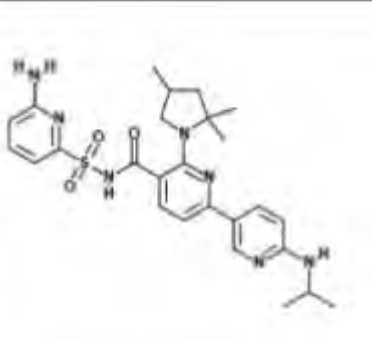
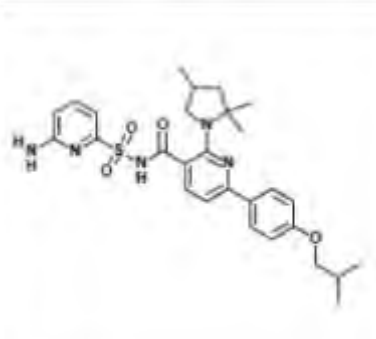
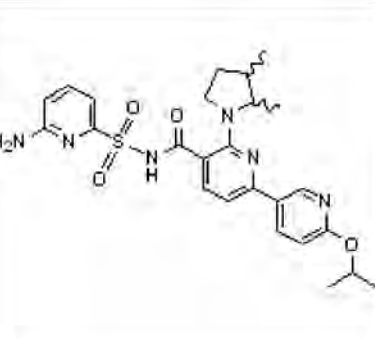
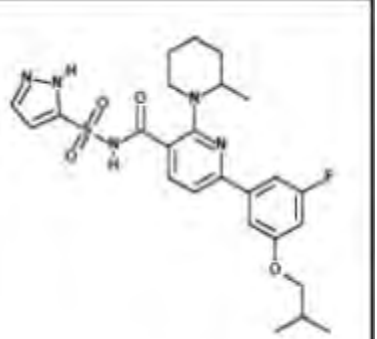
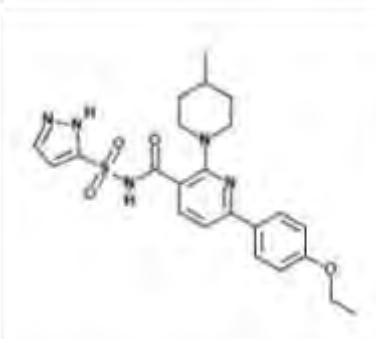
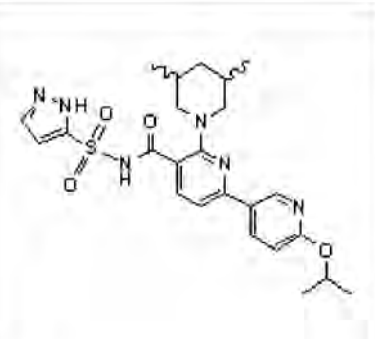
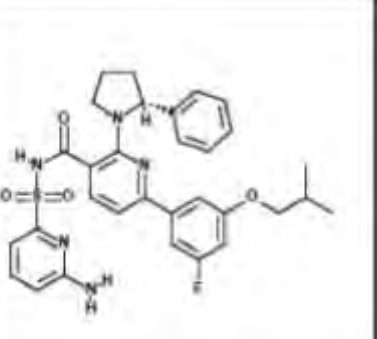
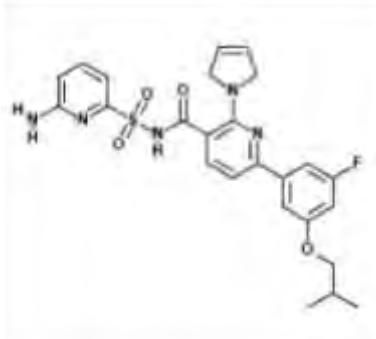
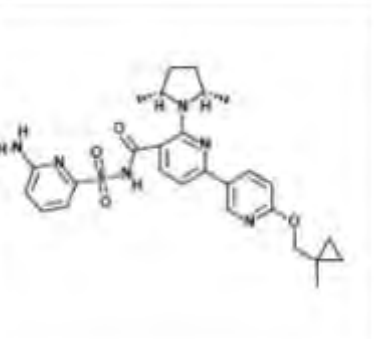
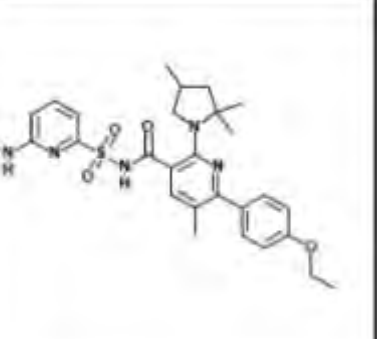
17. The compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:



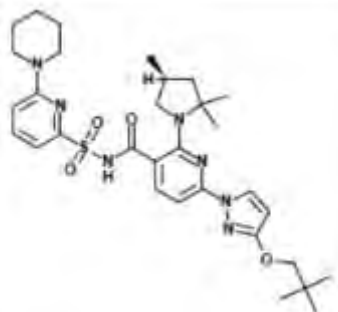
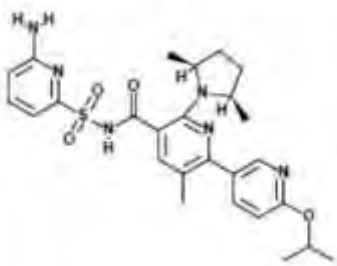
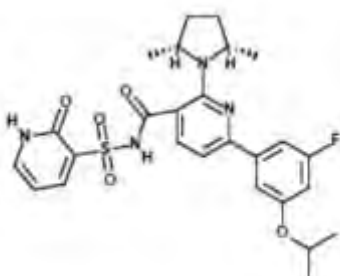
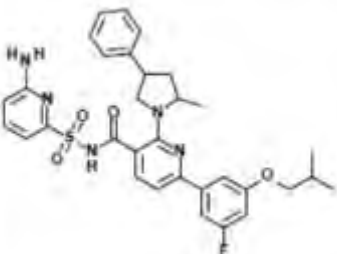
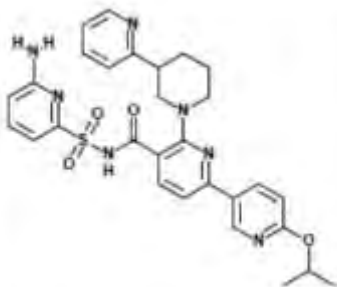
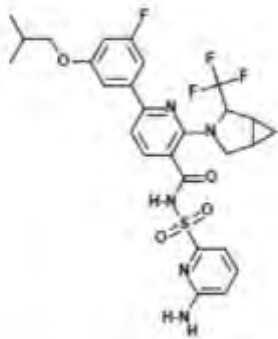
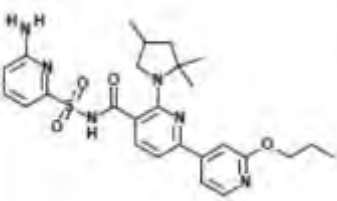
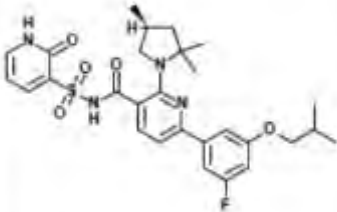
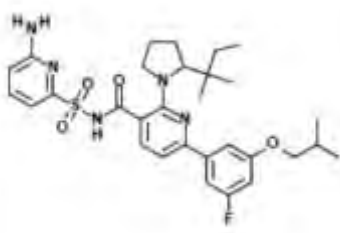
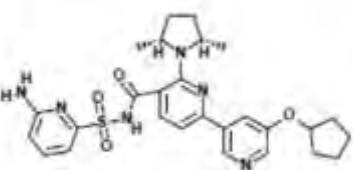
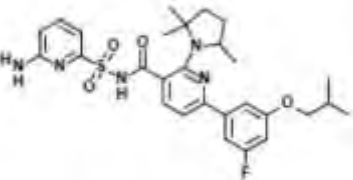
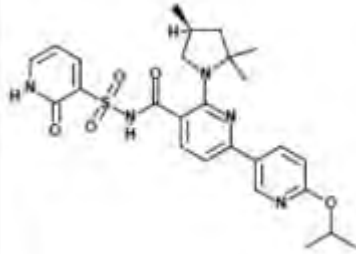
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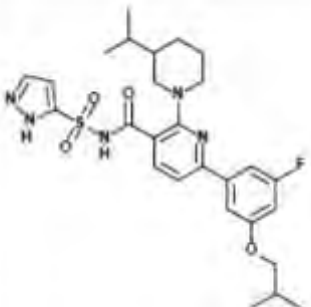
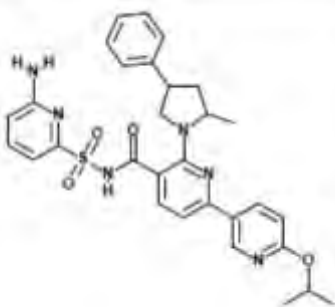
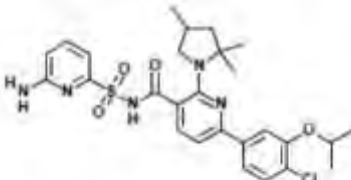
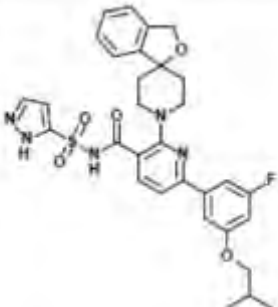
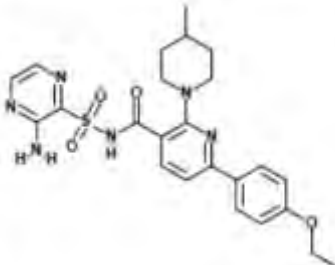
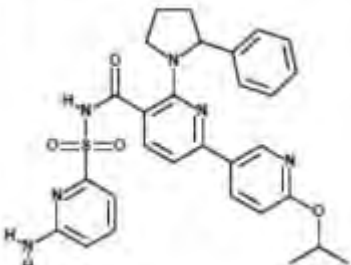
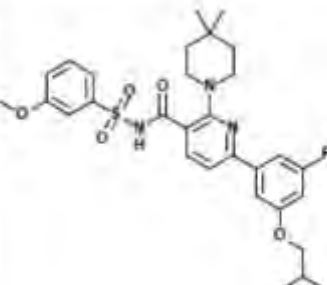
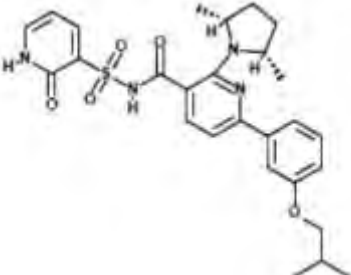
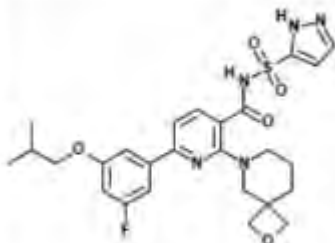
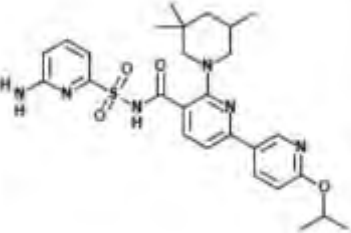
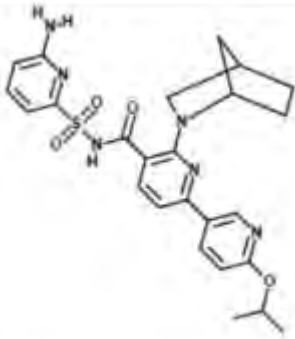
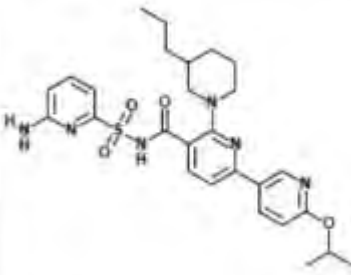
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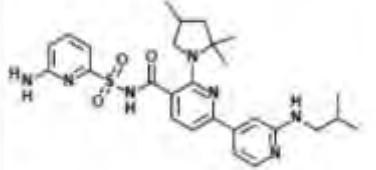
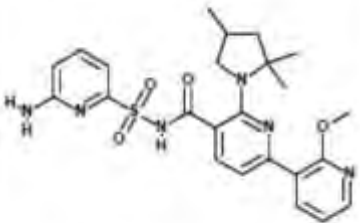
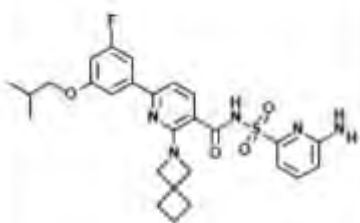
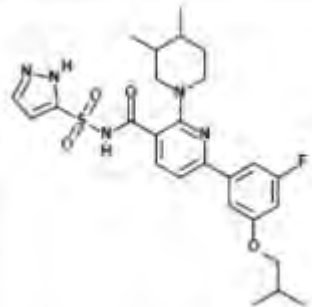
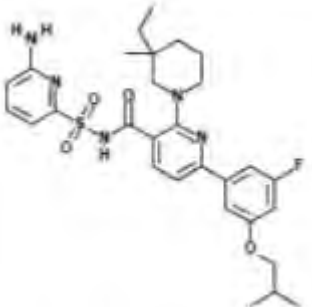
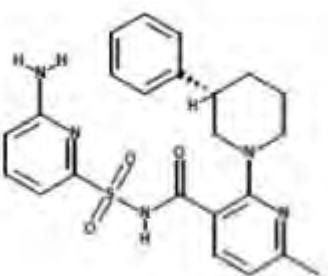
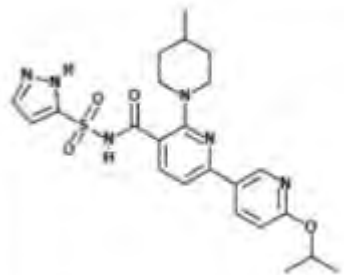
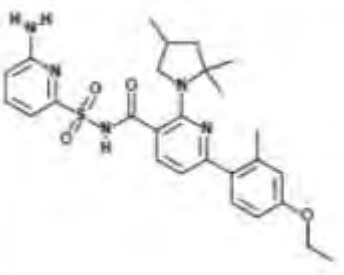
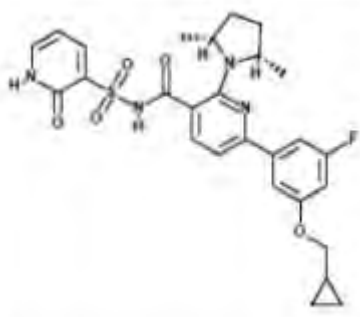
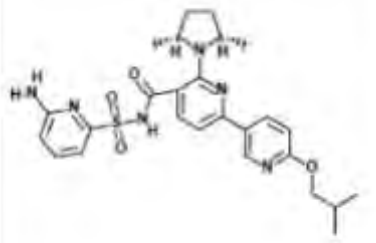
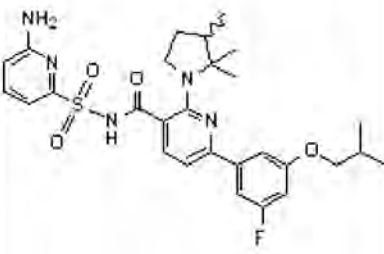
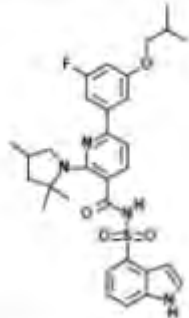
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453	454	455
		

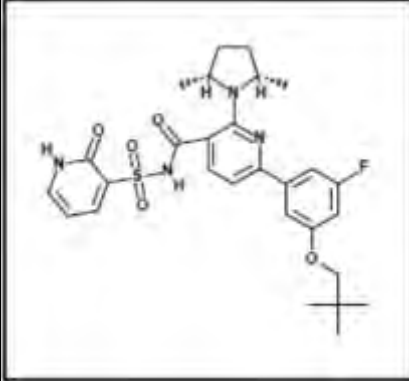
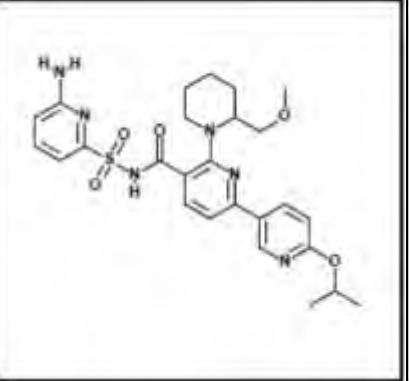
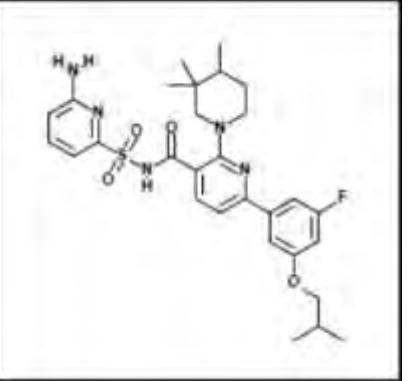
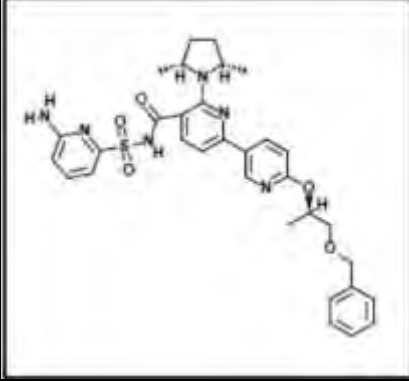
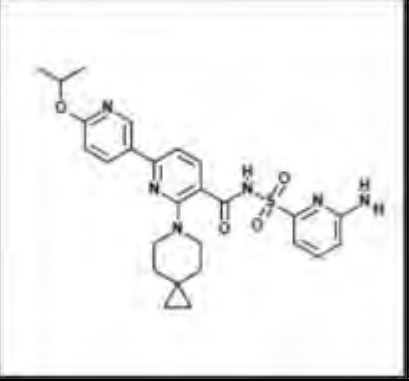
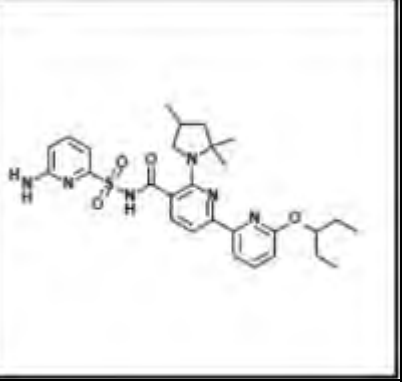
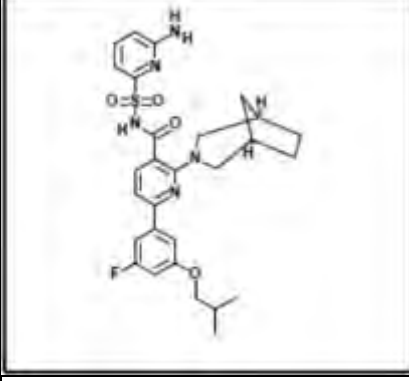
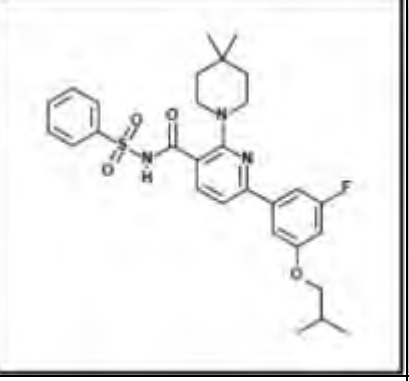
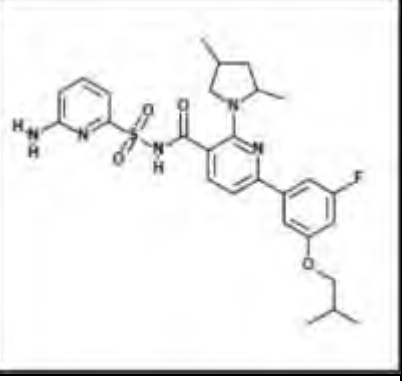
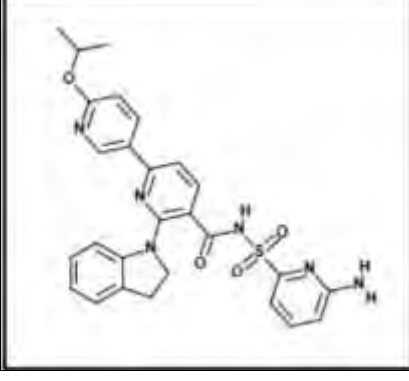
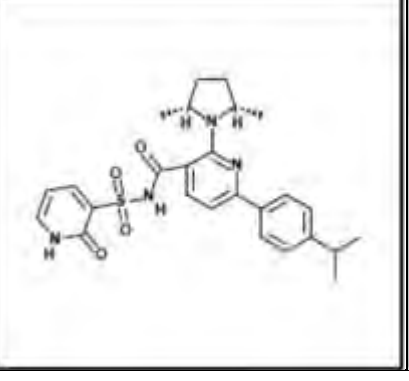
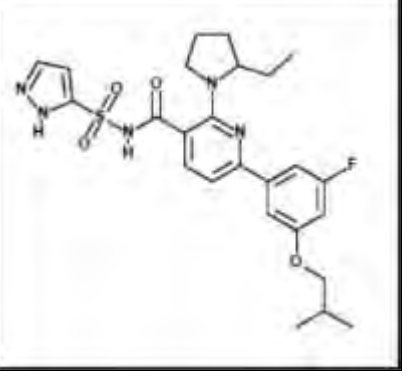
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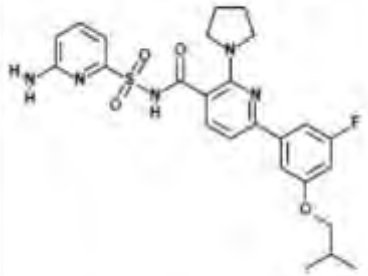
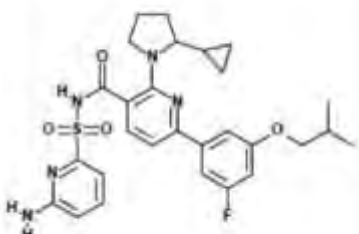
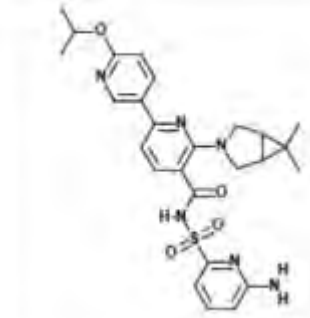
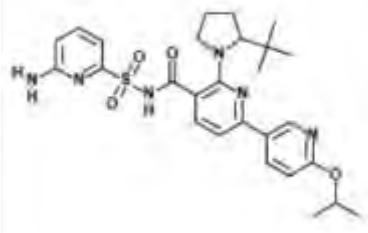
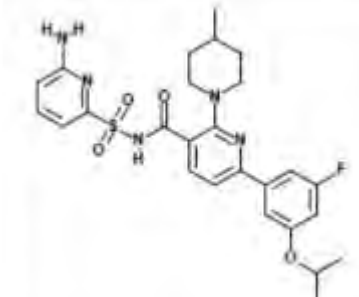
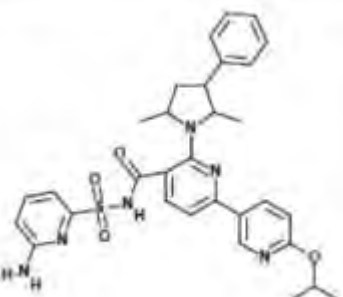
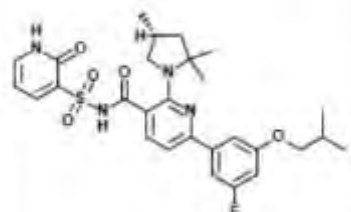
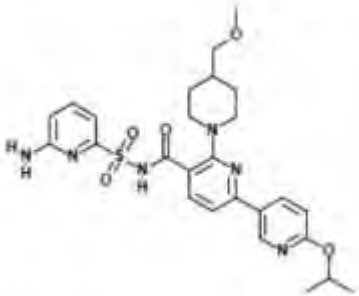
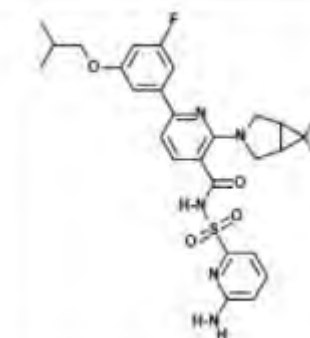
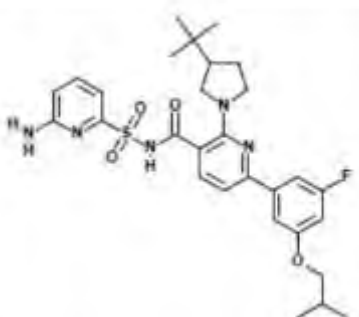
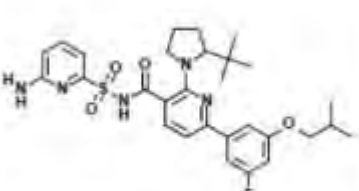
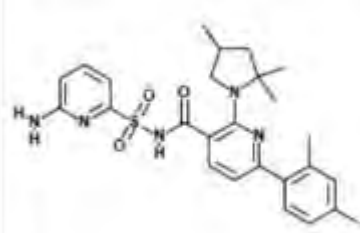
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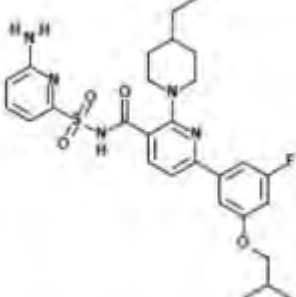
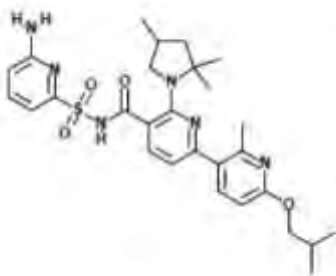
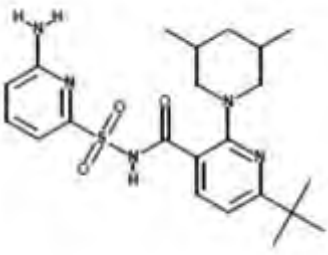
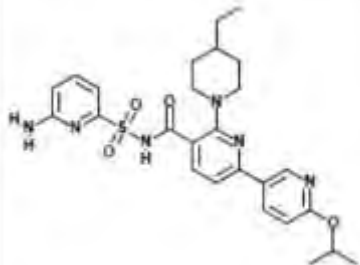
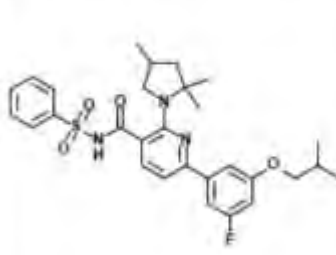
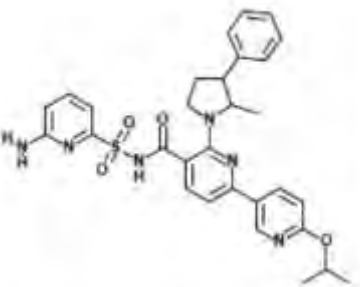
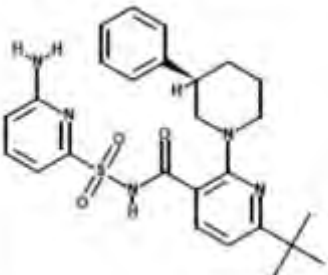
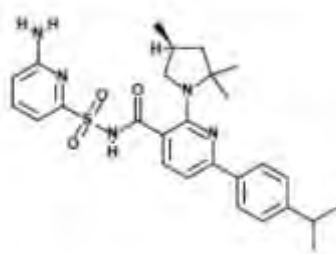
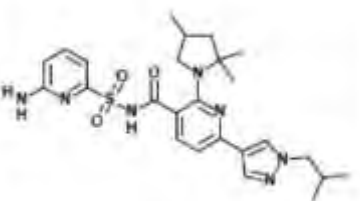
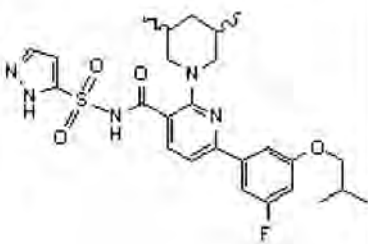
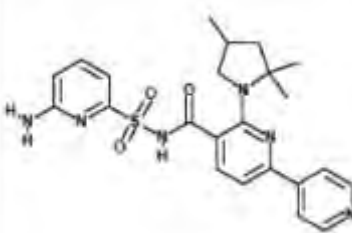
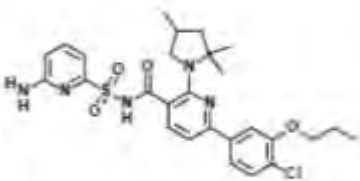
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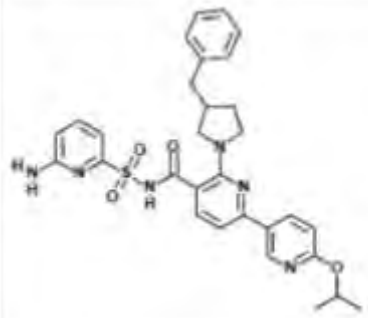
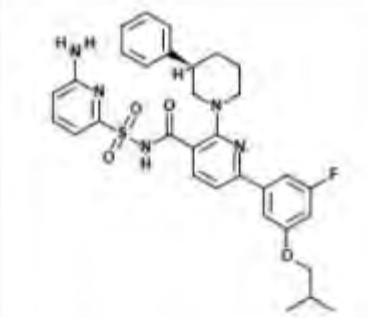
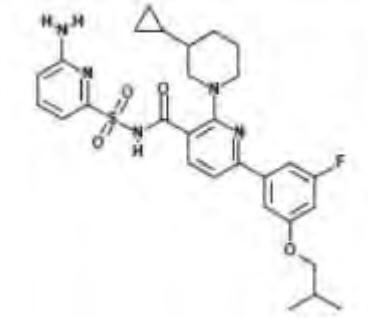
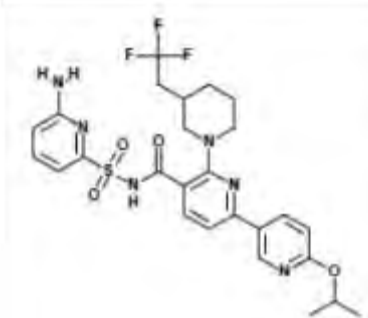
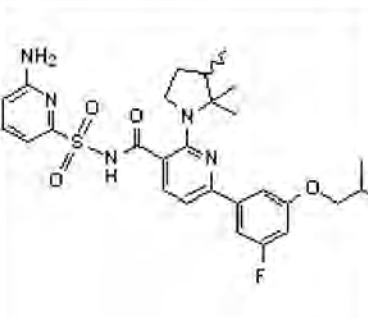
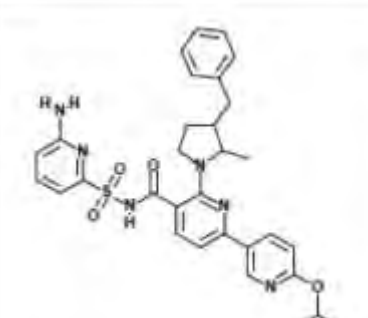
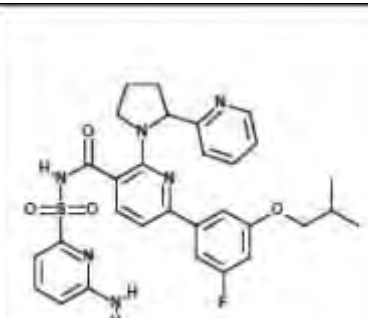
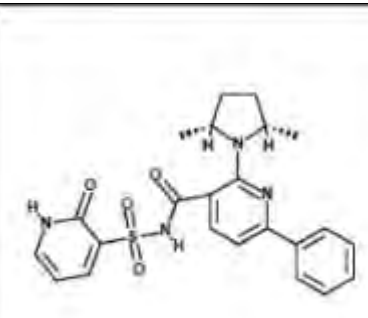
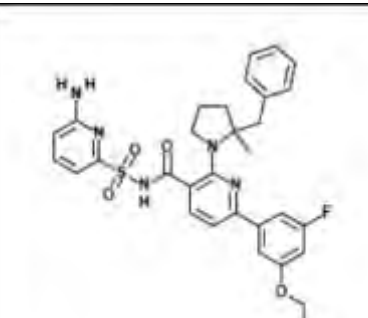
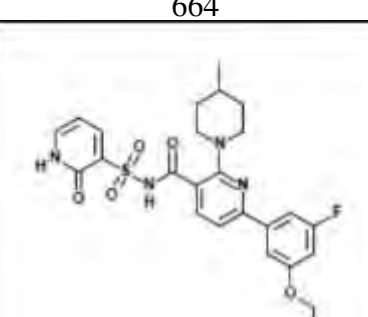
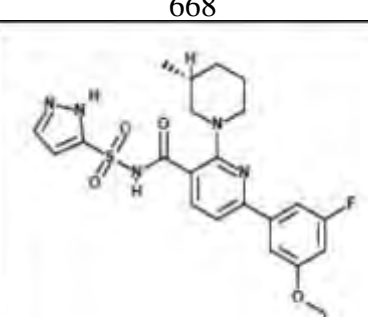
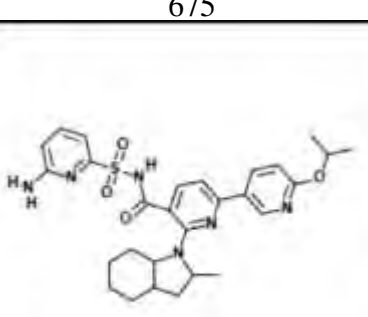
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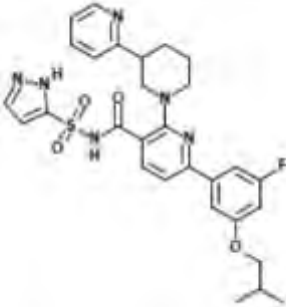
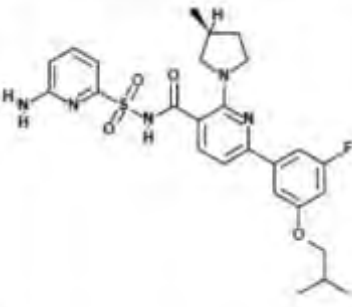
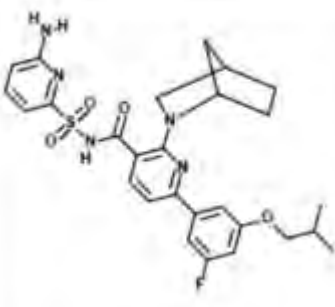
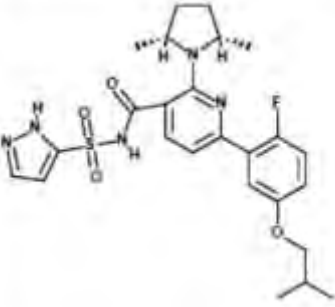
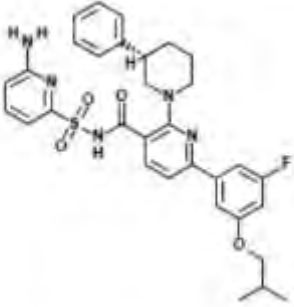
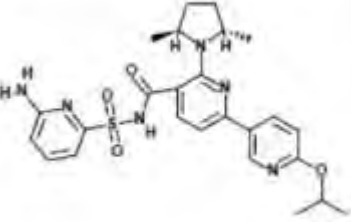
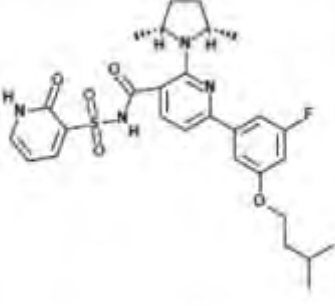
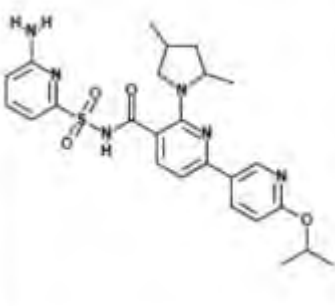
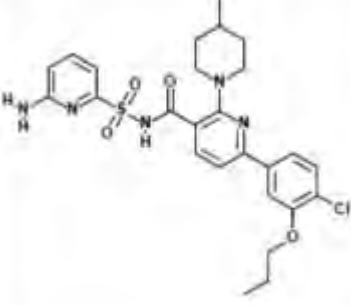
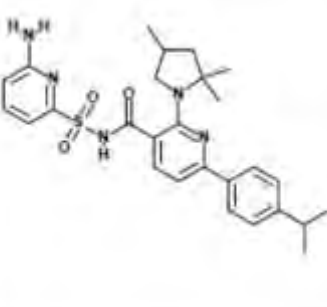
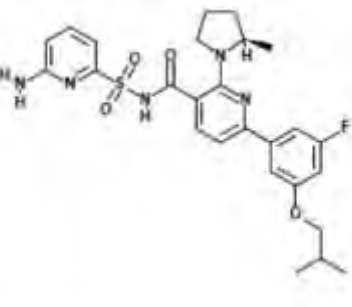
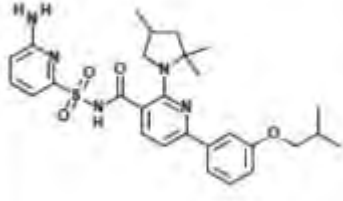
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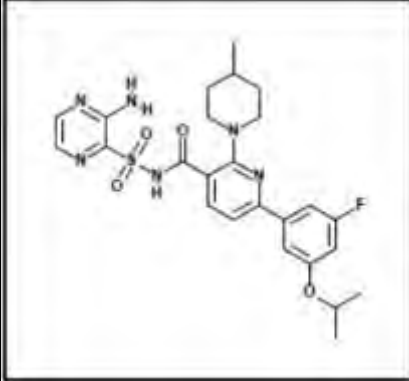
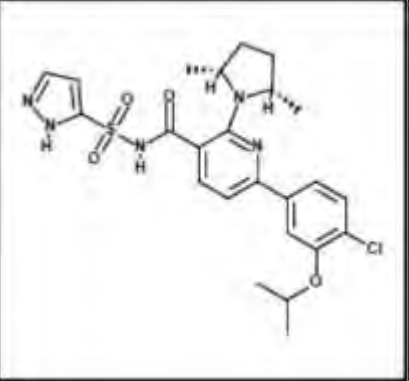
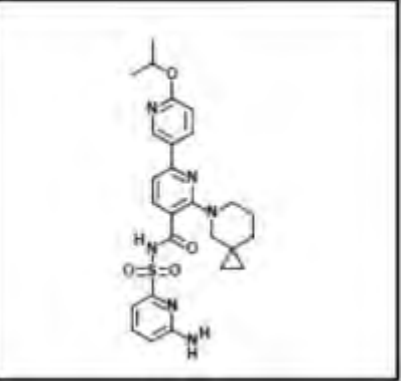
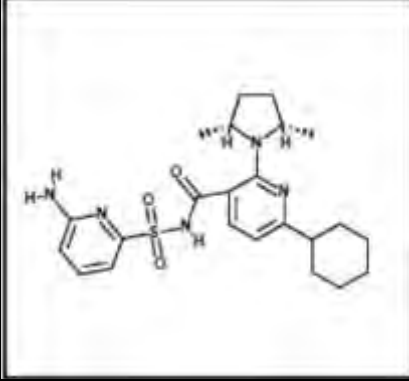
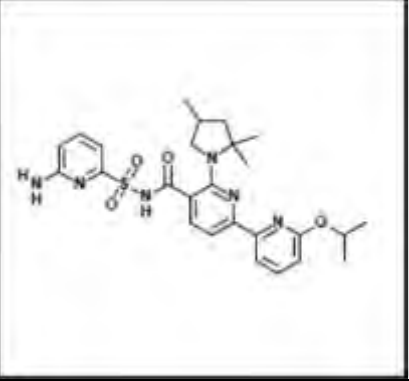
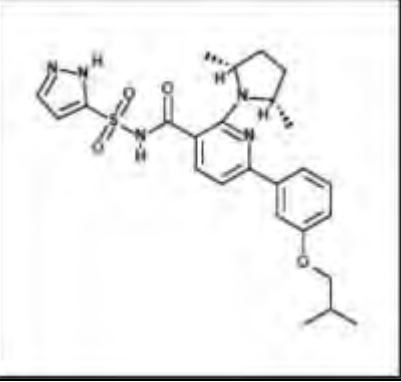
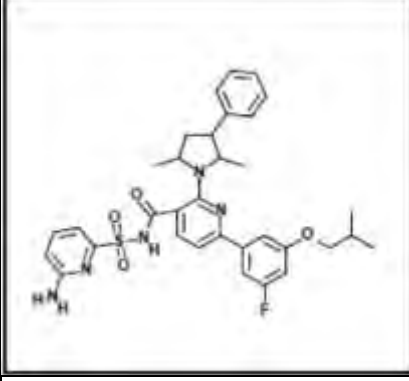
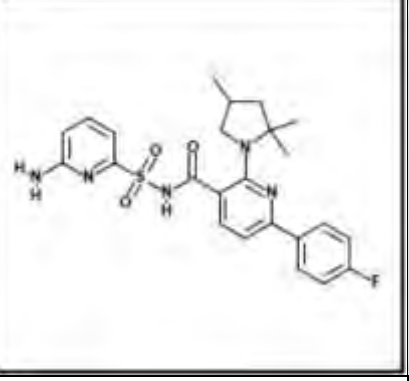
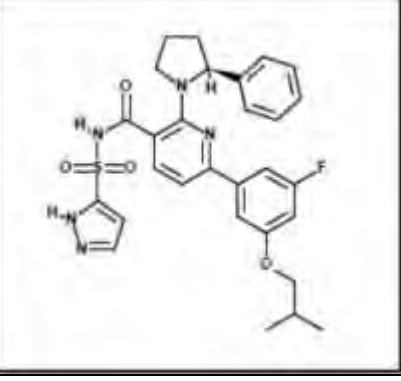
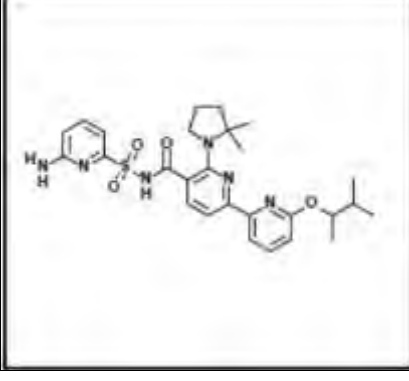
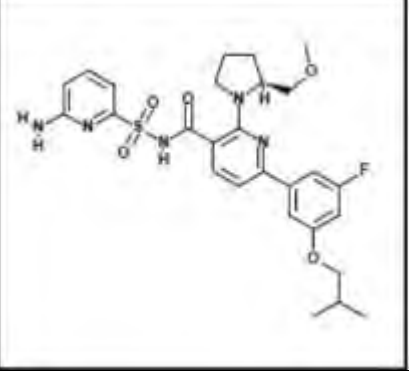
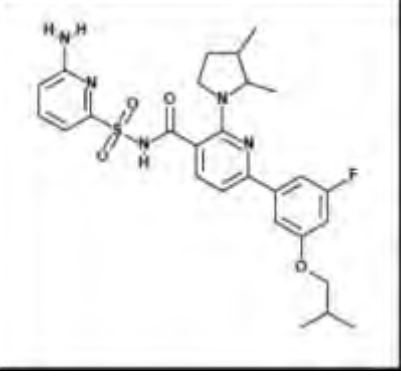
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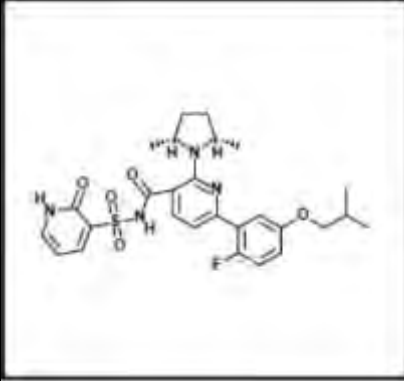
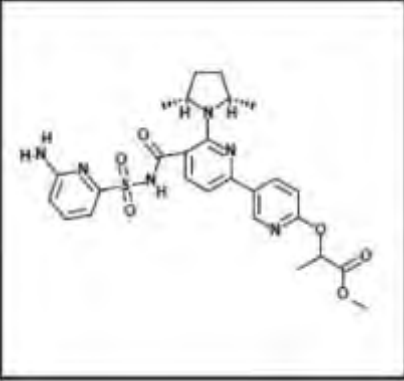
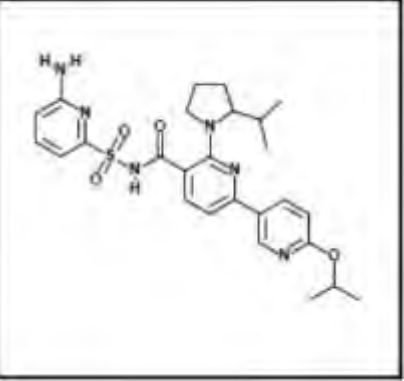
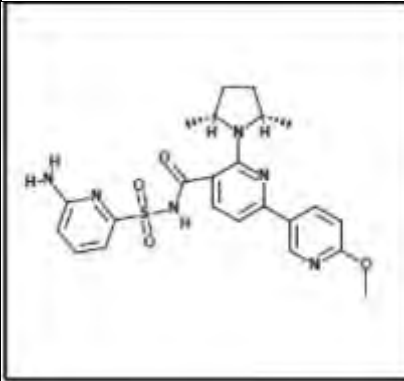
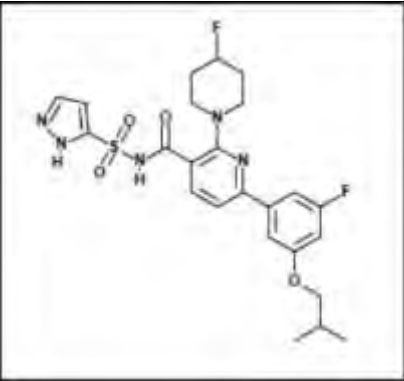
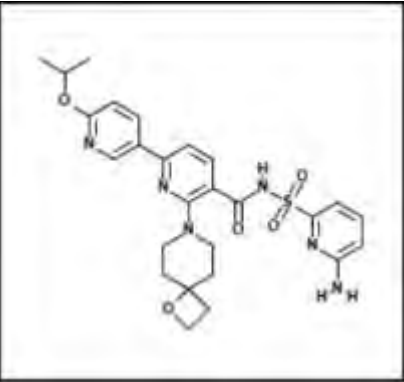
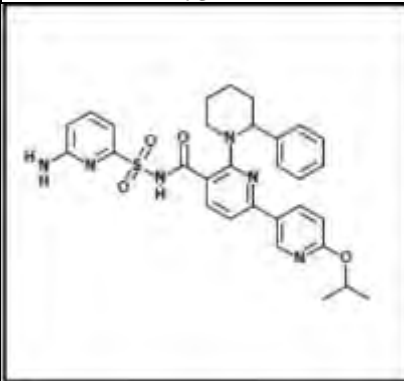
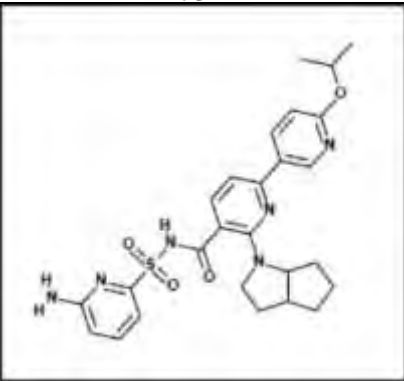
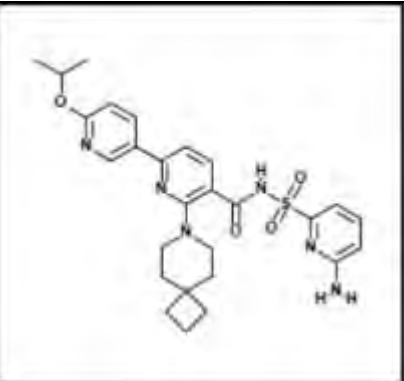
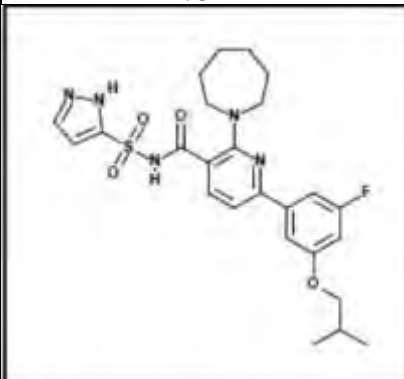
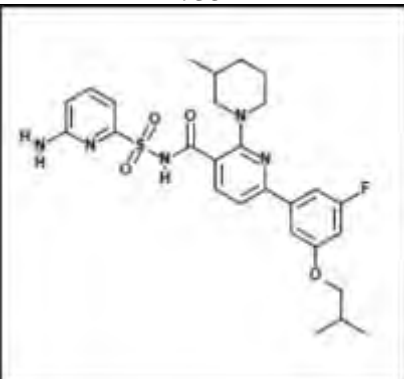
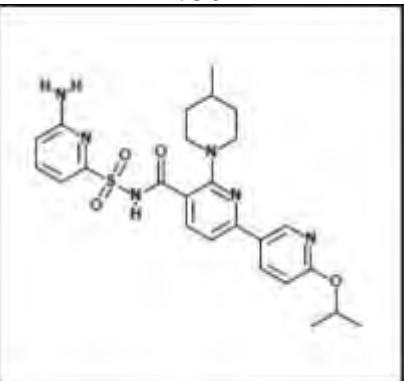
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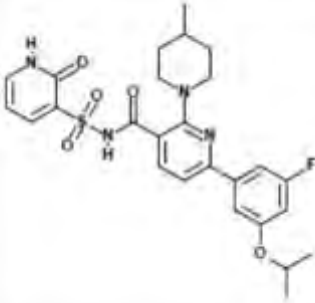
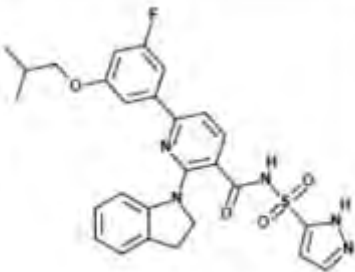
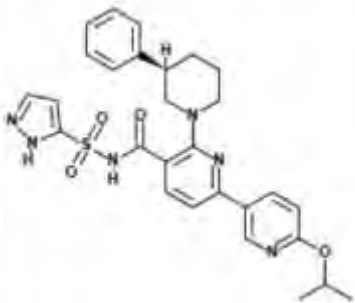
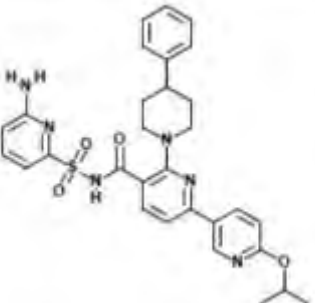
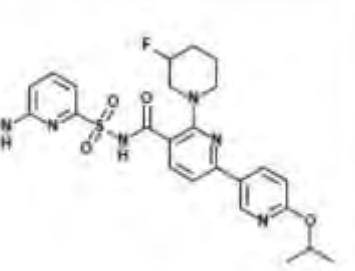
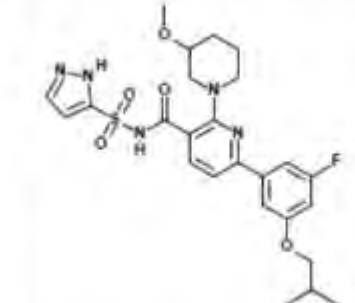
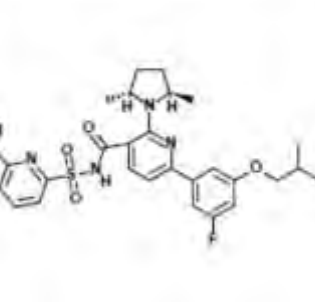
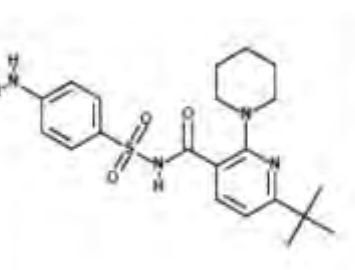
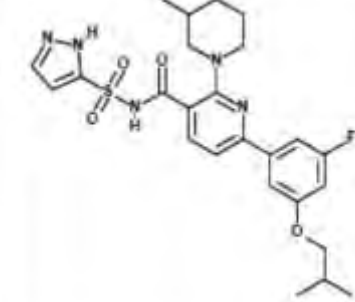
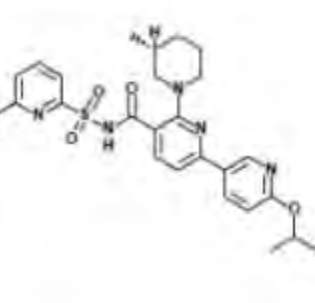
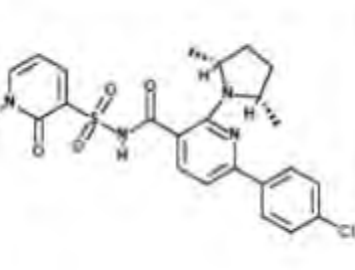
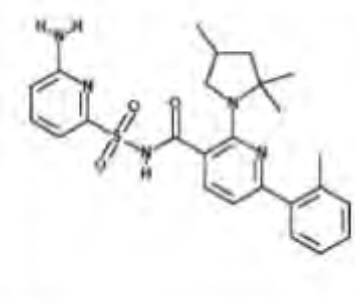
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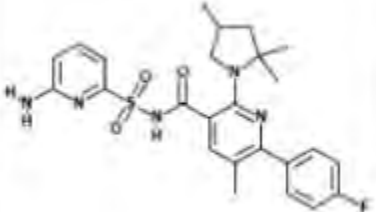
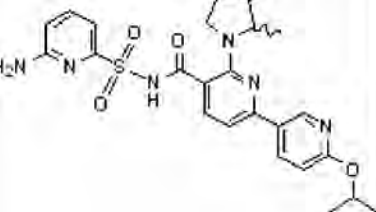
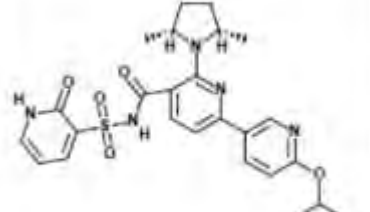
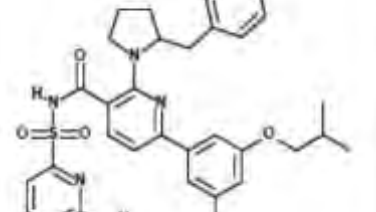
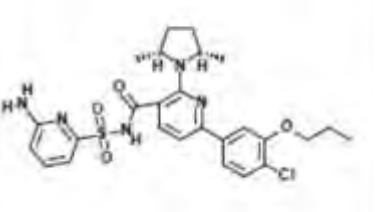
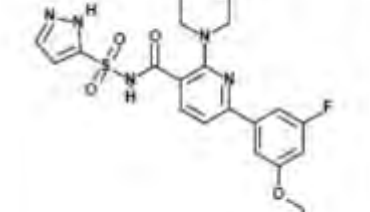
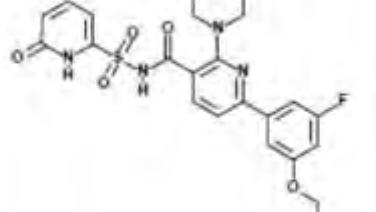
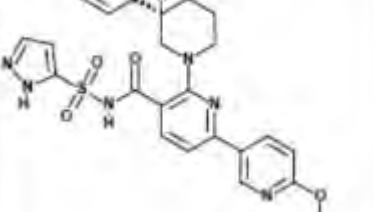
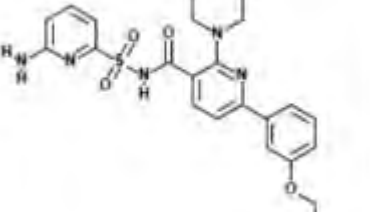
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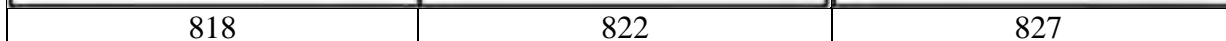
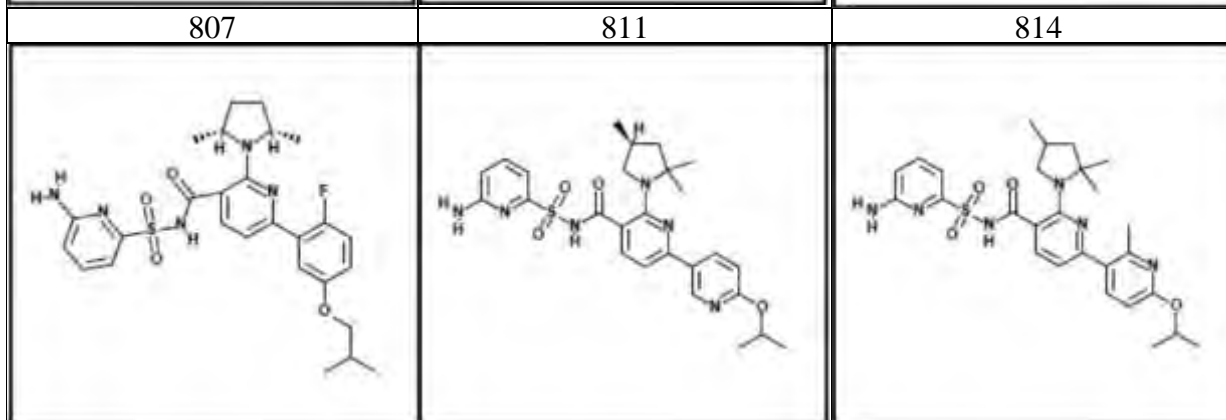
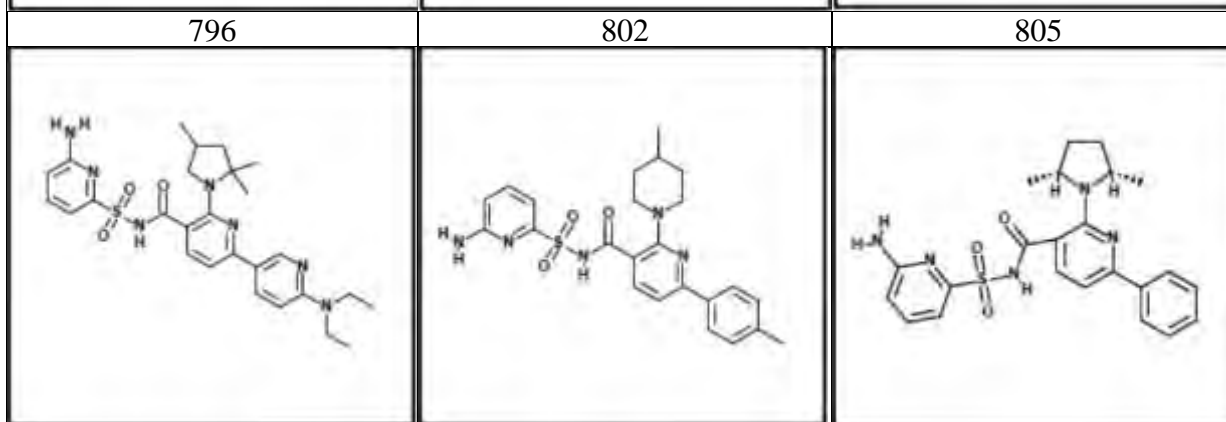
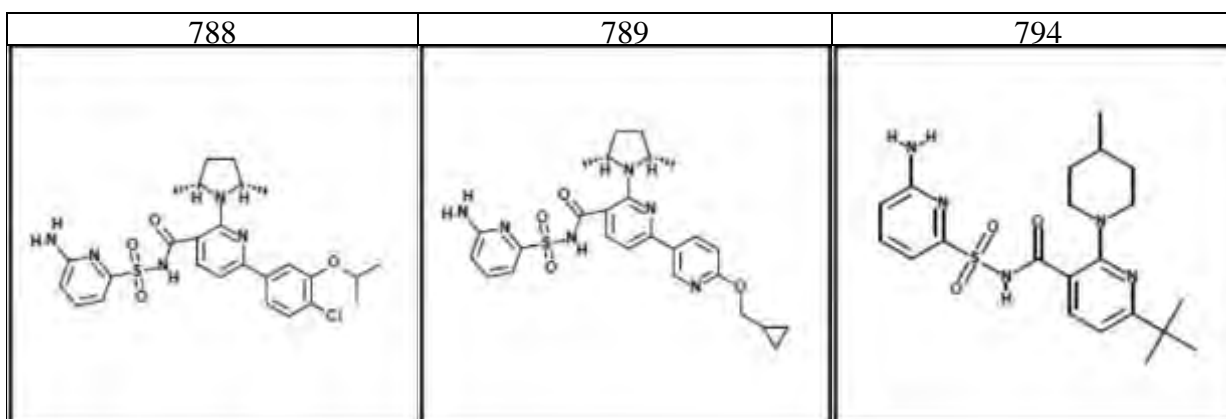
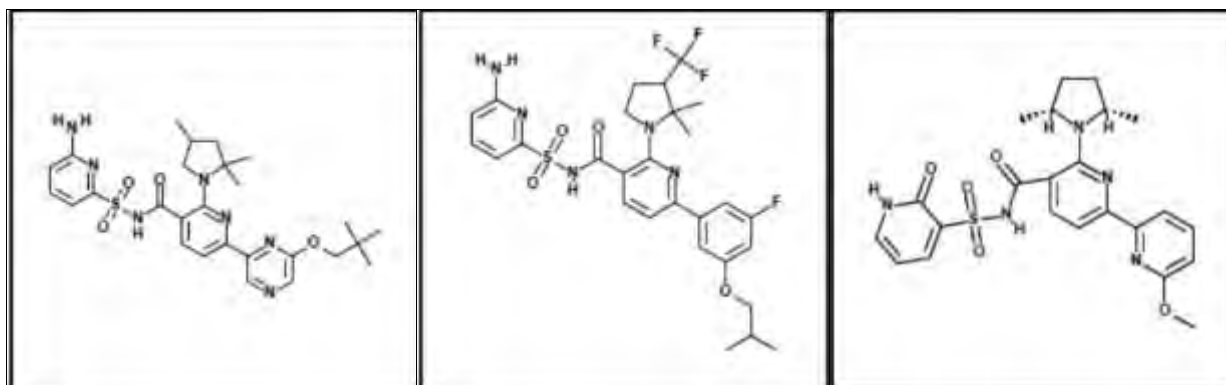
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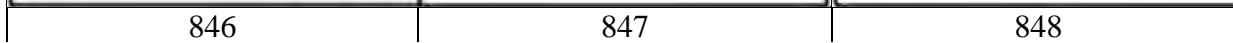
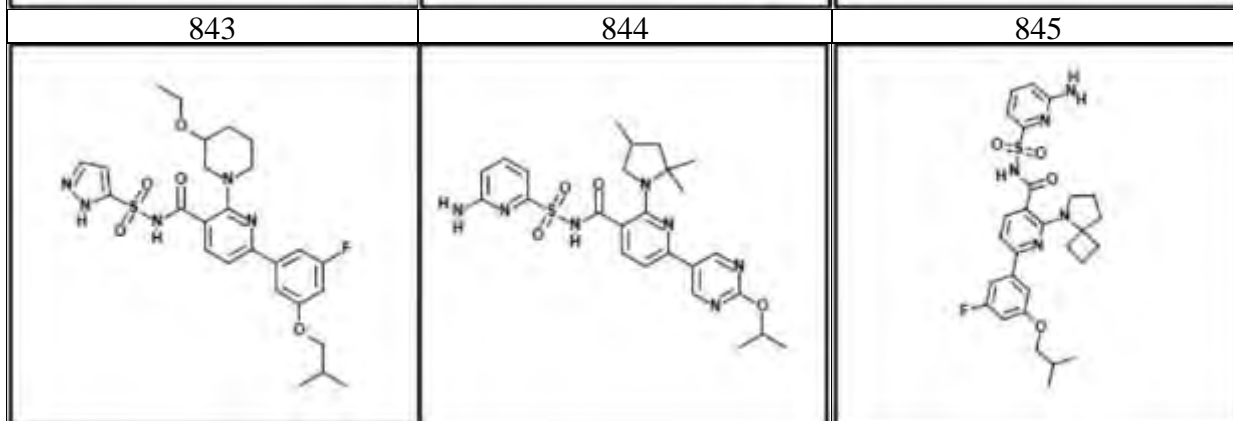
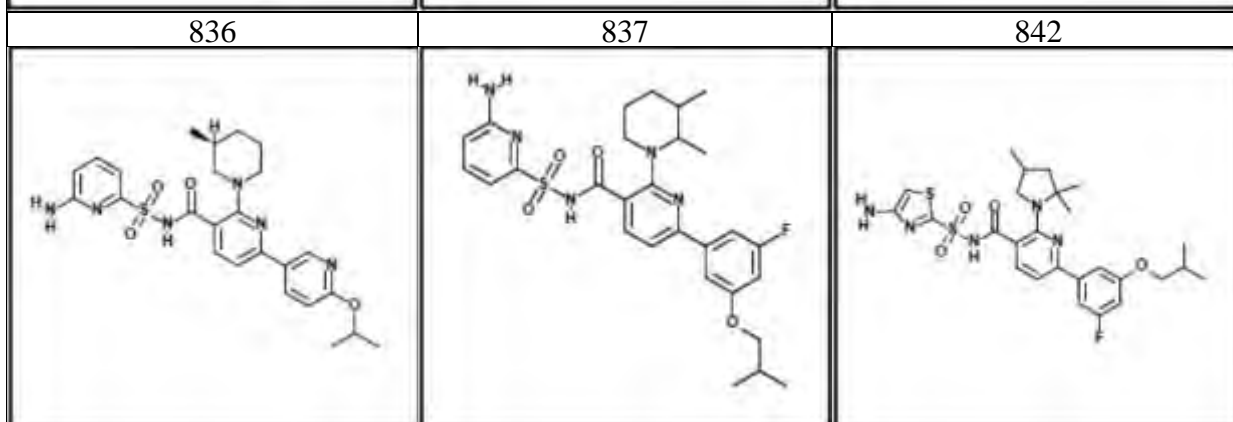
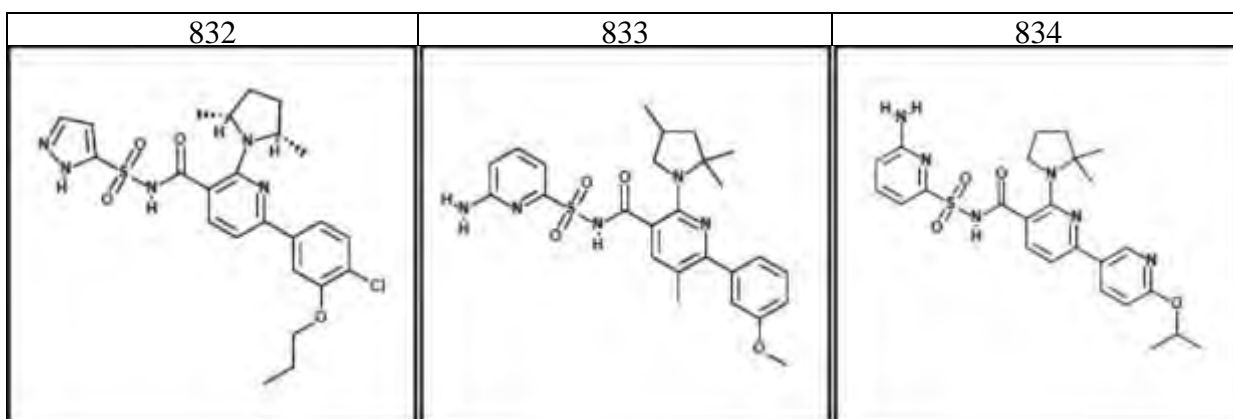
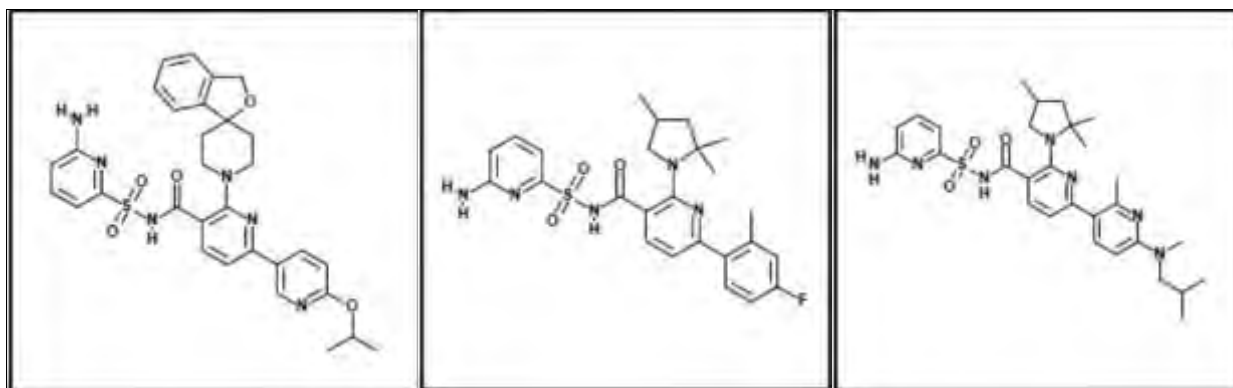
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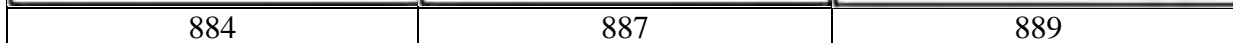
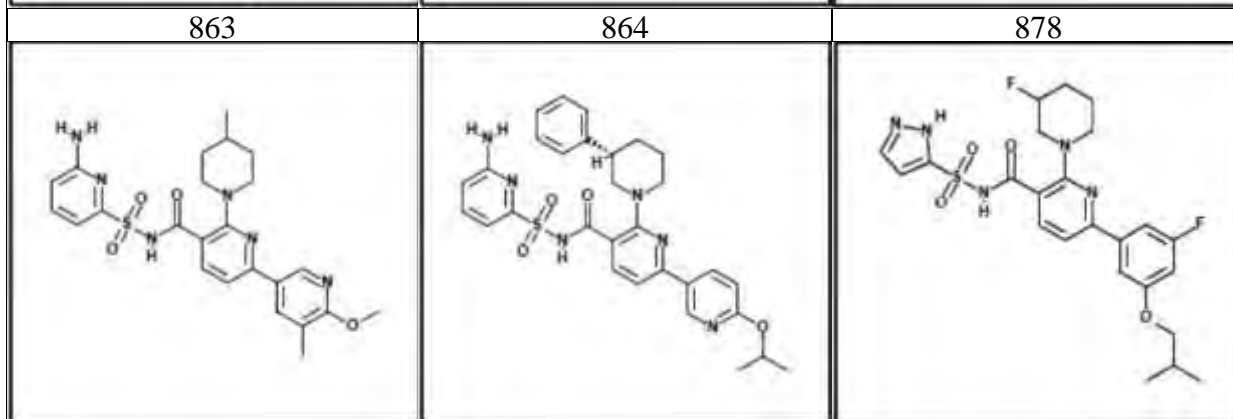
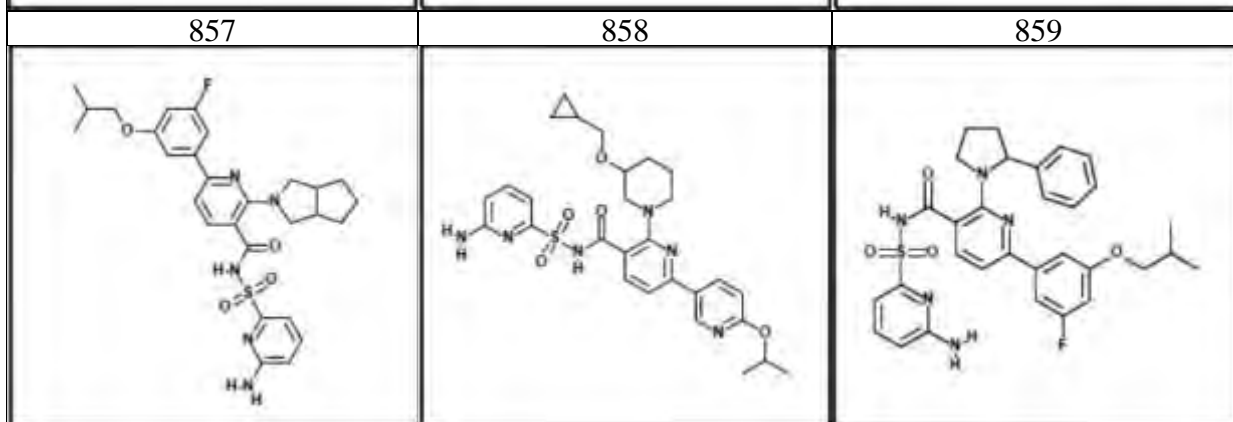
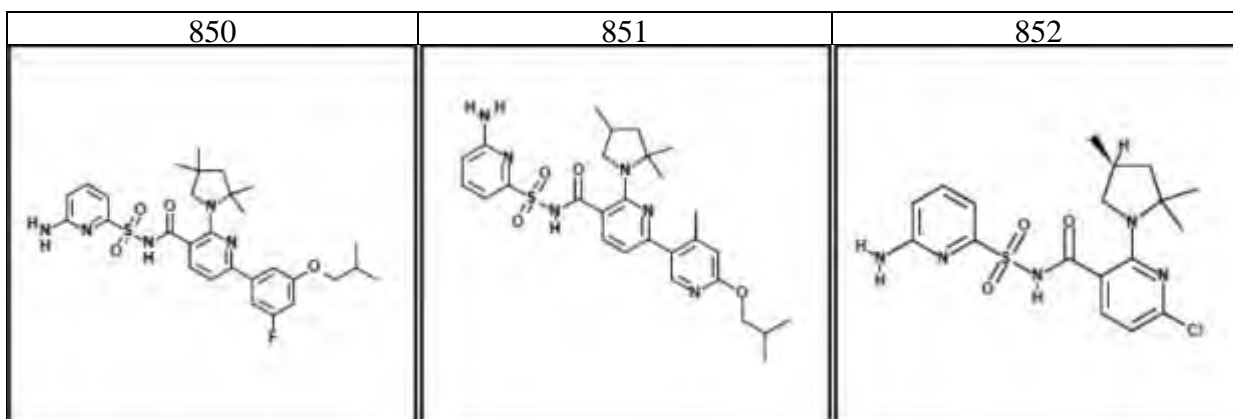
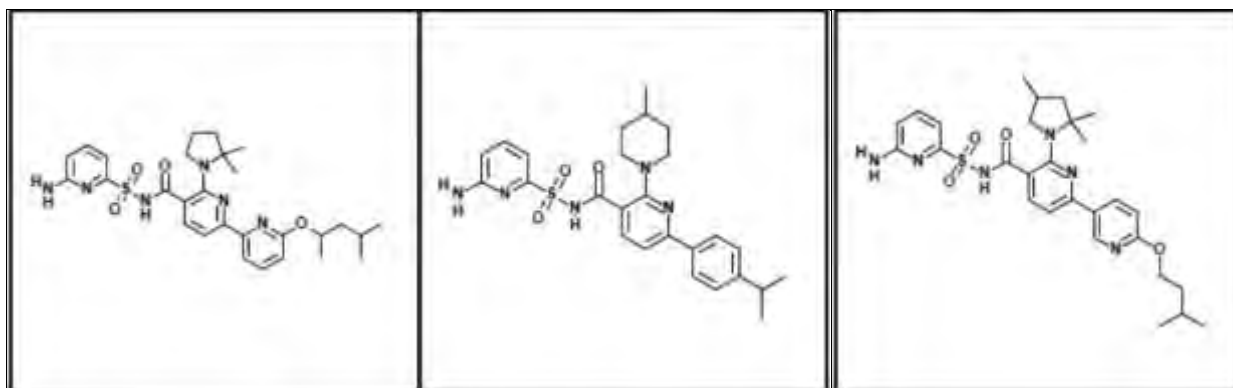
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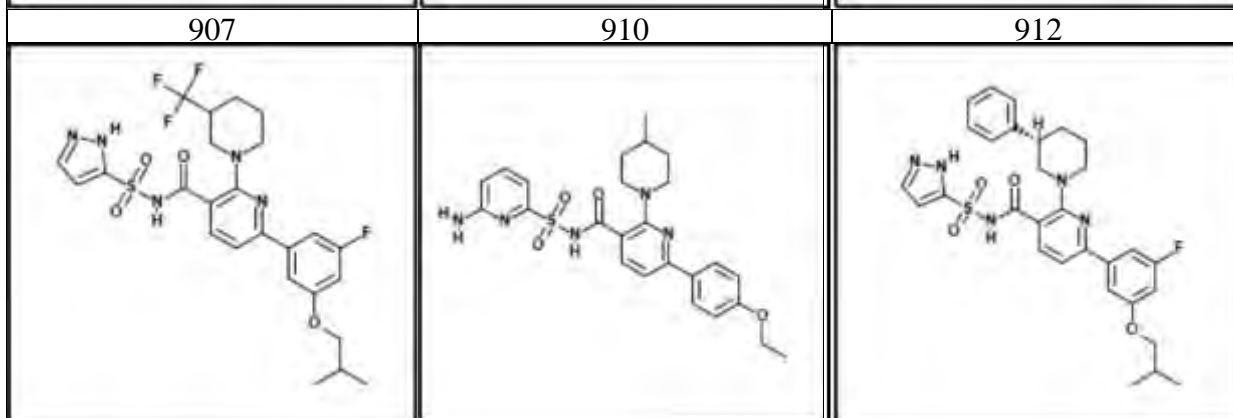
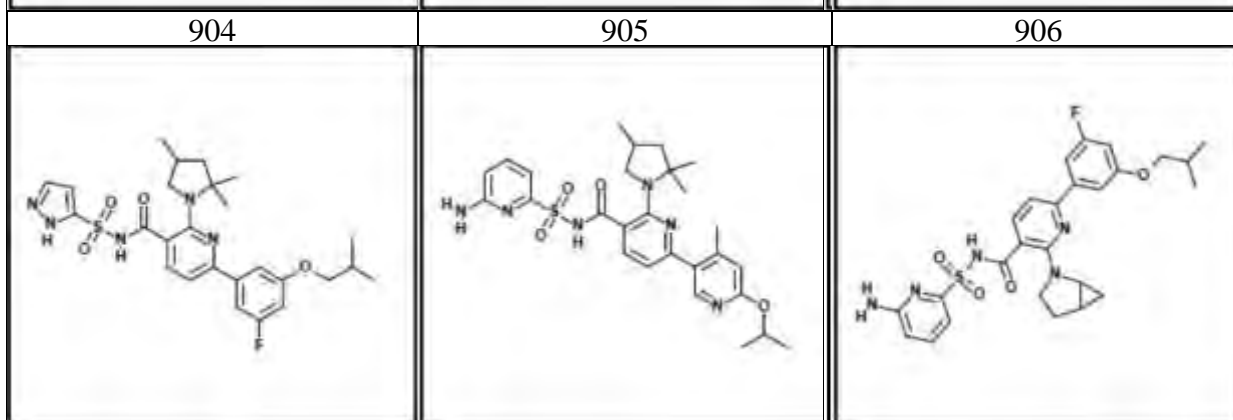
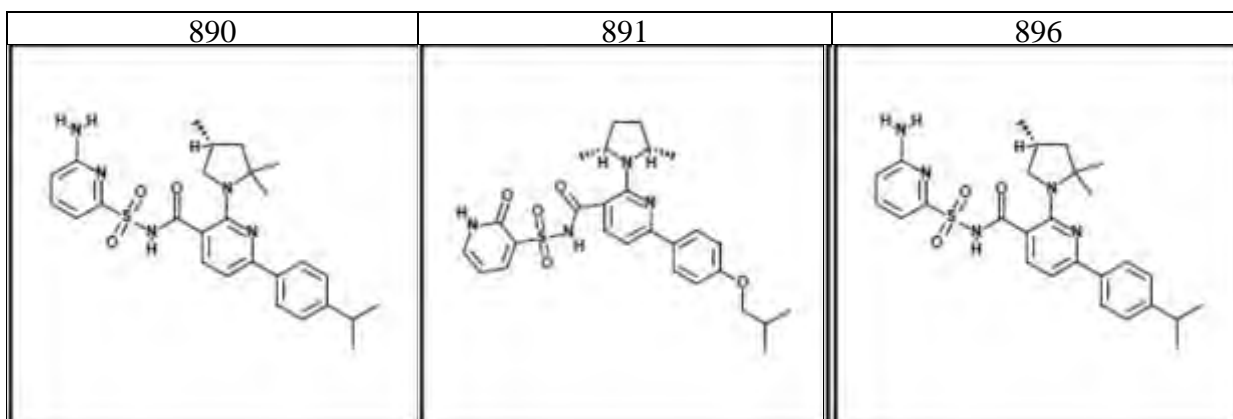
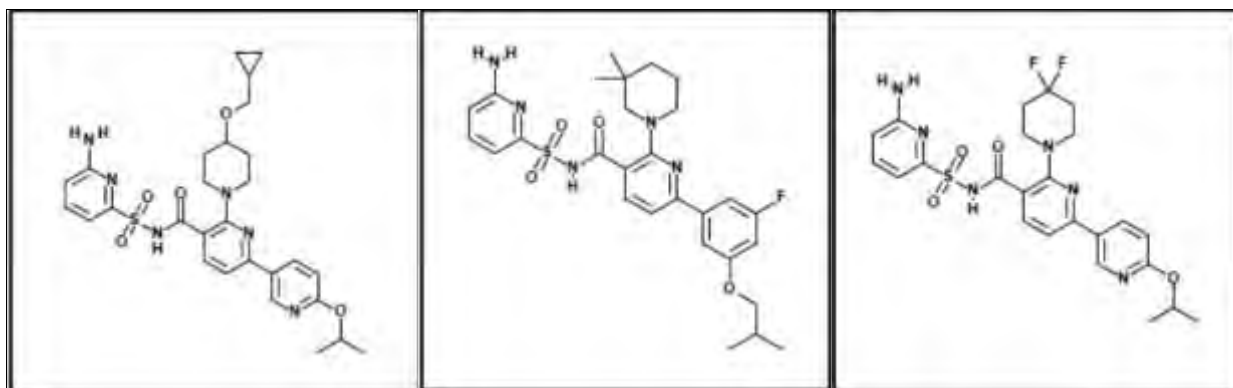
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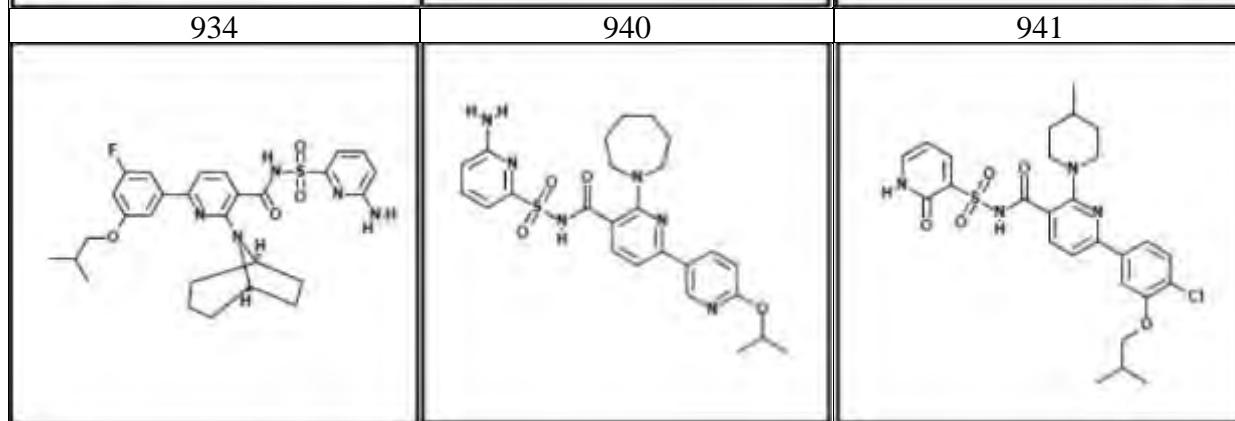
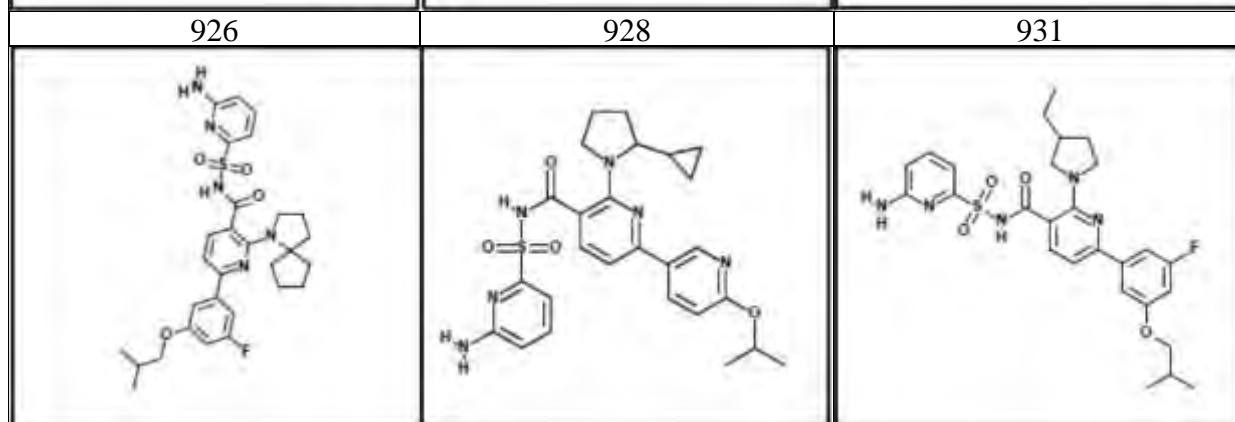
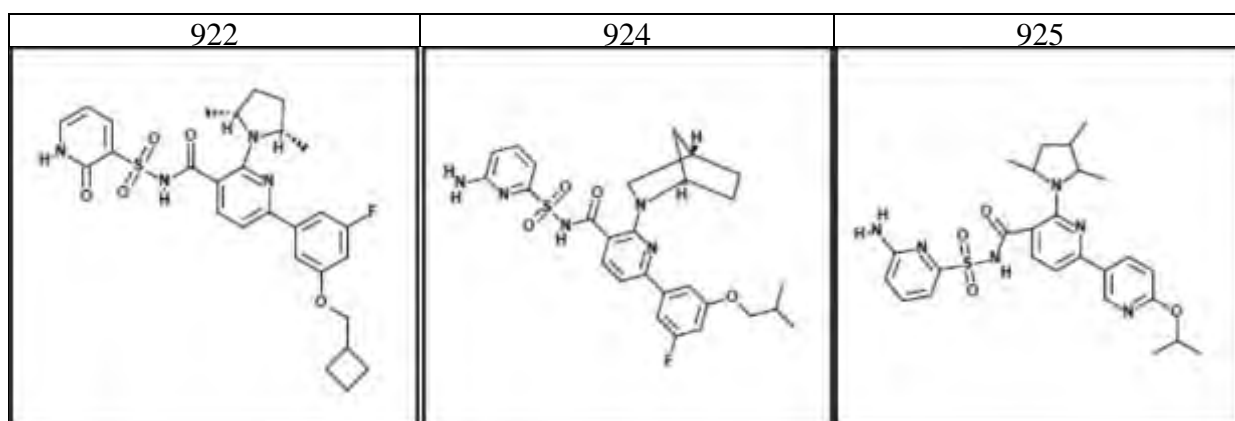
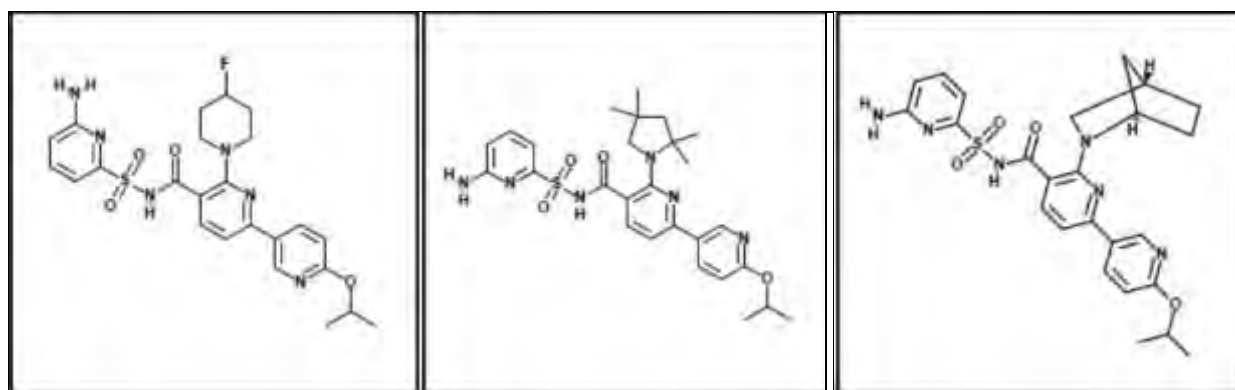




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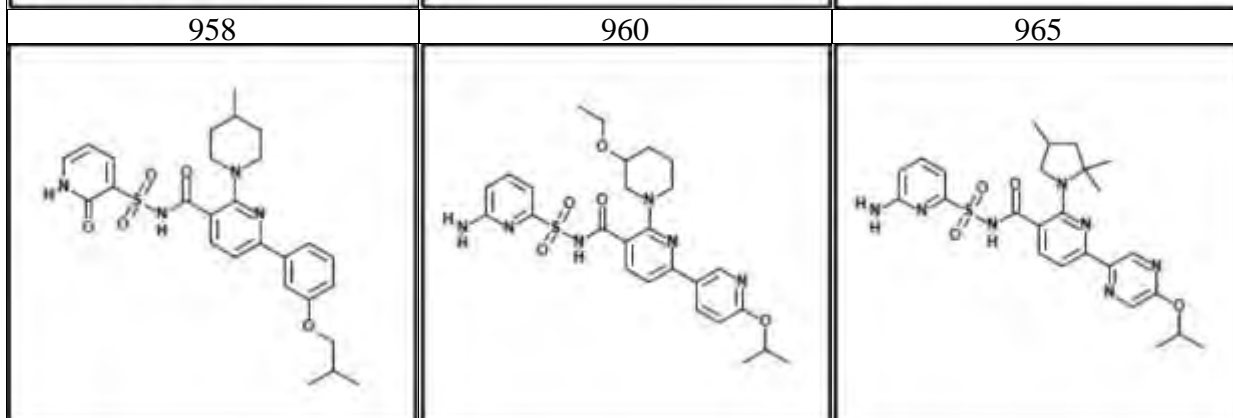
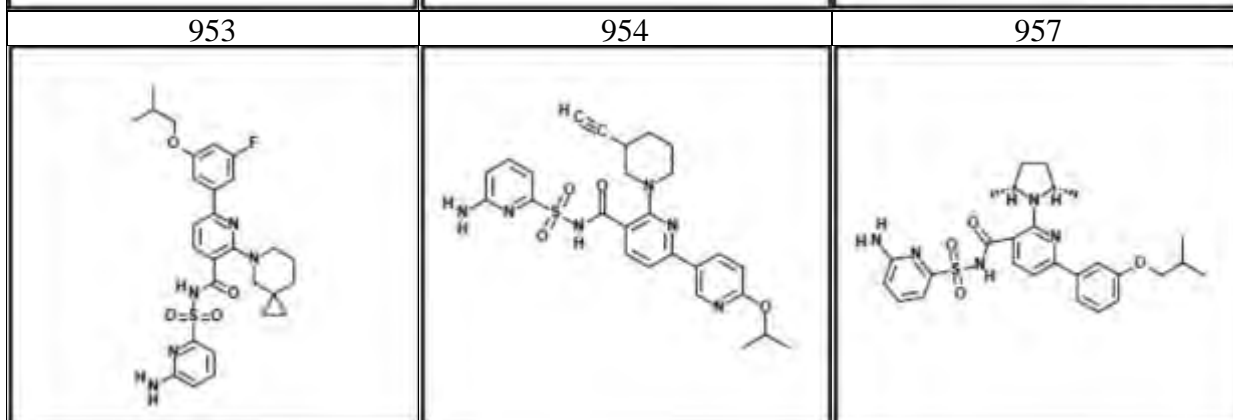
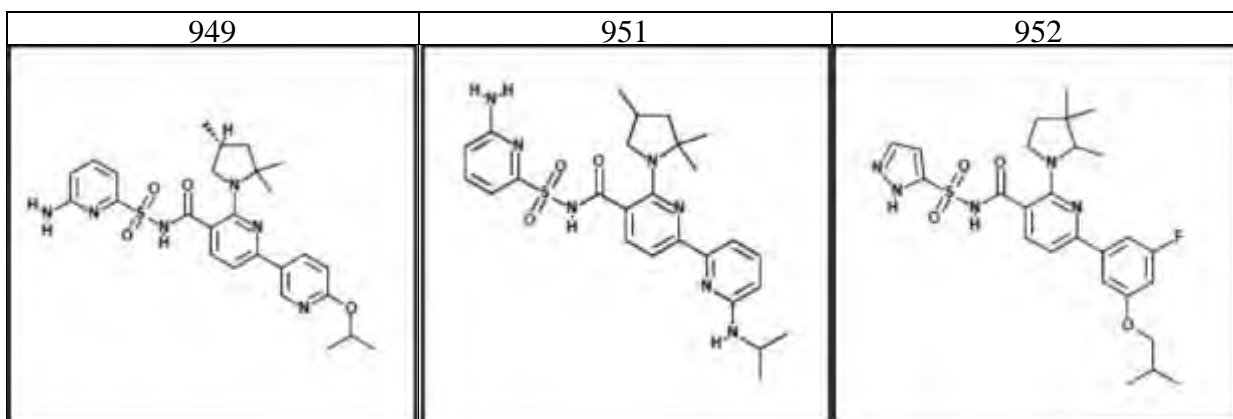
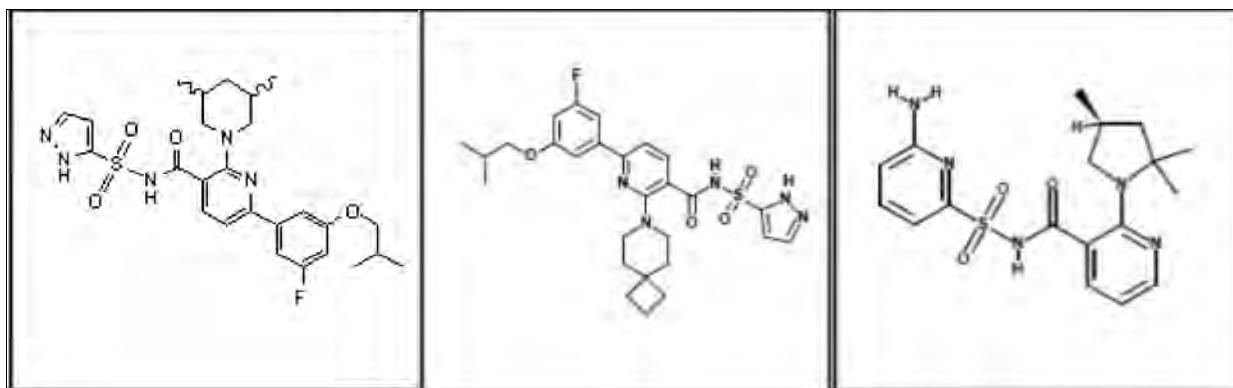
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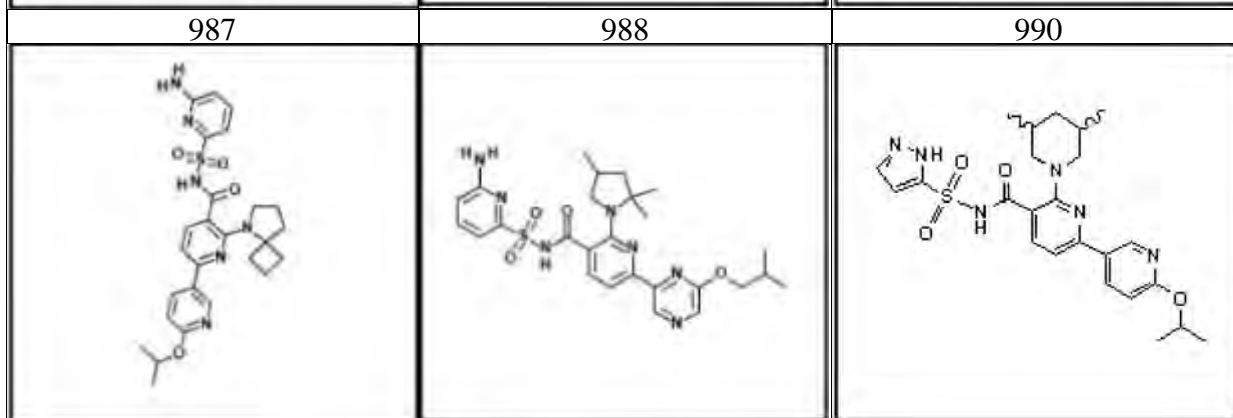
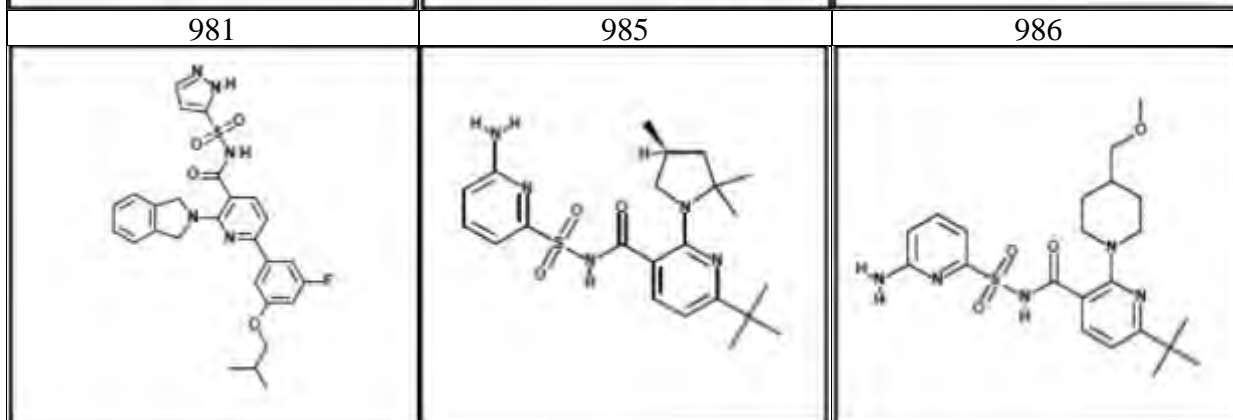
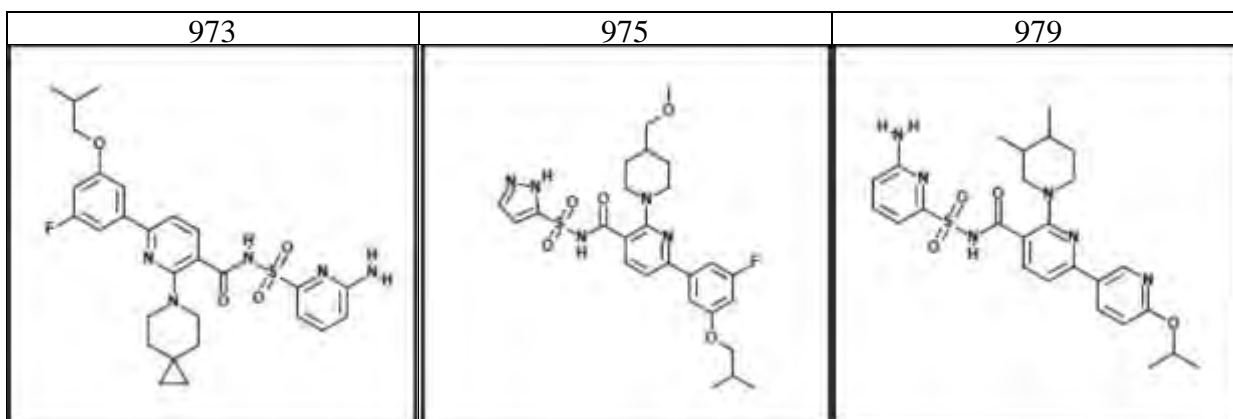
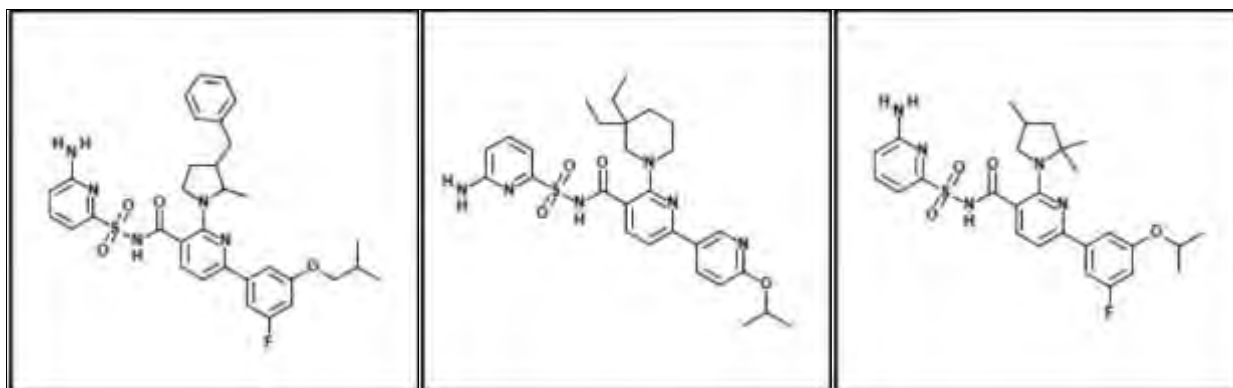
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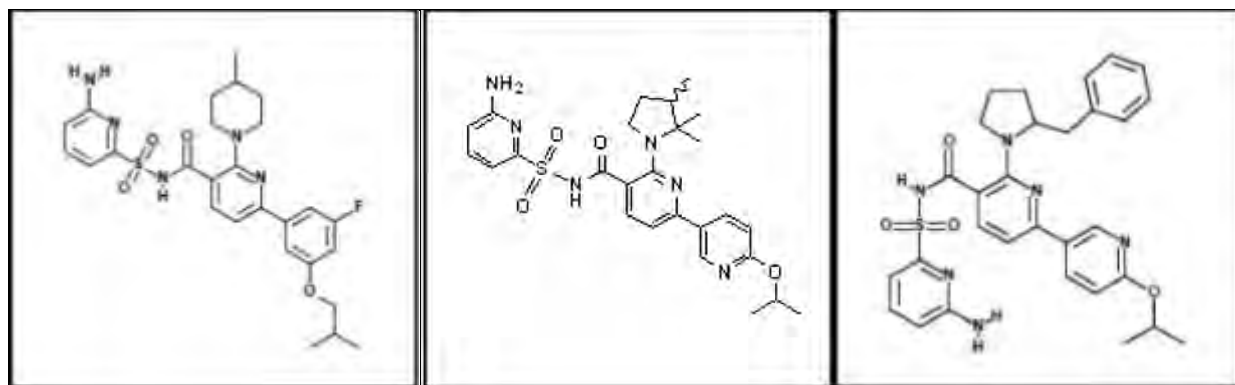
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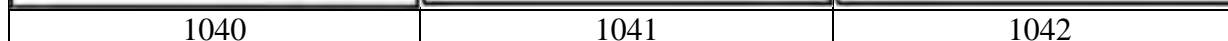
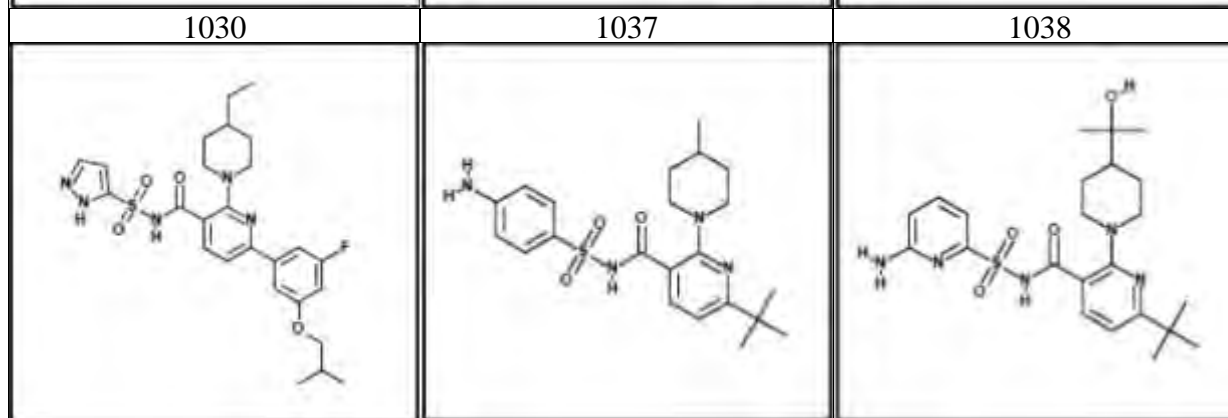
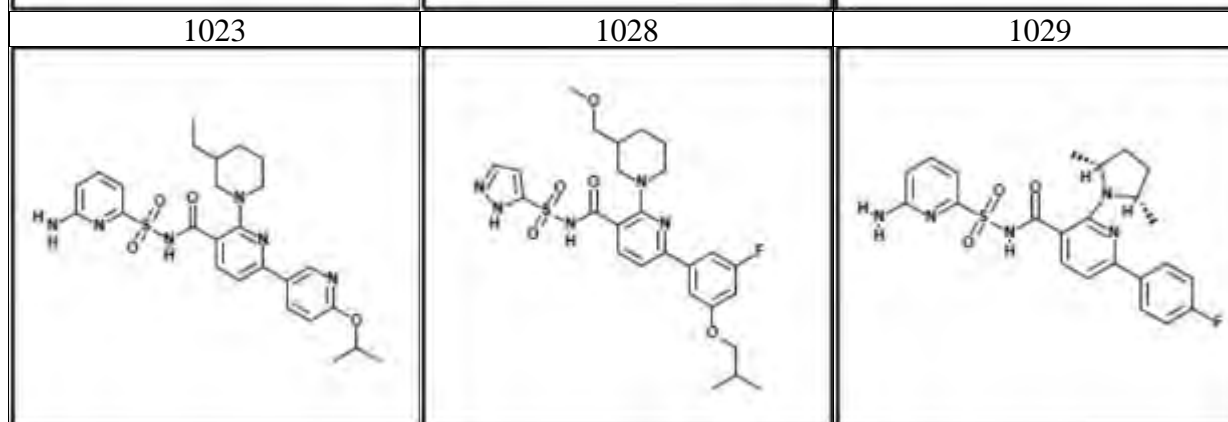
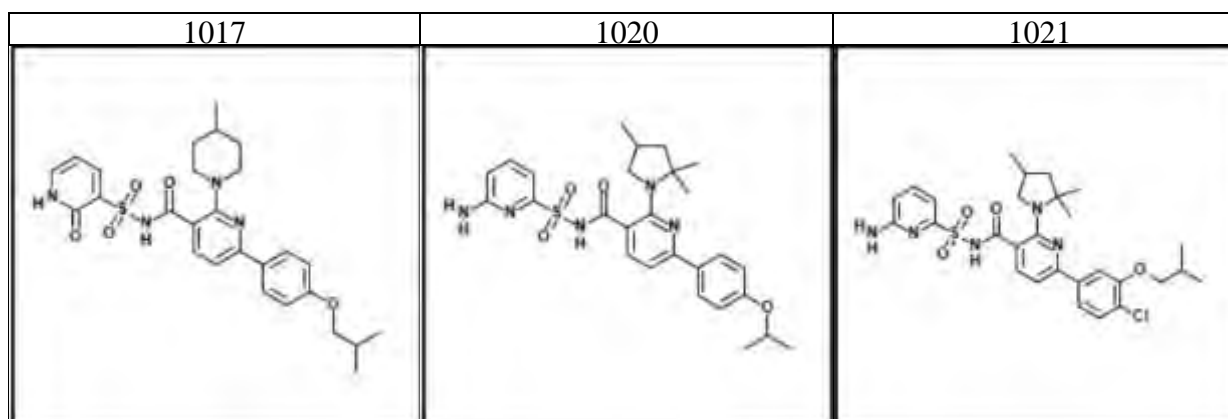
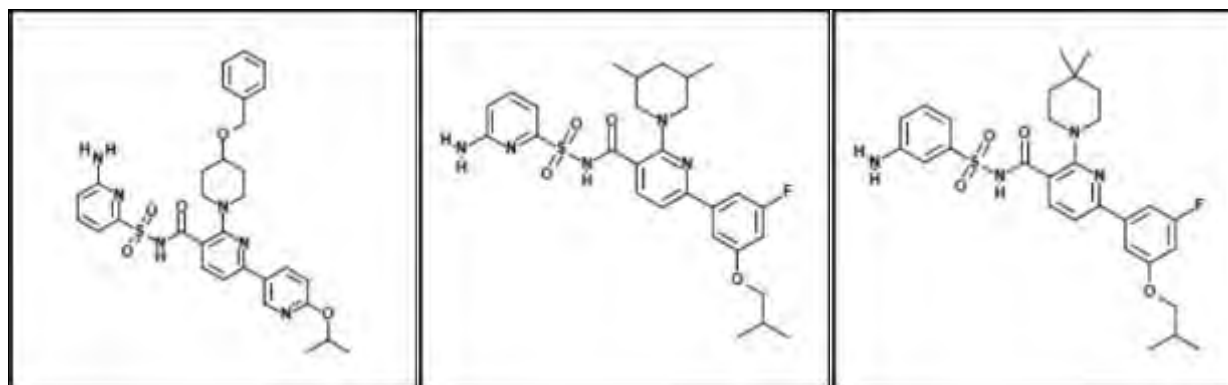
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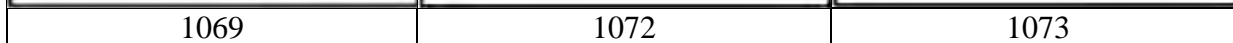
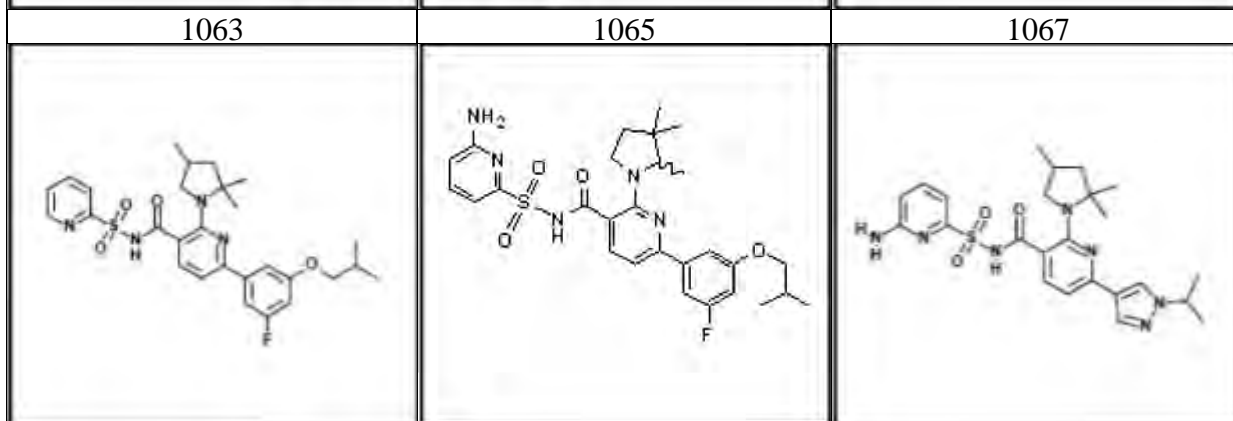
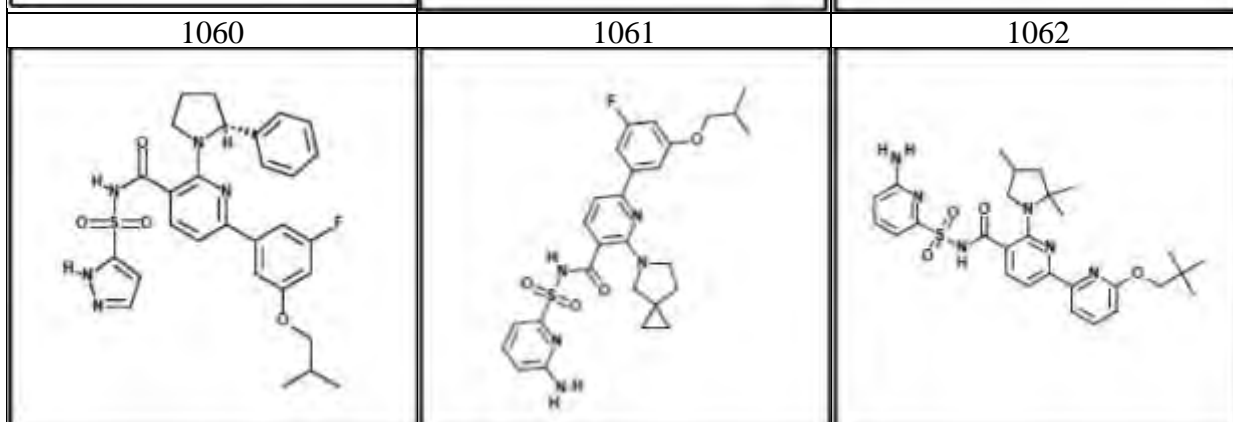
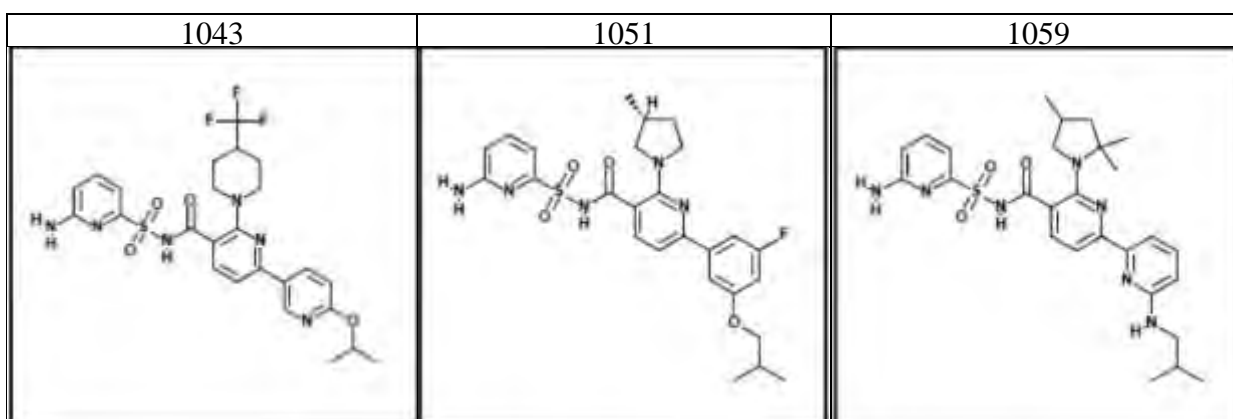
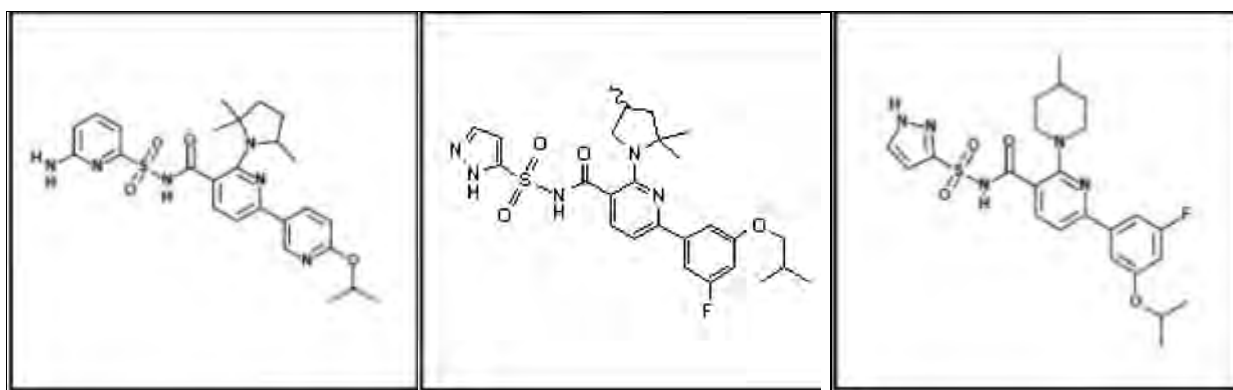
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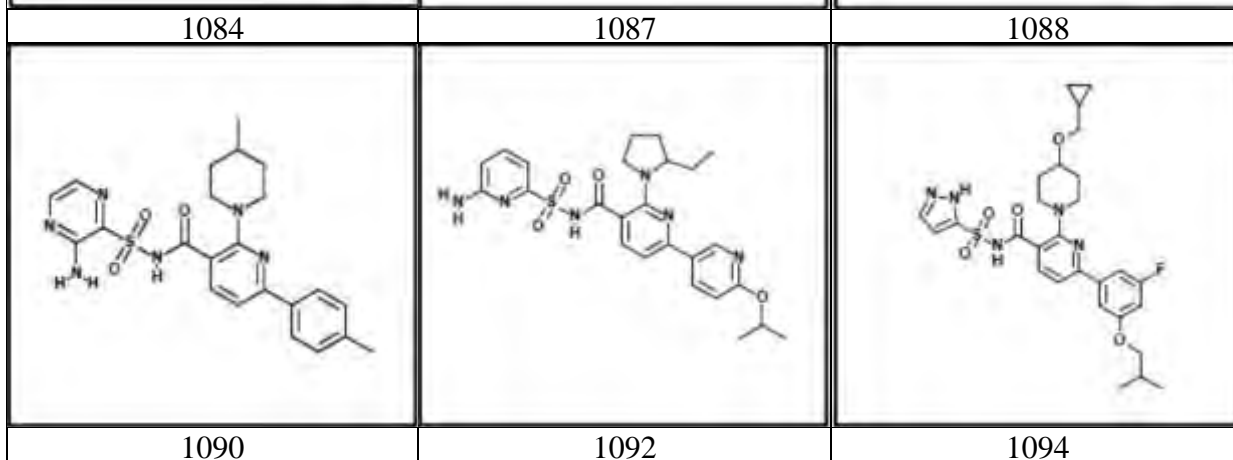
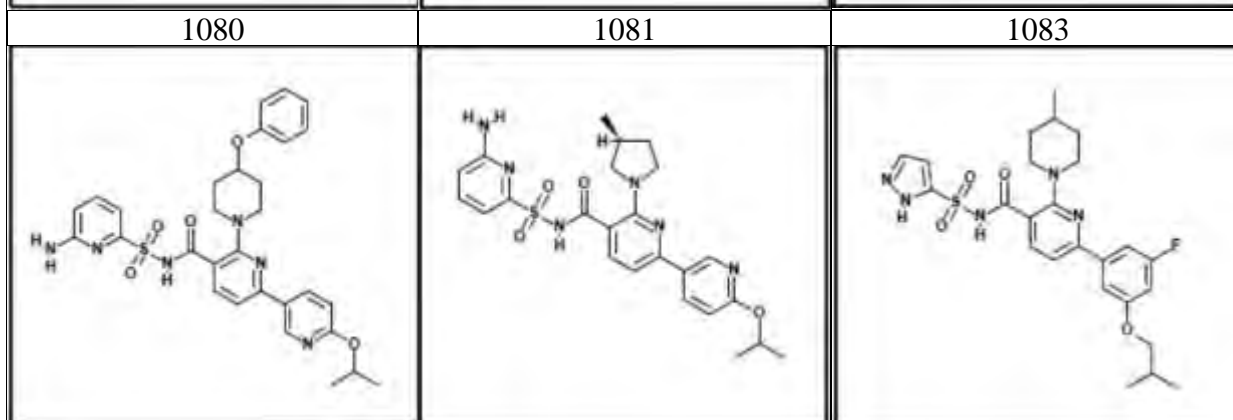
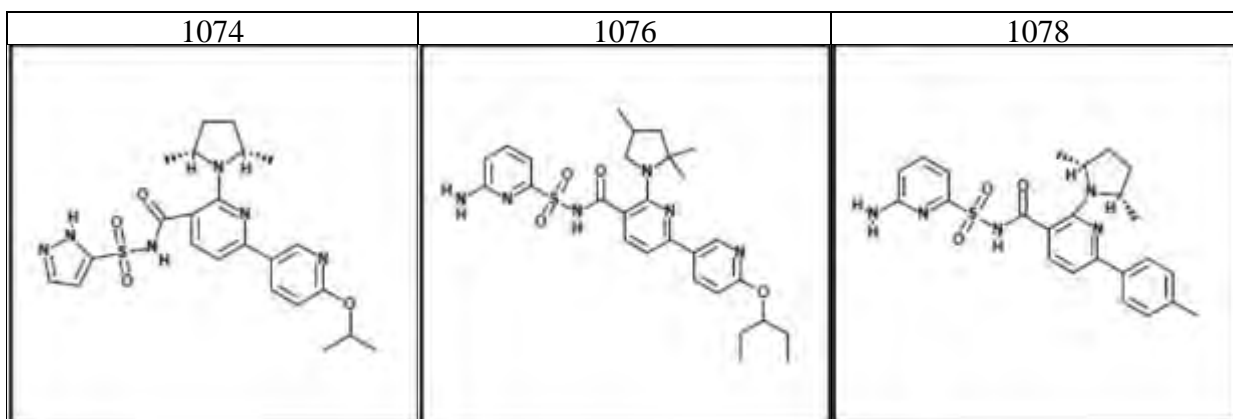
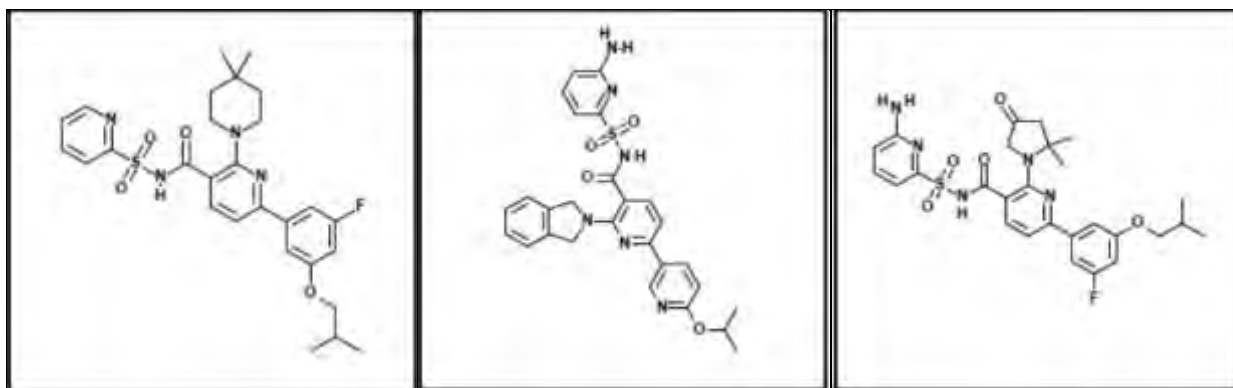
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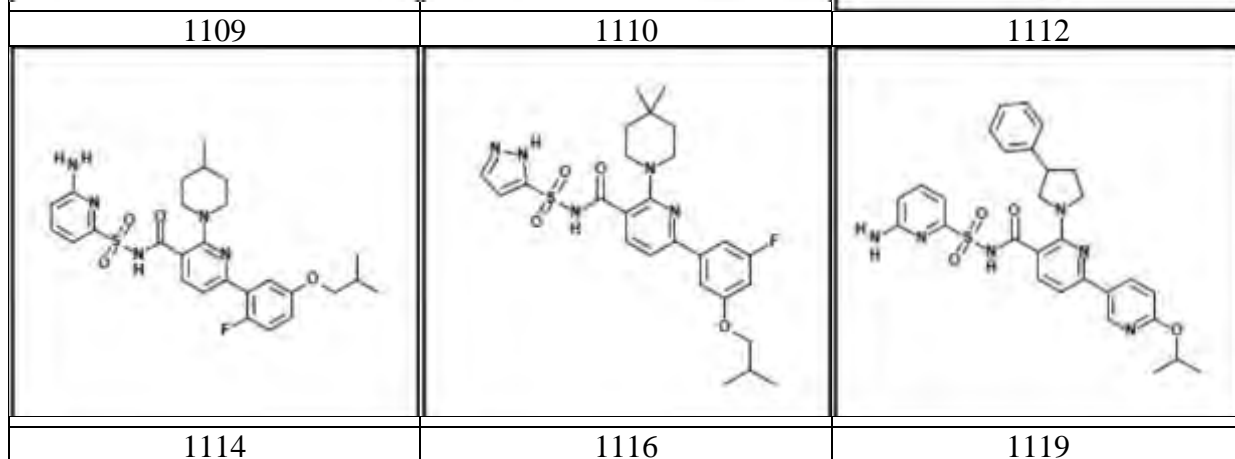
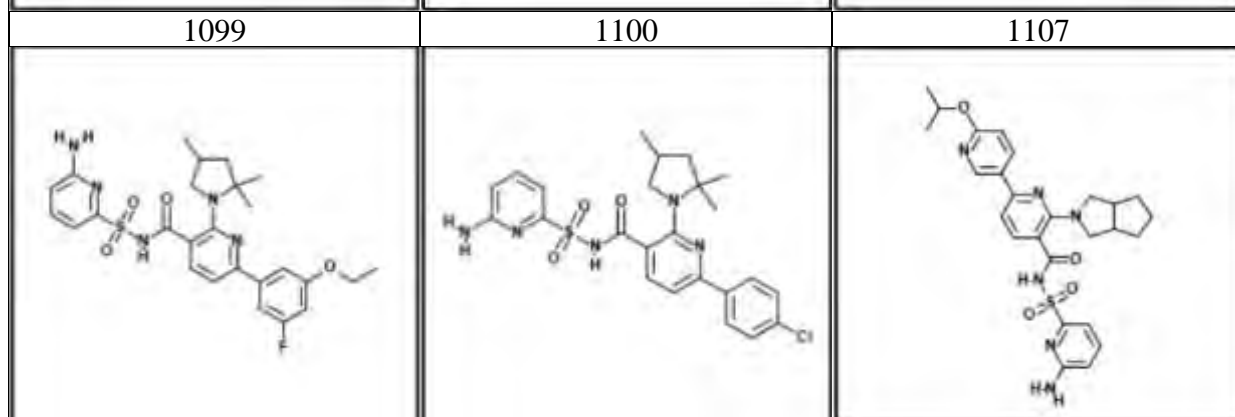
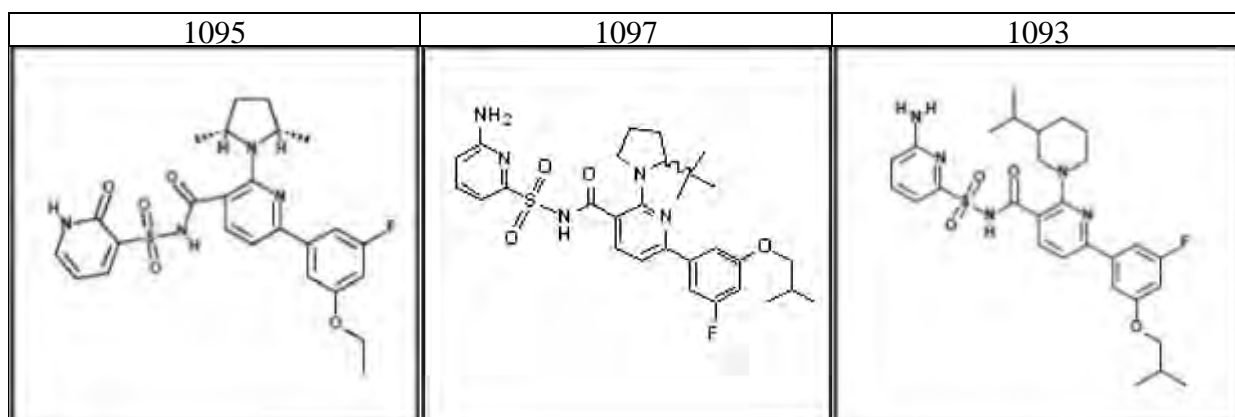
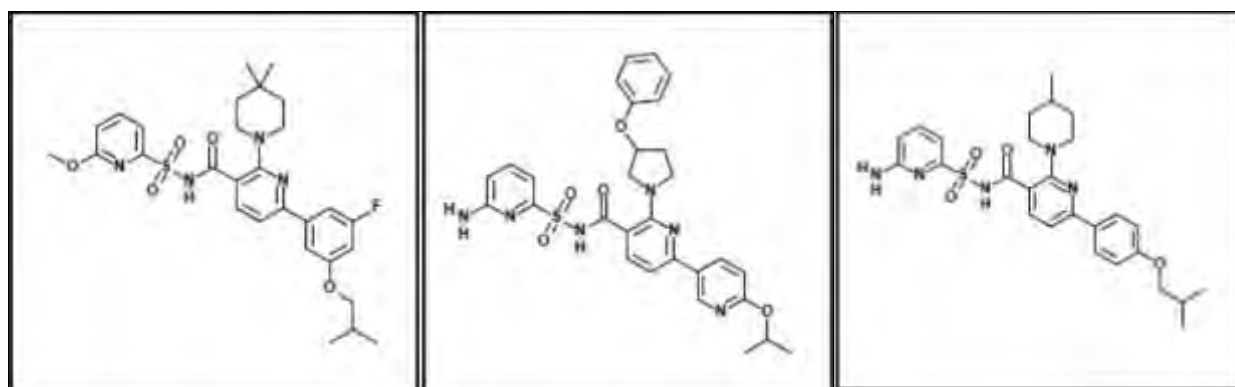


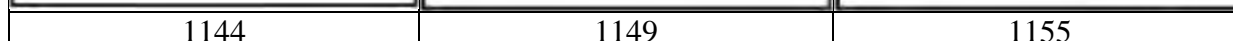
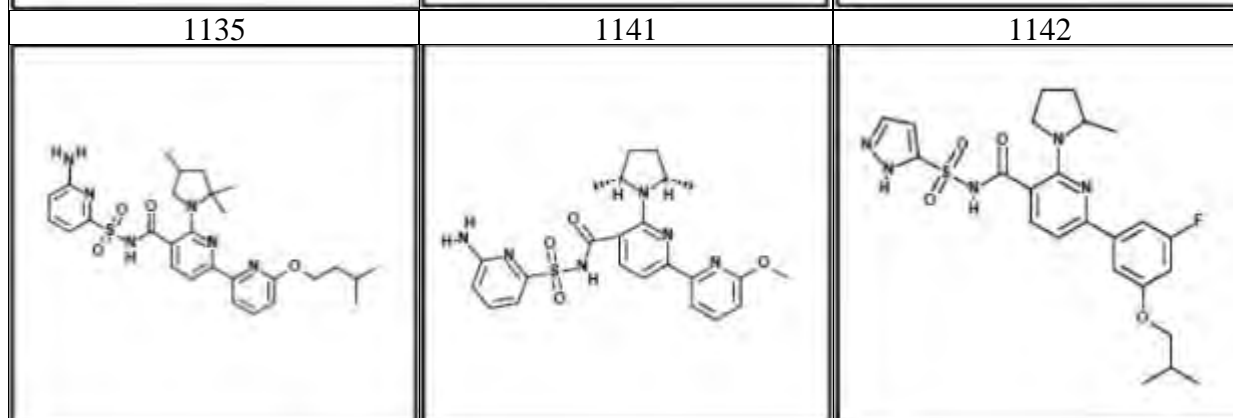
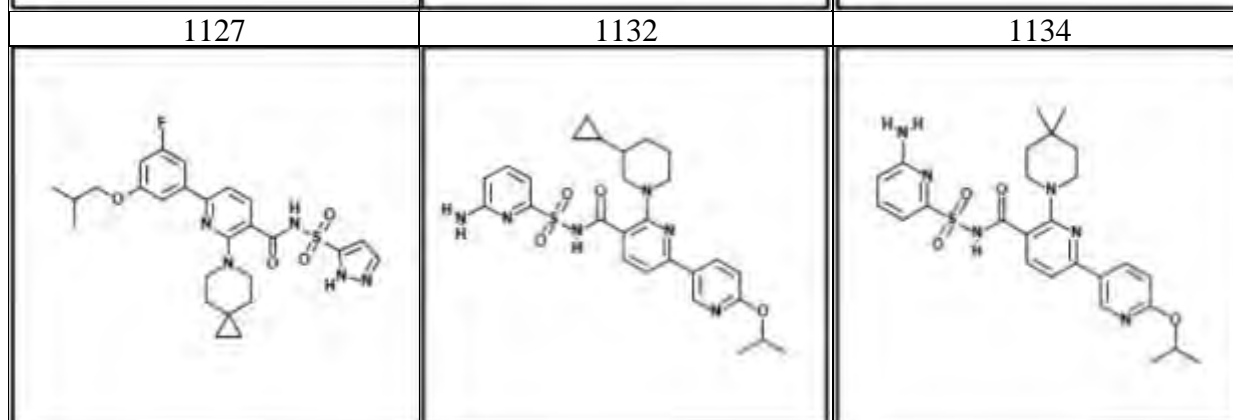
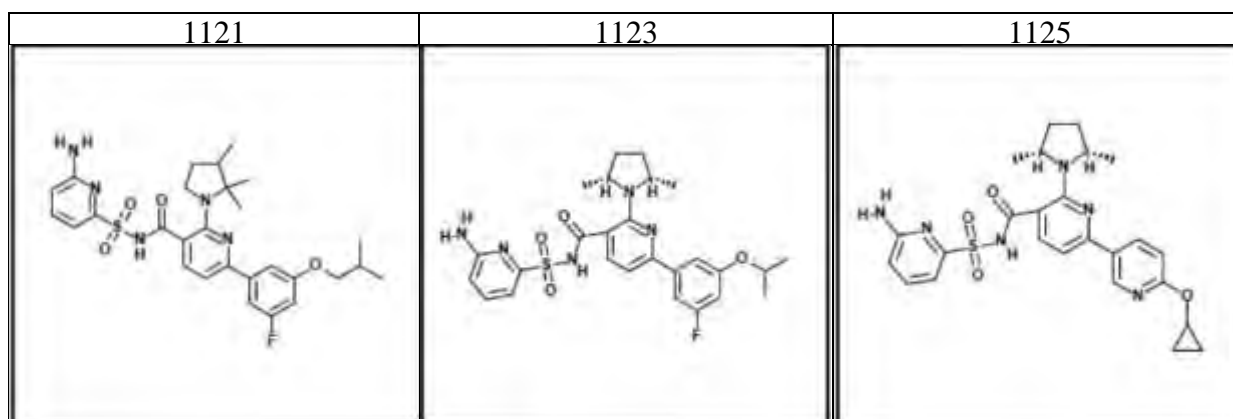
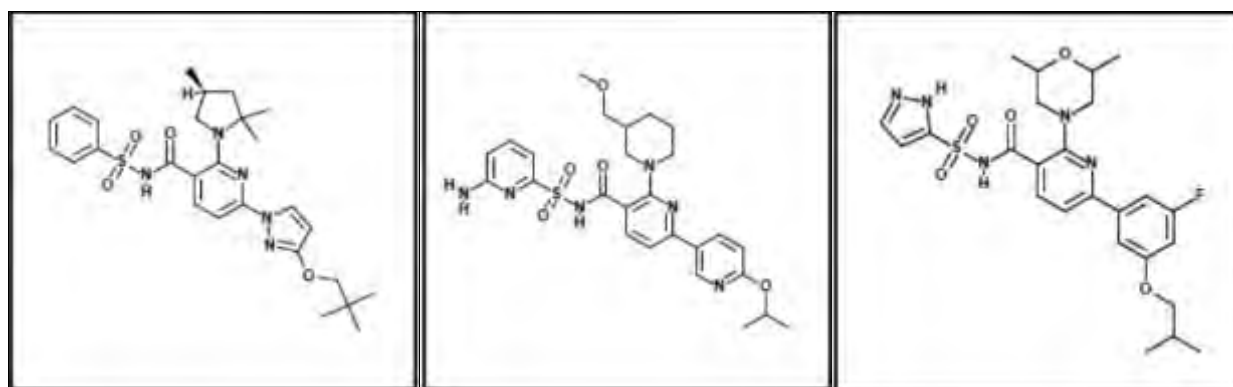
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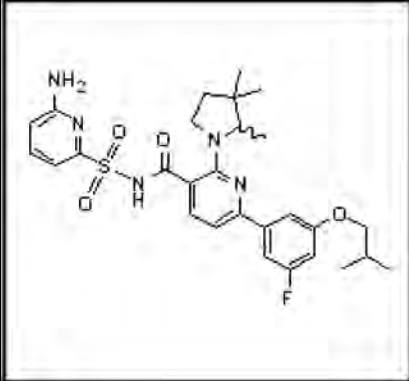
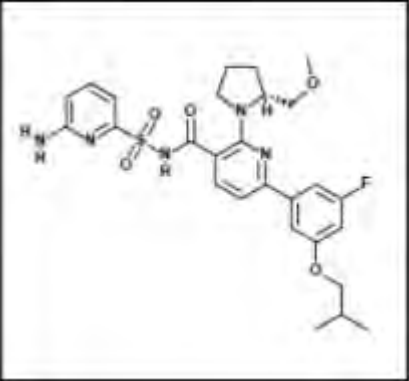
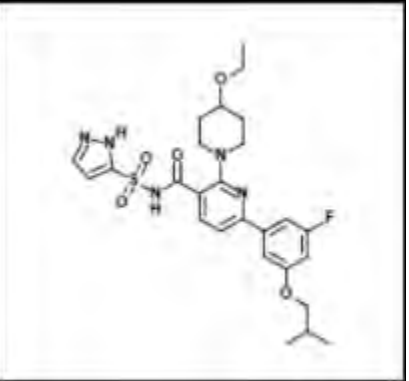
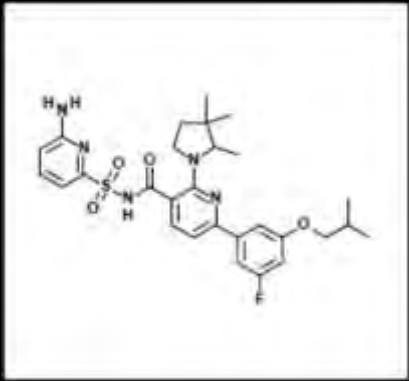
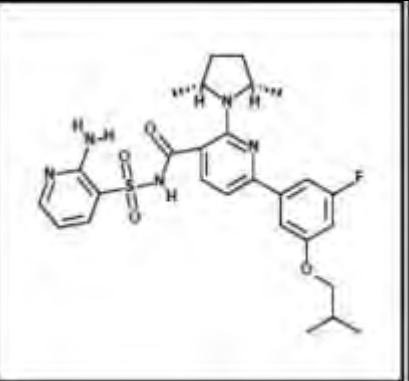
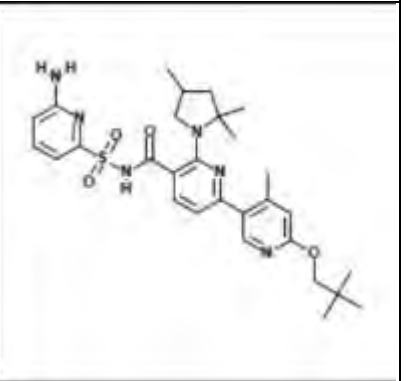
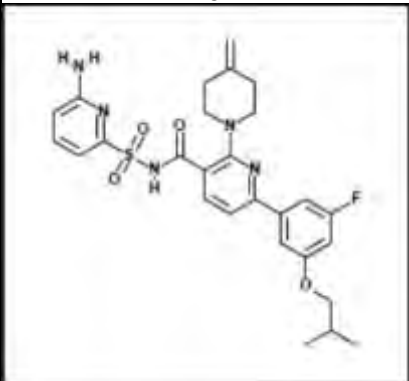
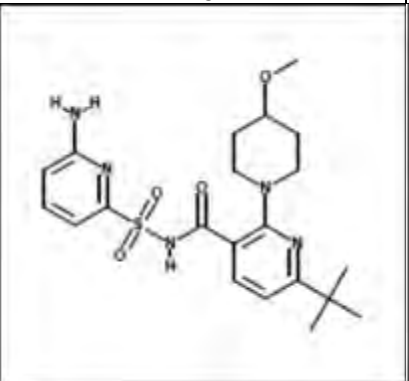
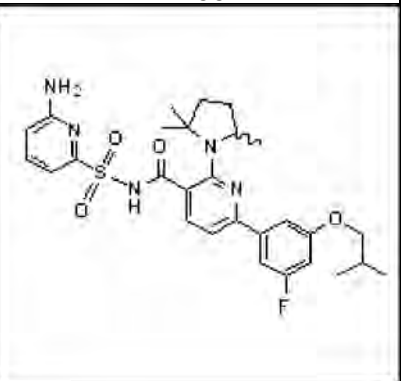
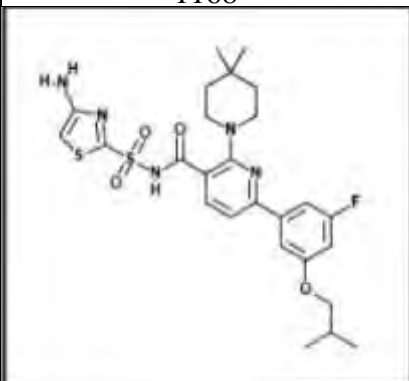
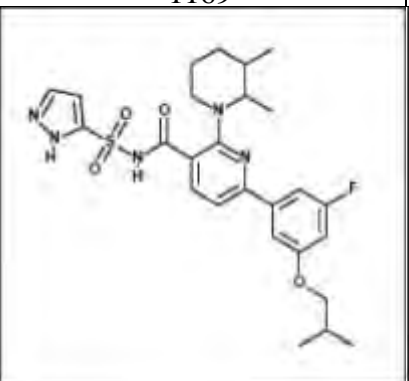
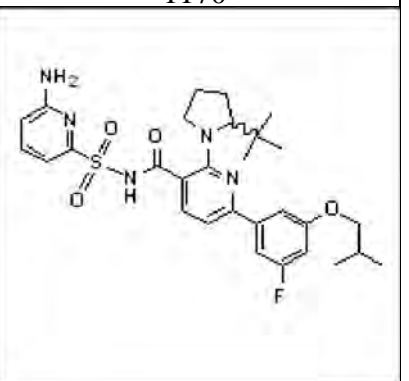


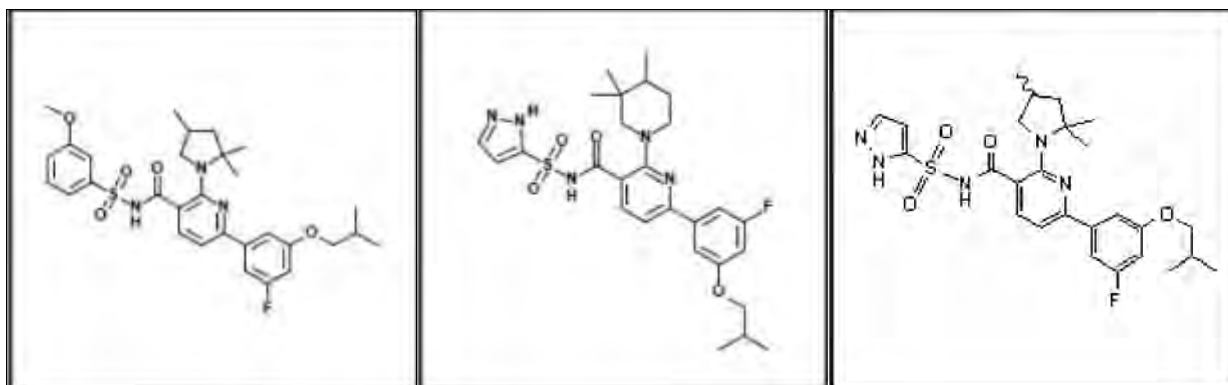


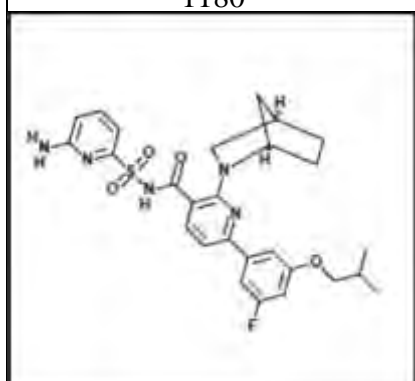
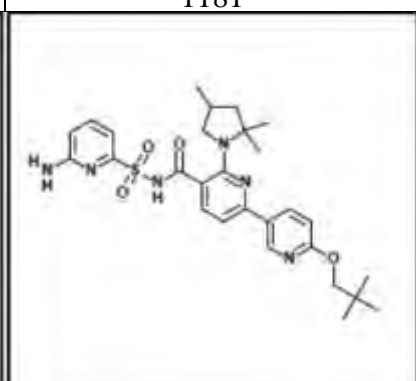
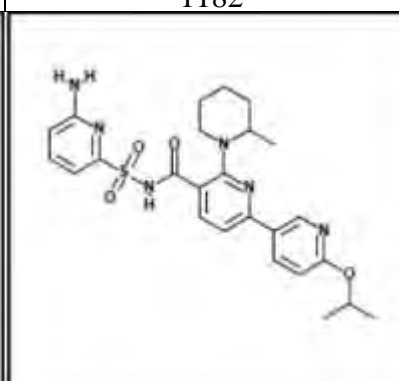
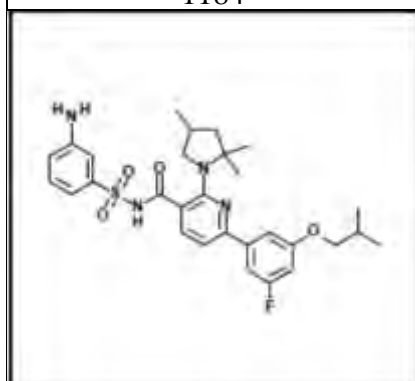
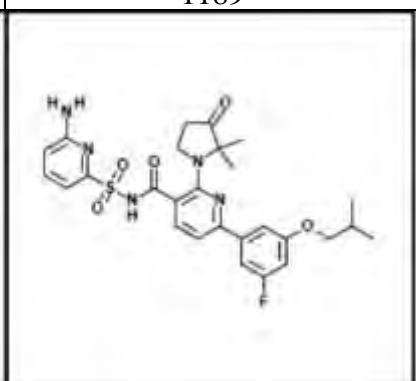
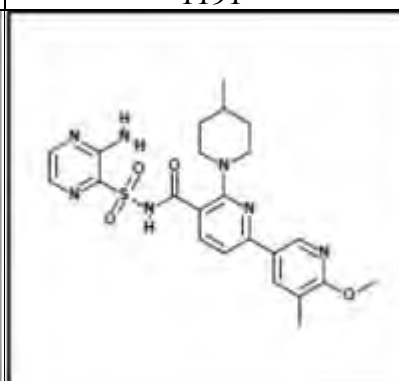
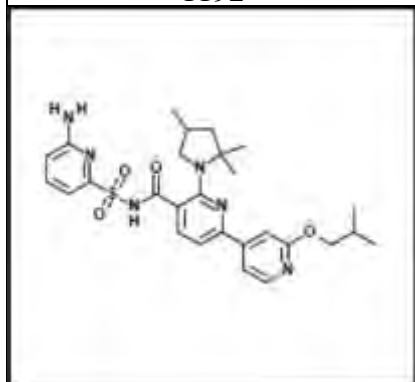
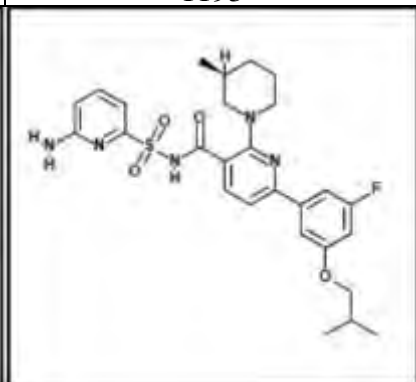
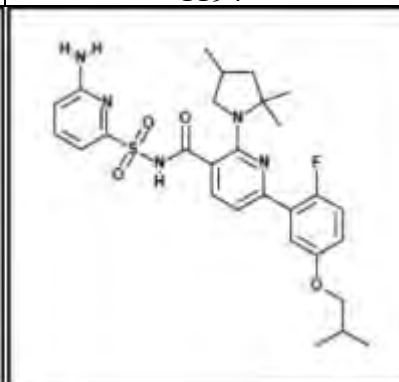


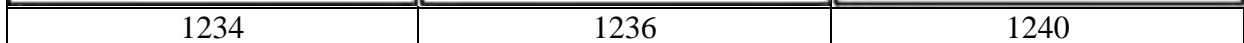
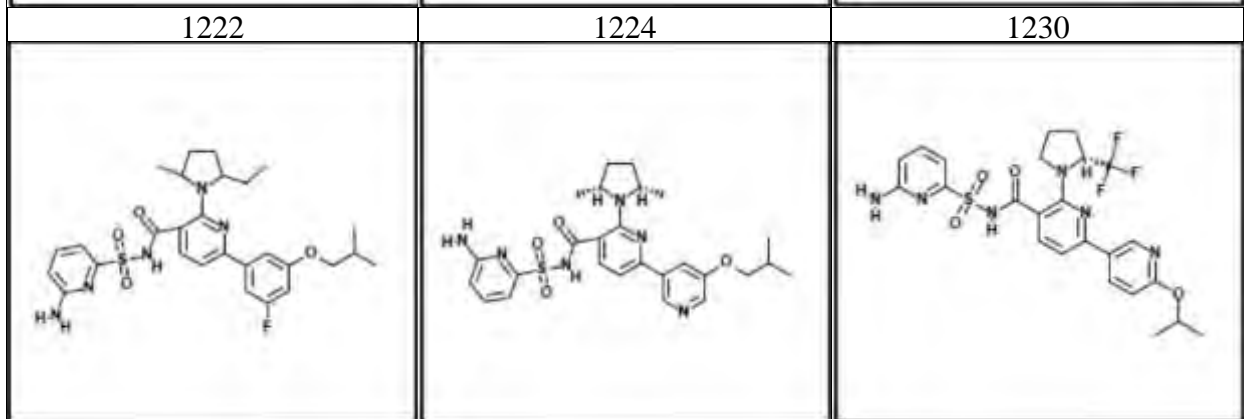
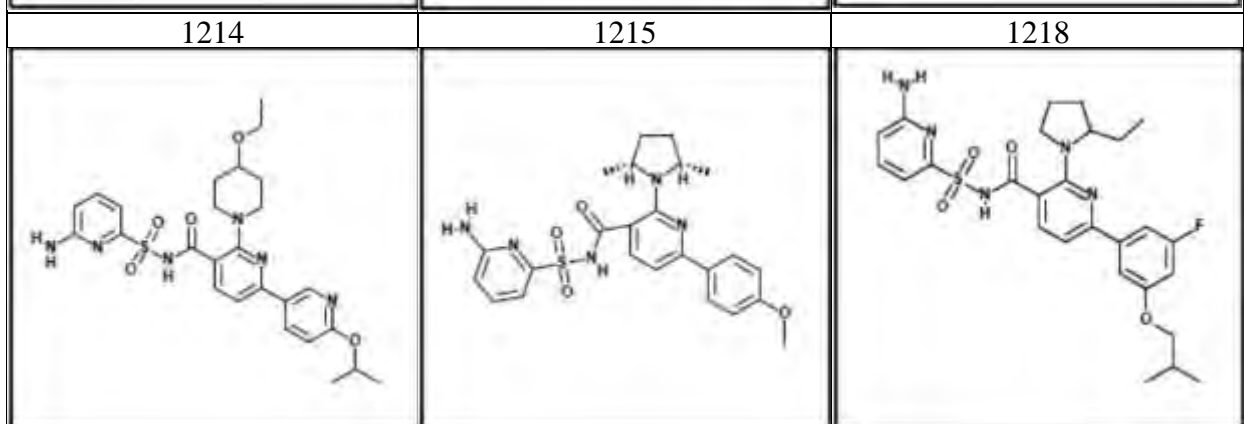
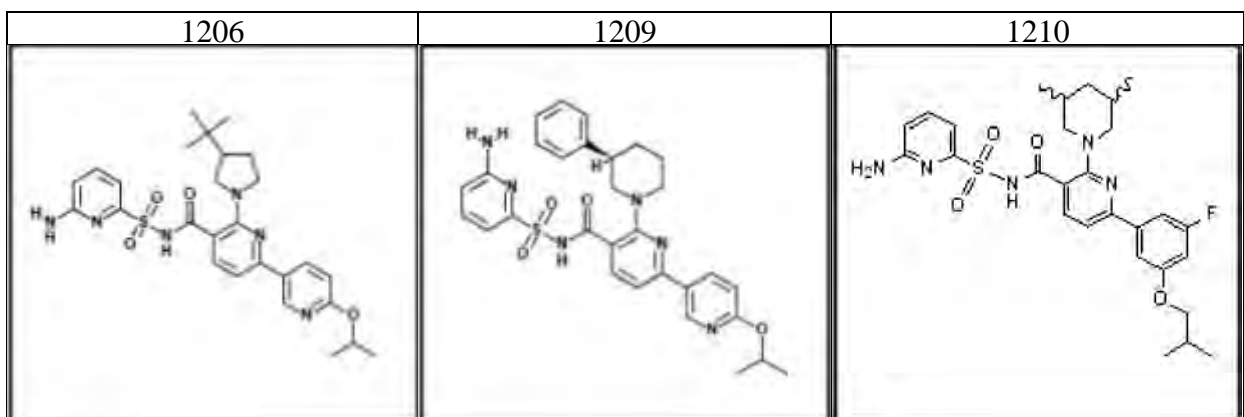
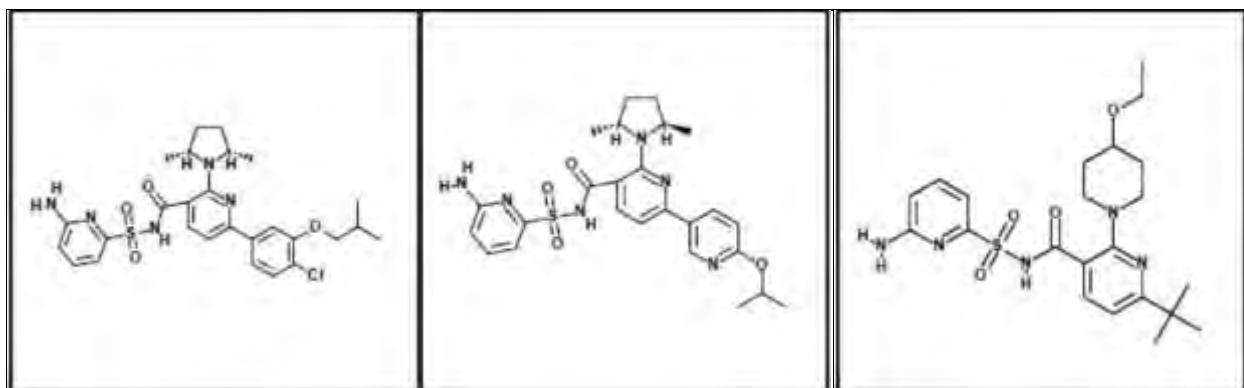


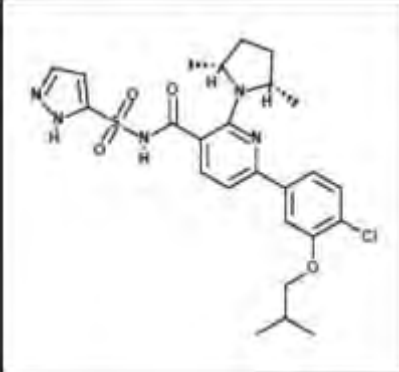
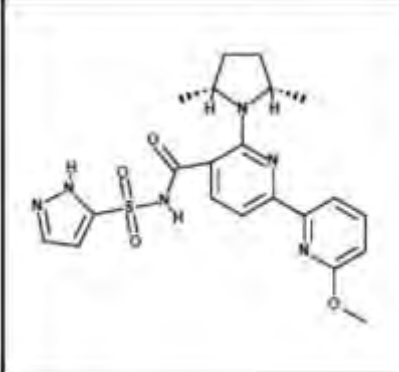
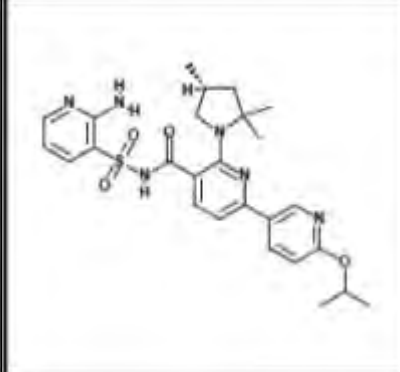
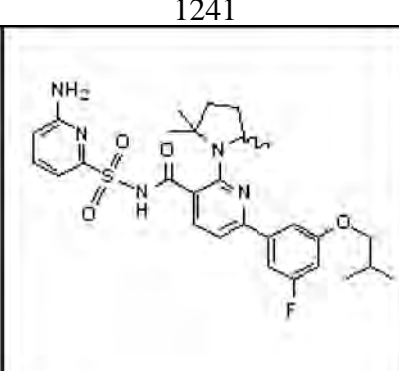
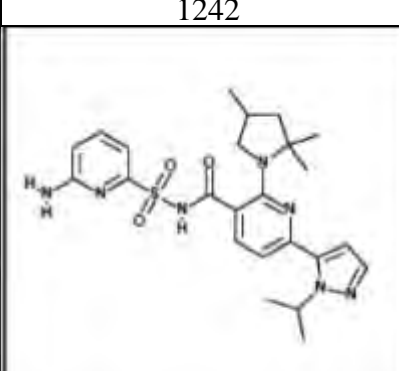
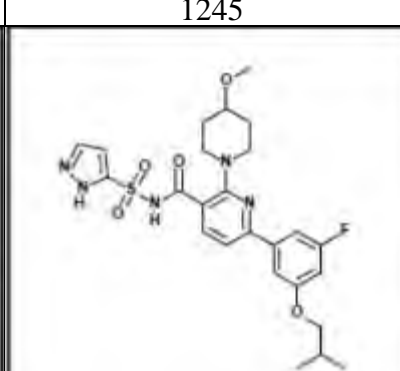
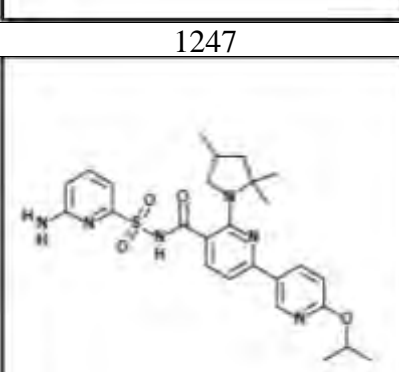
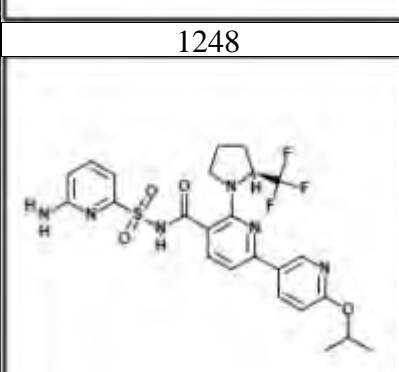
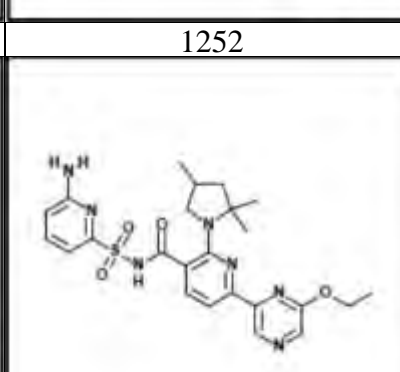
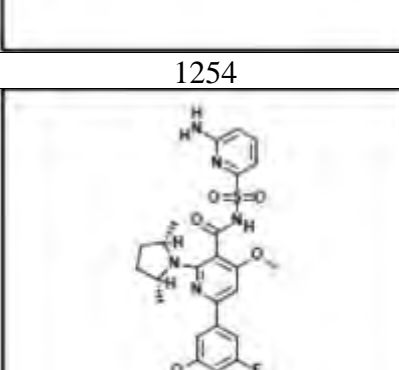
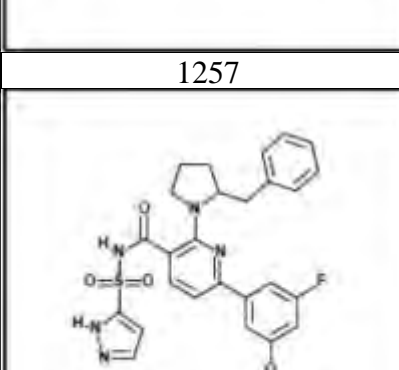
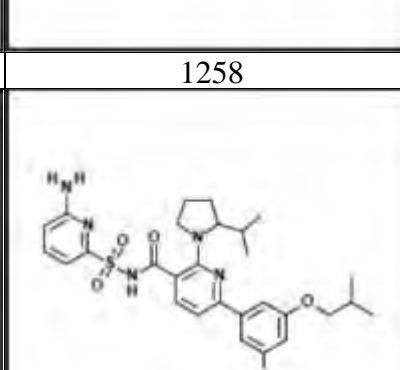


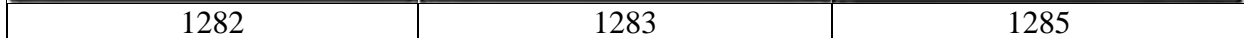
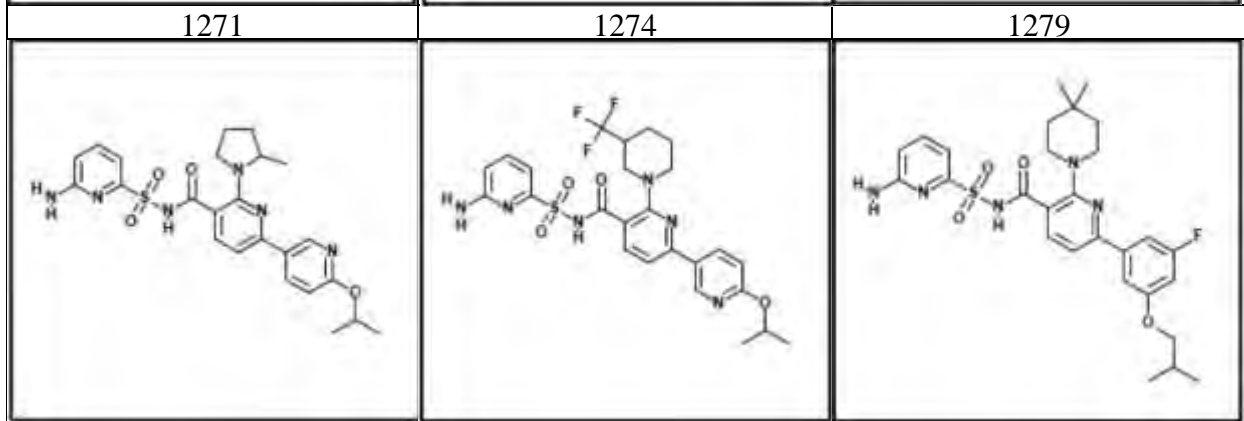
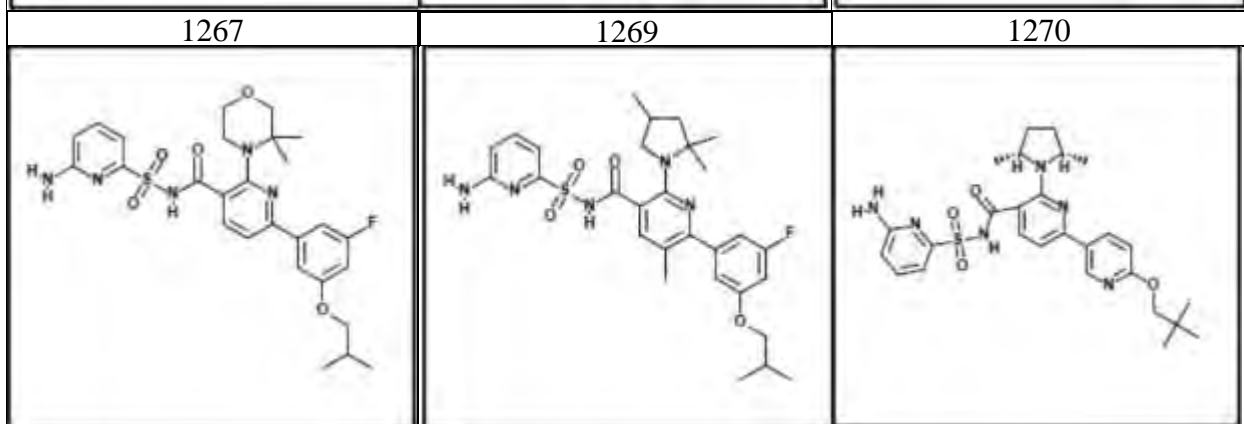
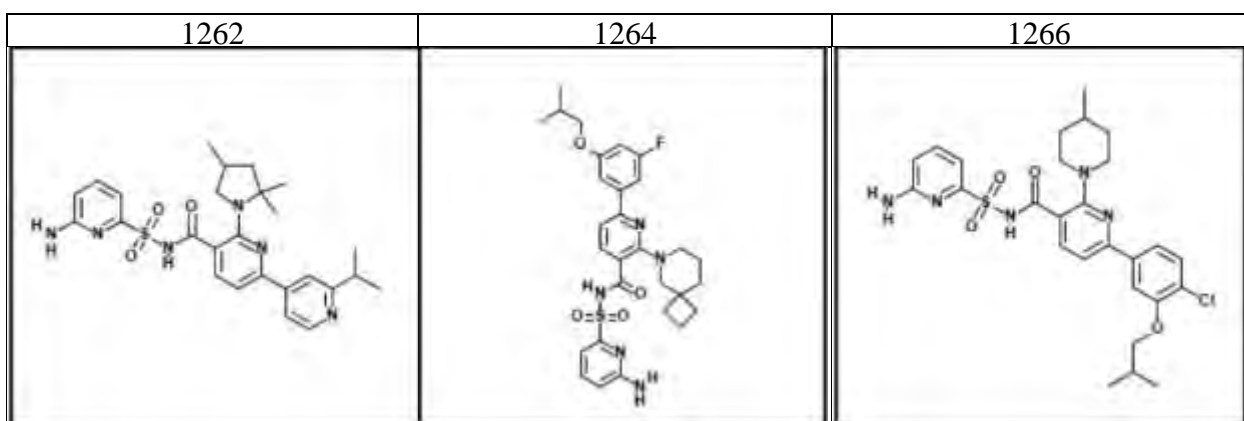
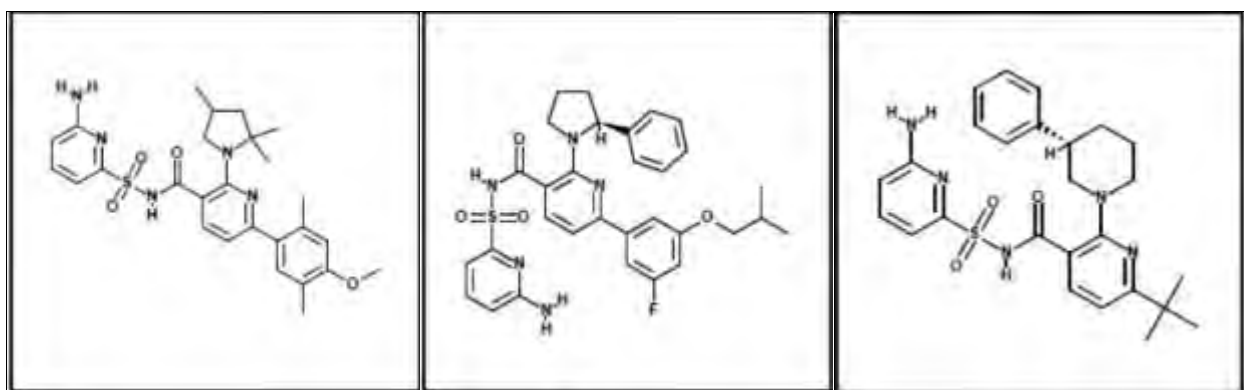
		
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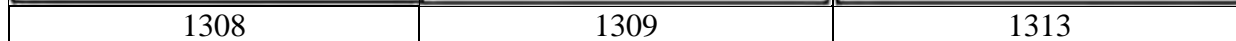
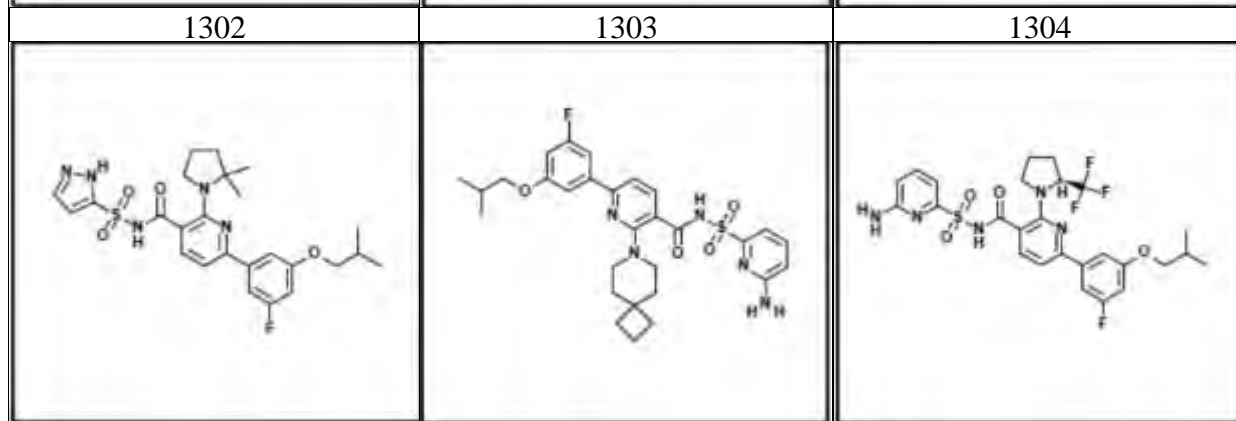
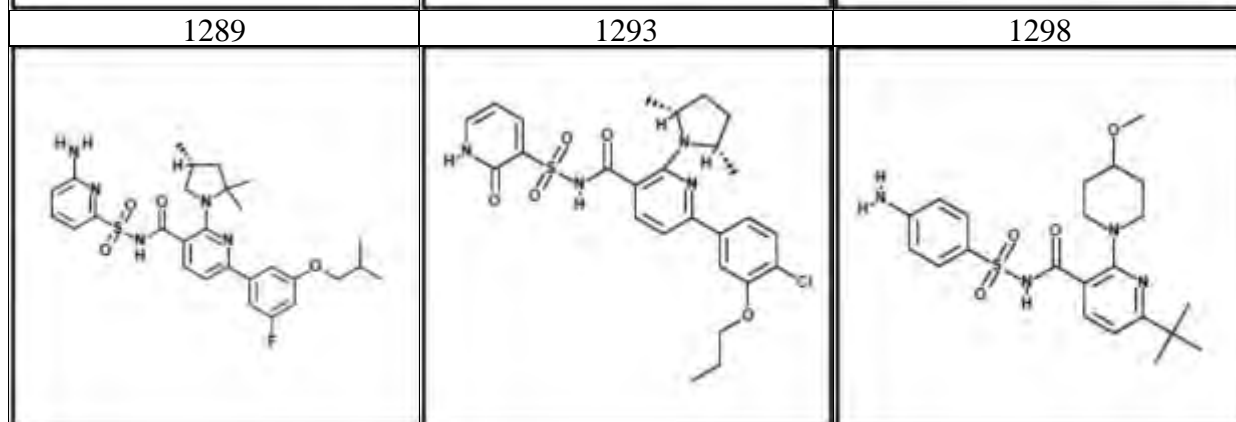
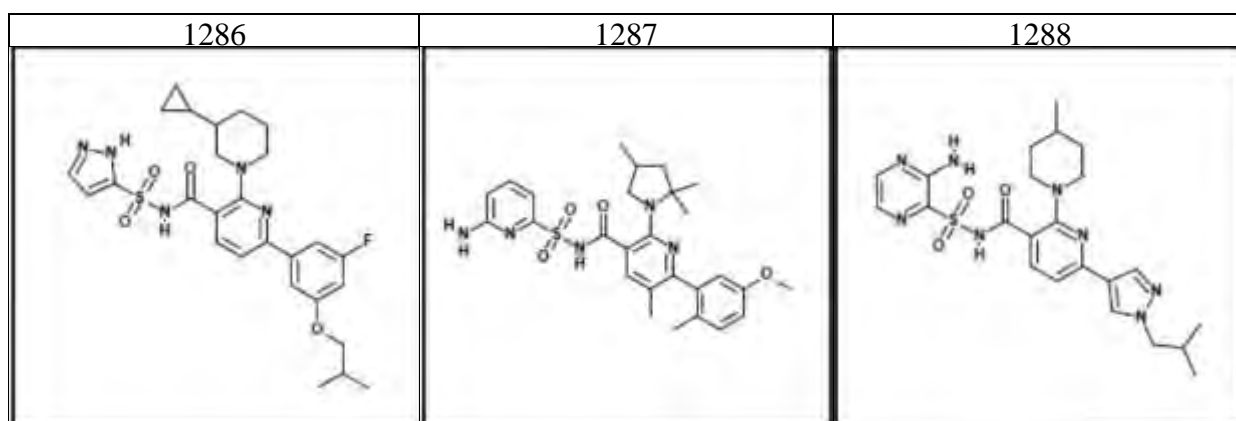
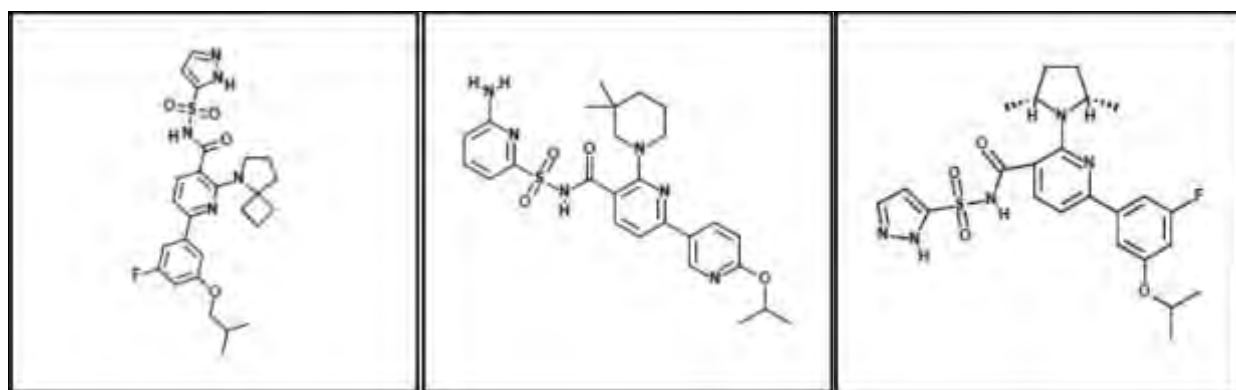


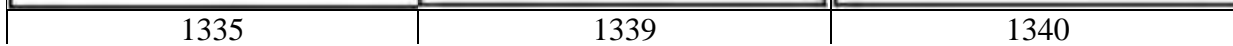
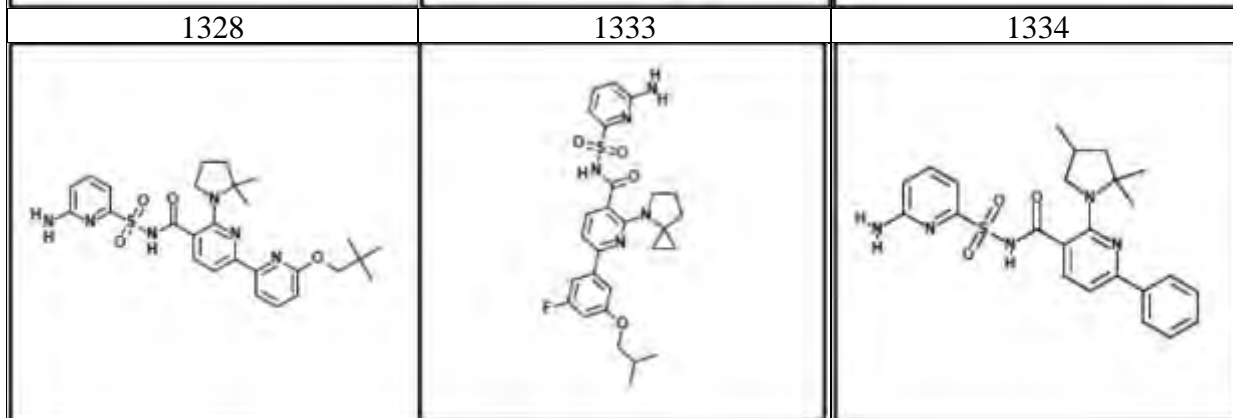
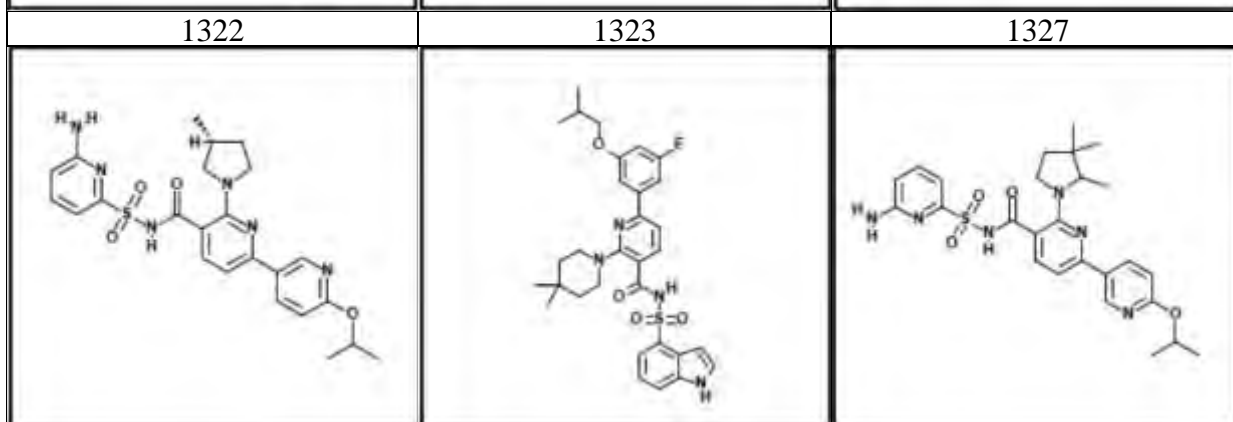
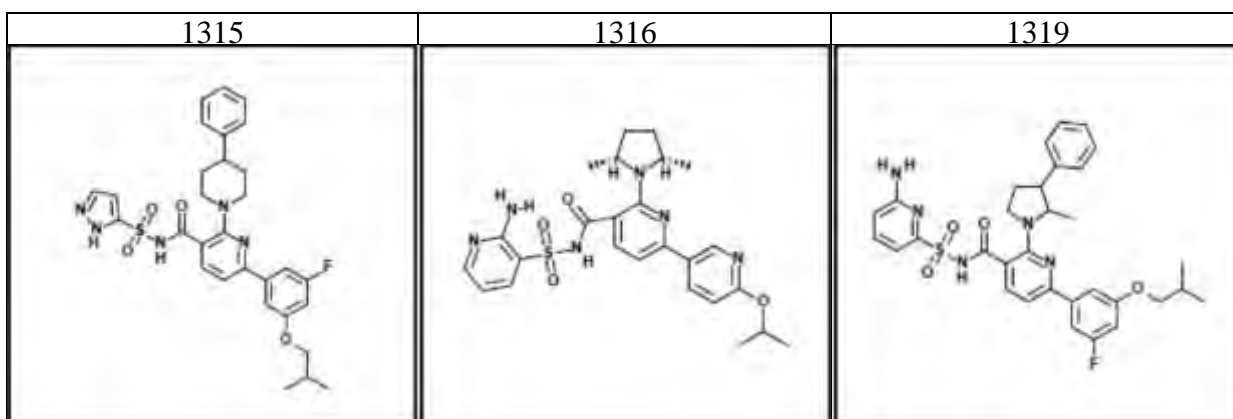
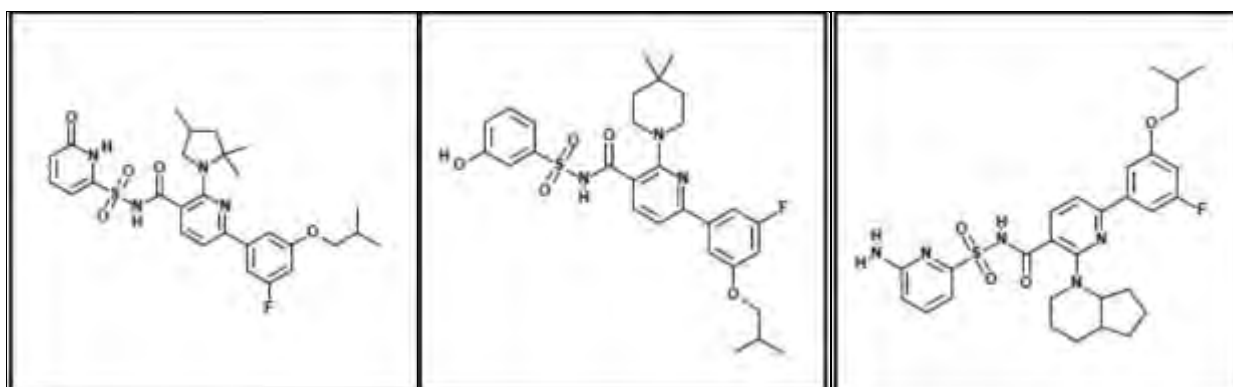
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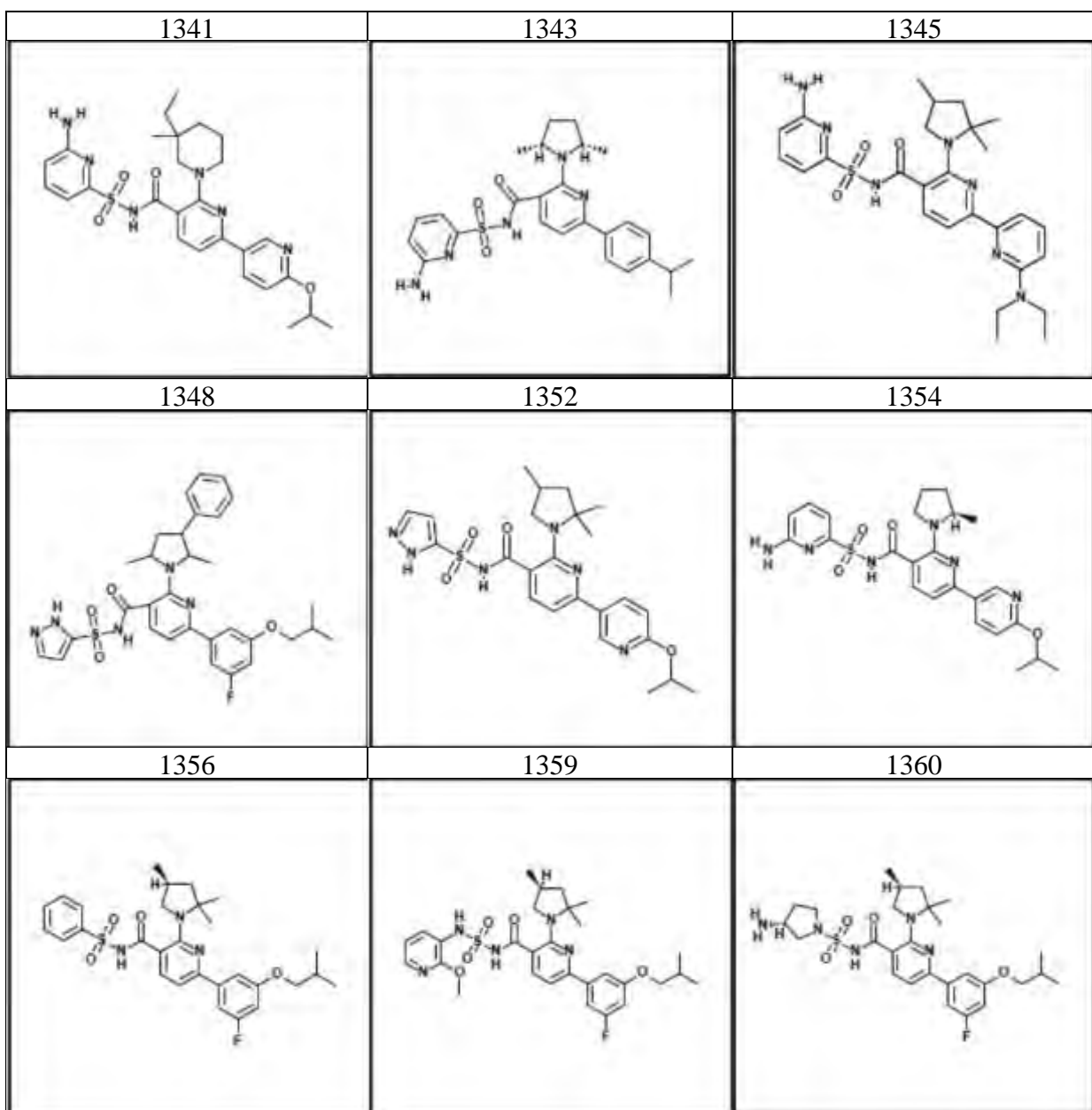
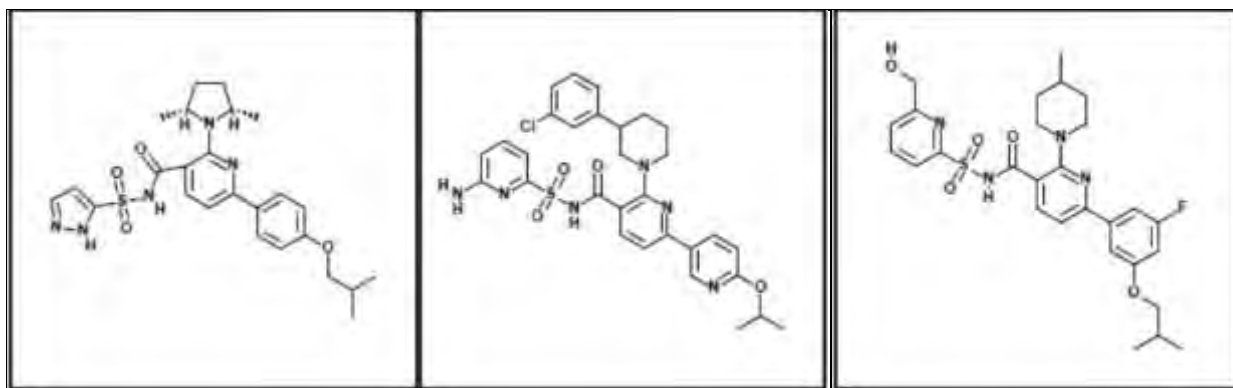


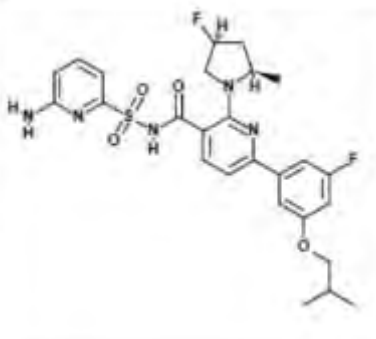
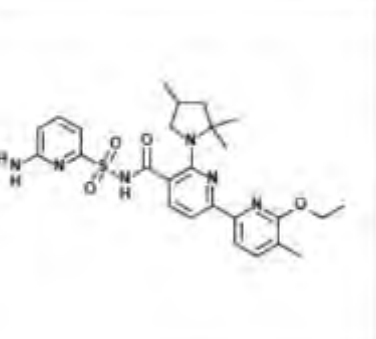
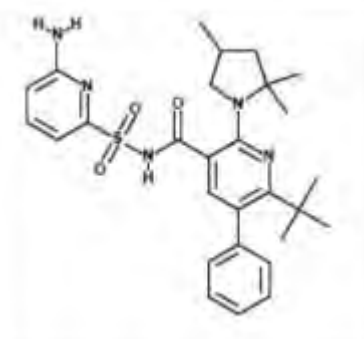
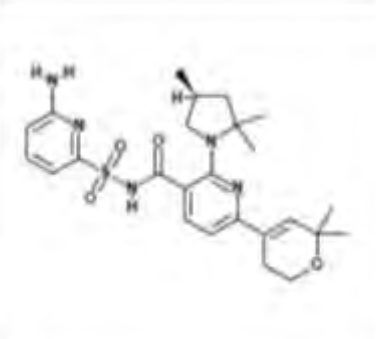
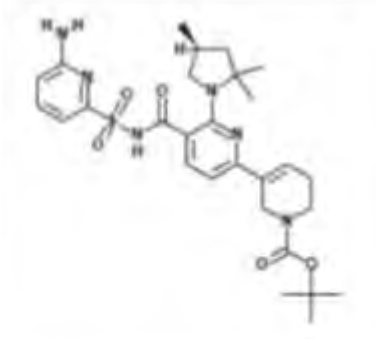
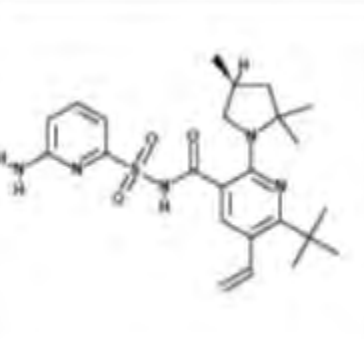
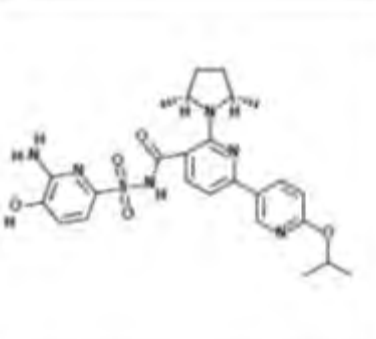
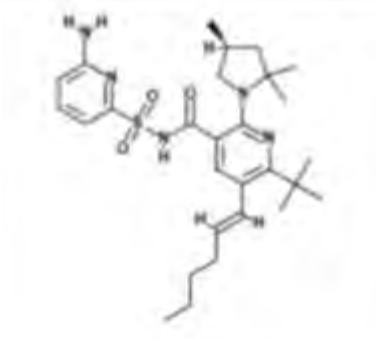
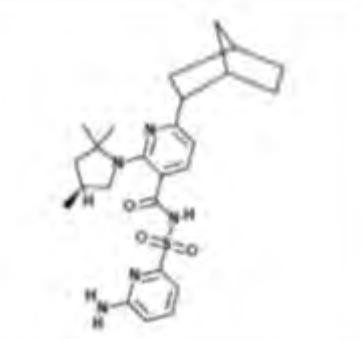
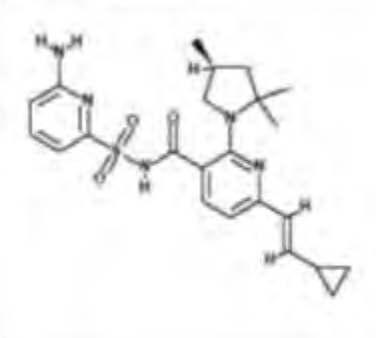
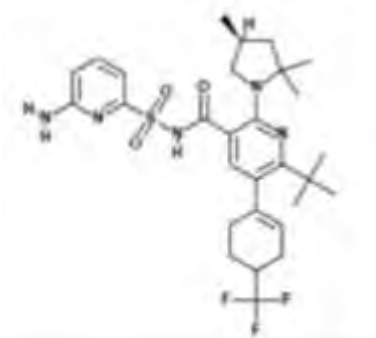
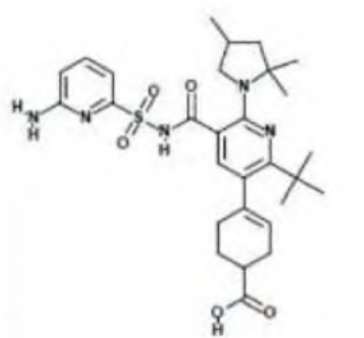
		
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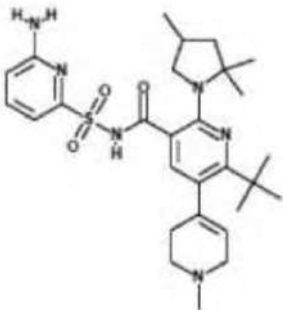
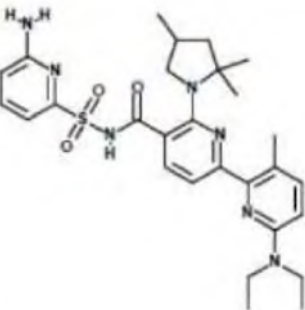
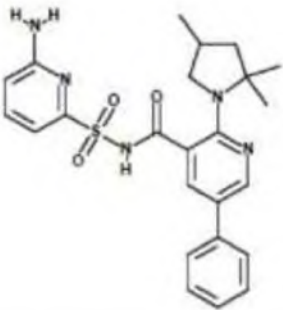
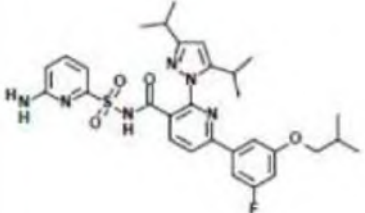
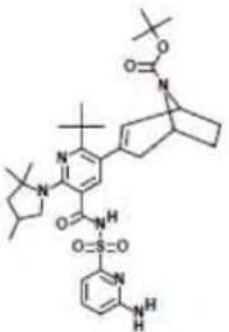
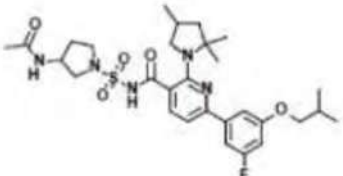
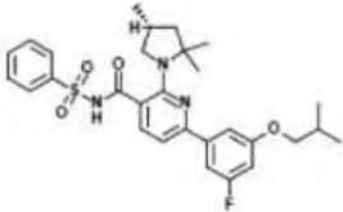
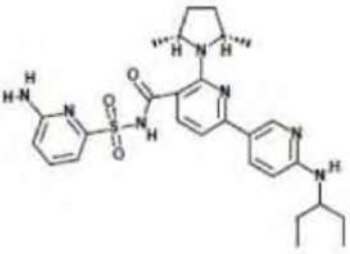
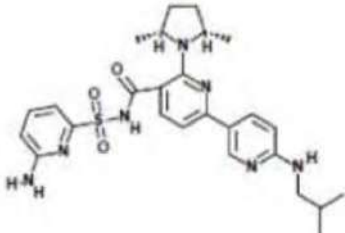
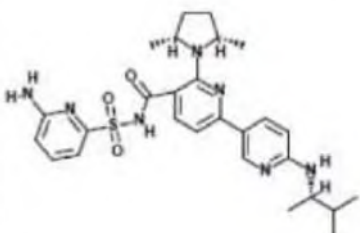
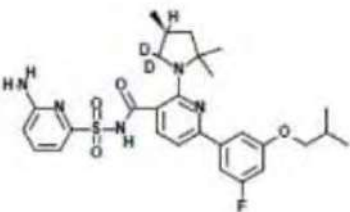
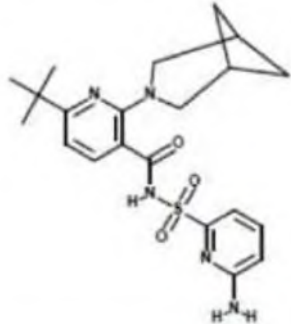


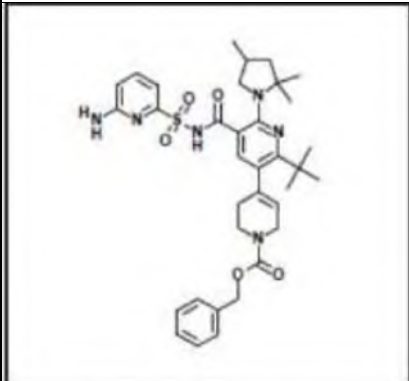
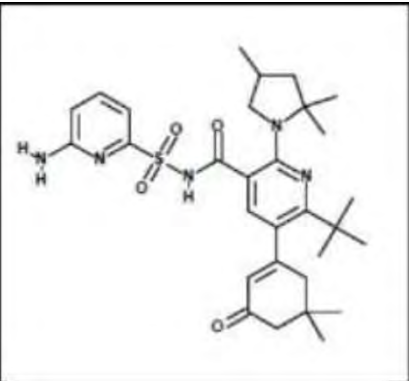
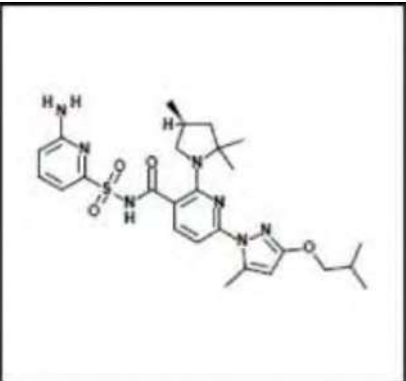
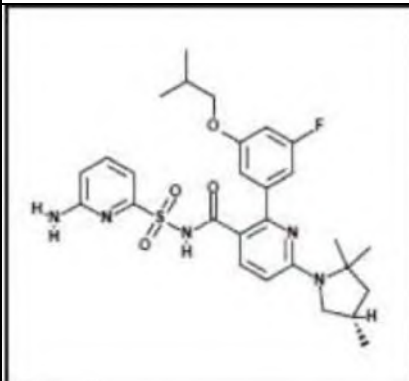
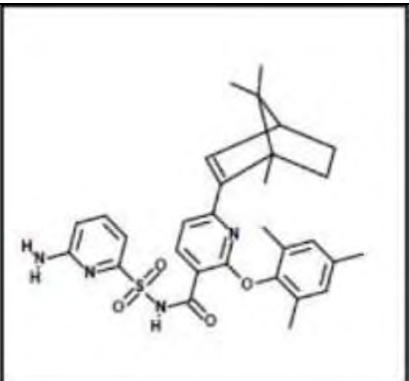
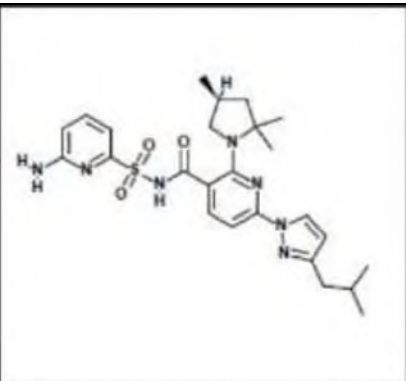
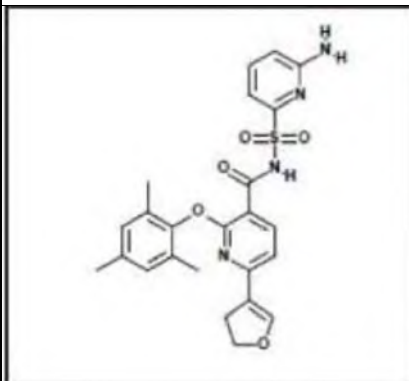
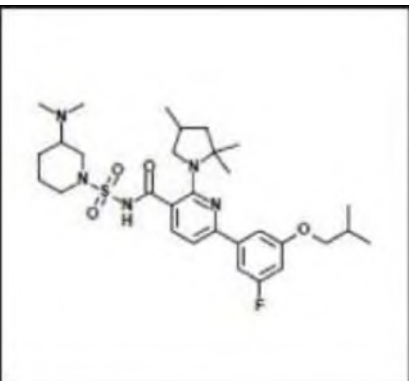
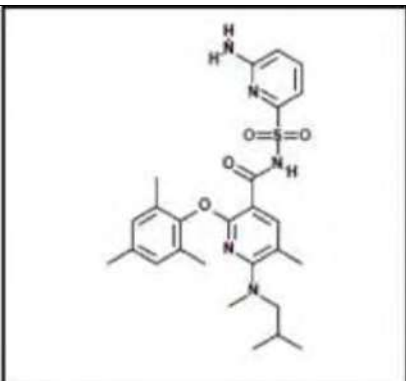
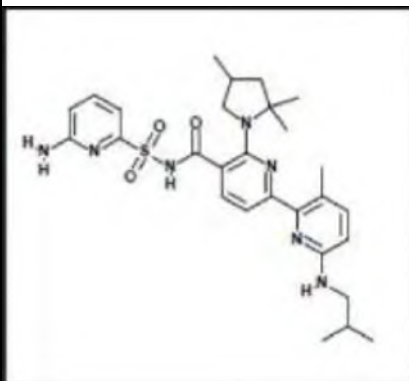
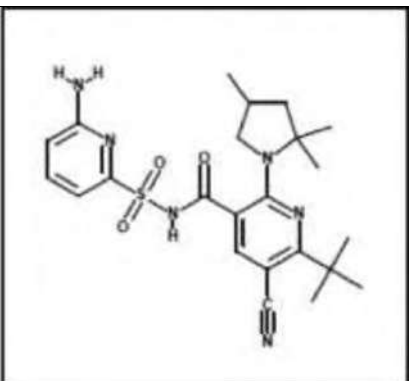
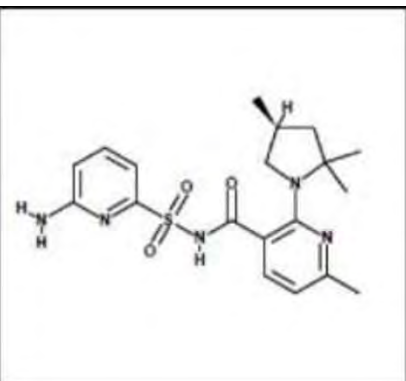


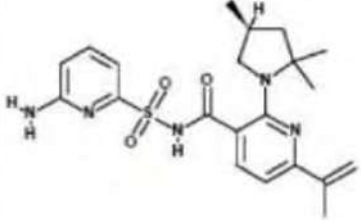
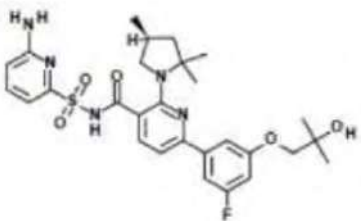
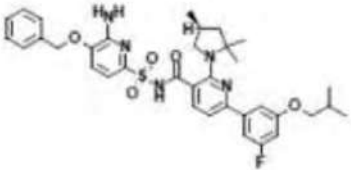
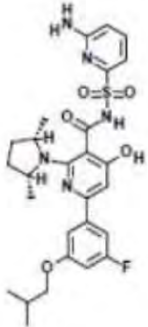
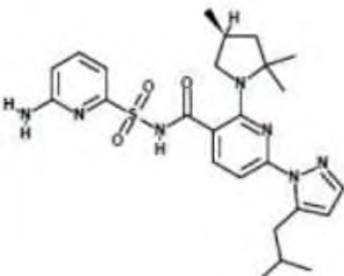
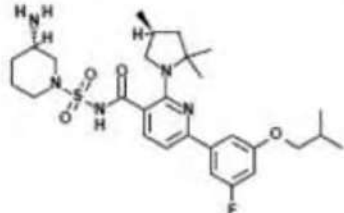
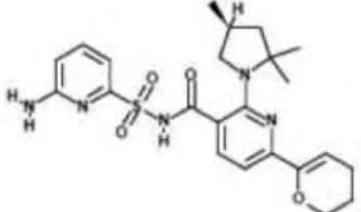
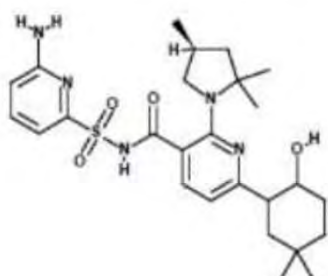
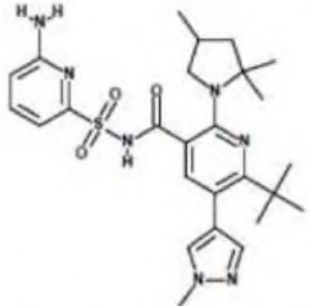
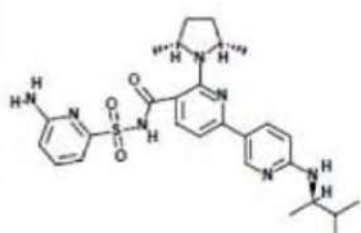
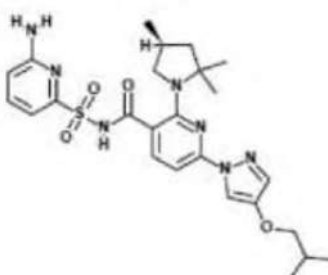
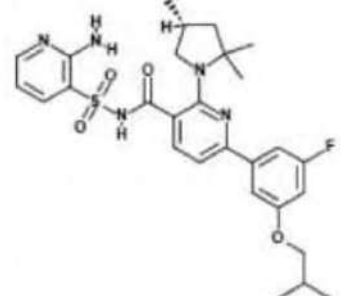




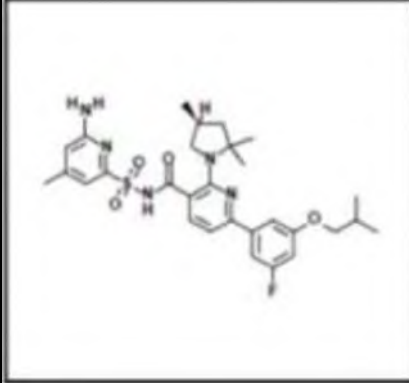
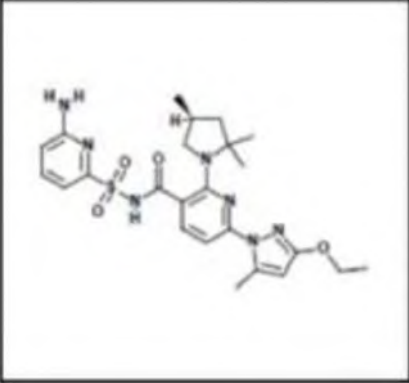
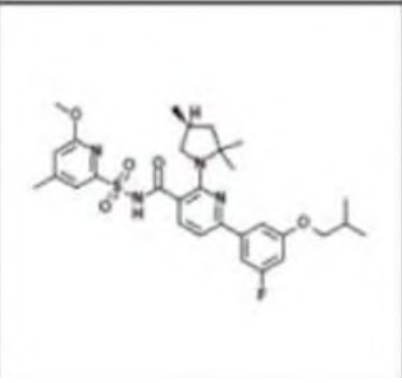
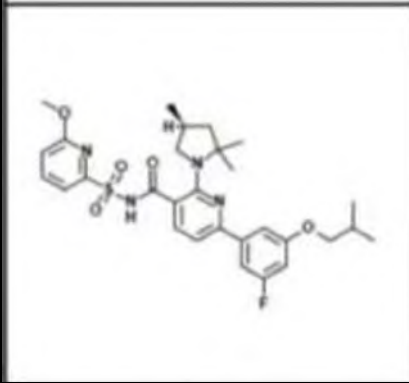
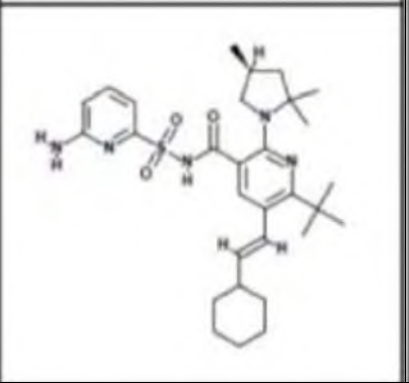
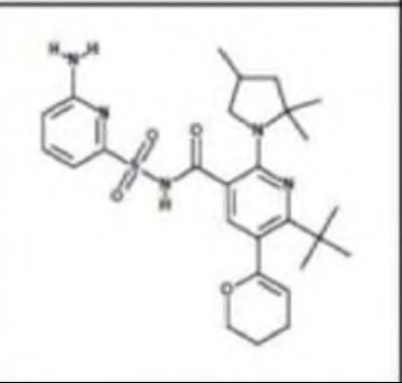
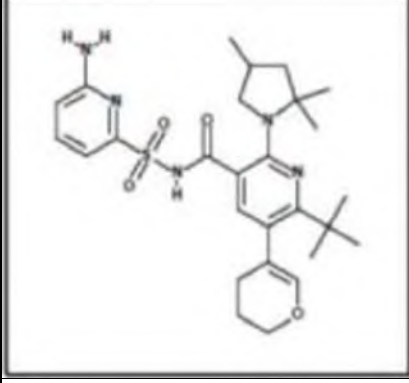
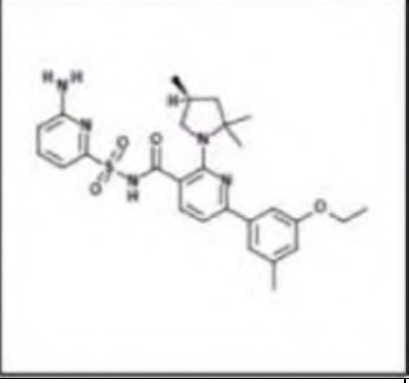
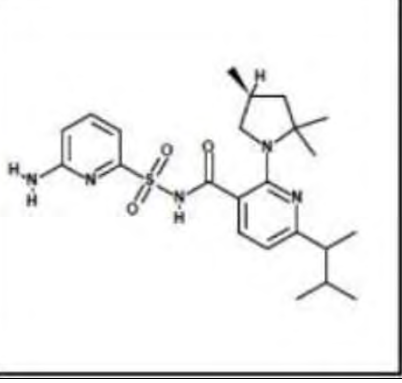
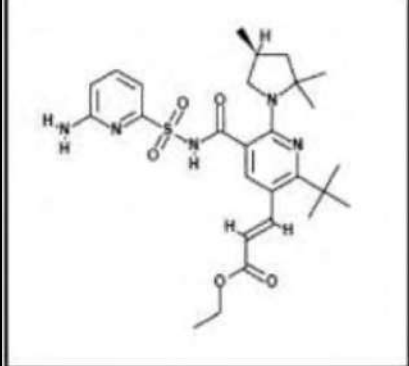
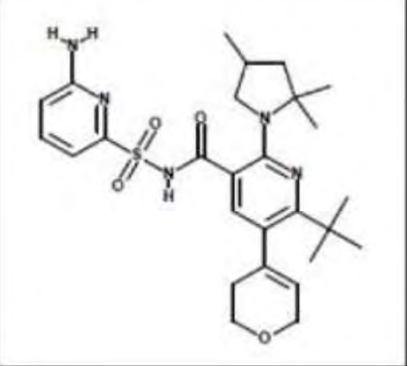
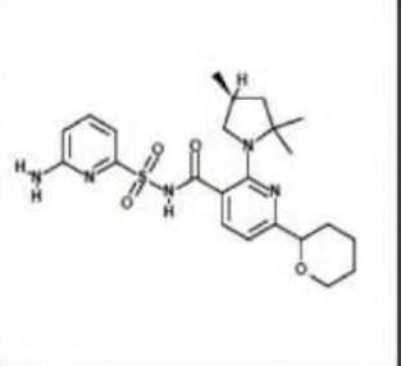
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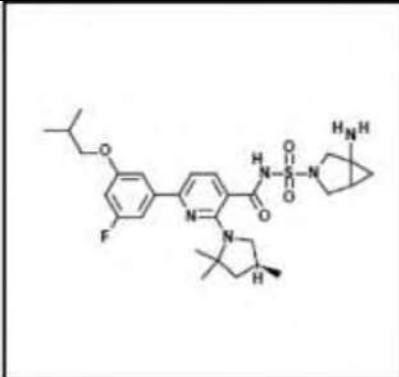
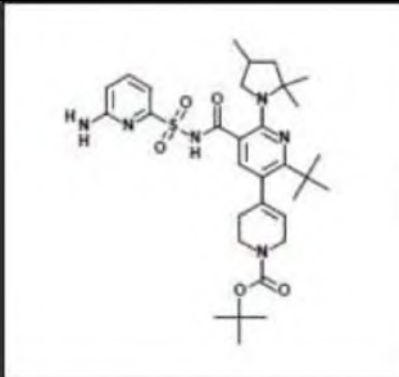
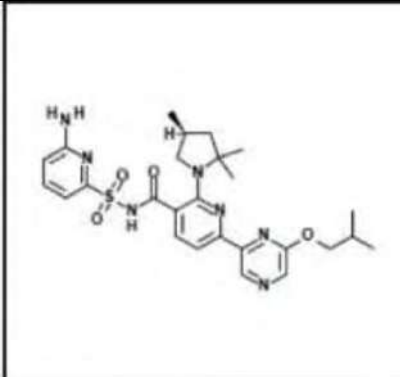
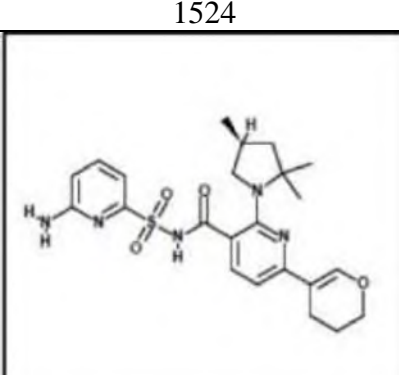
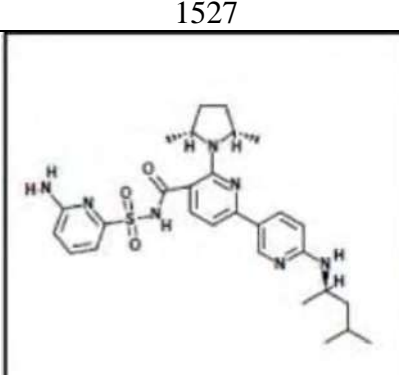
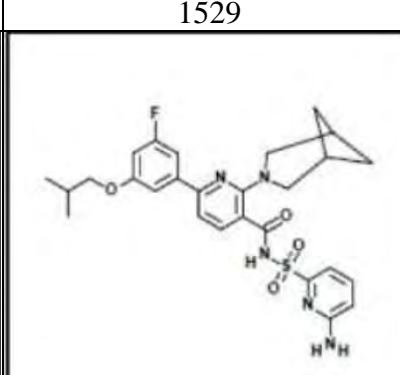
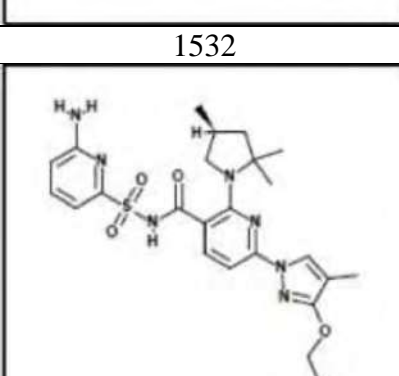
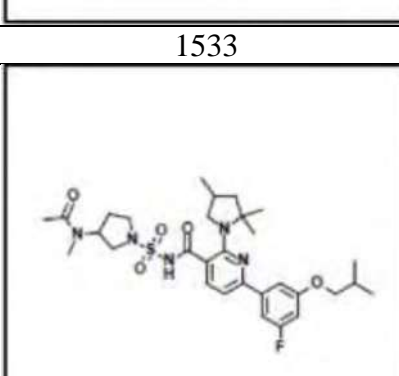
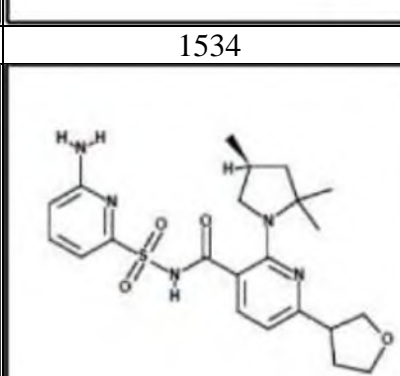
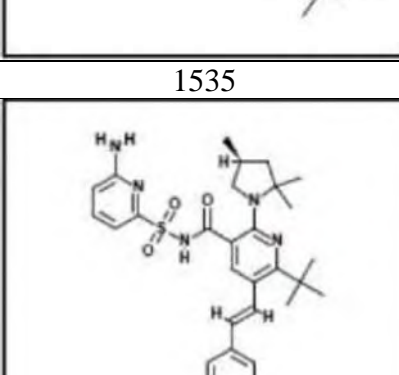
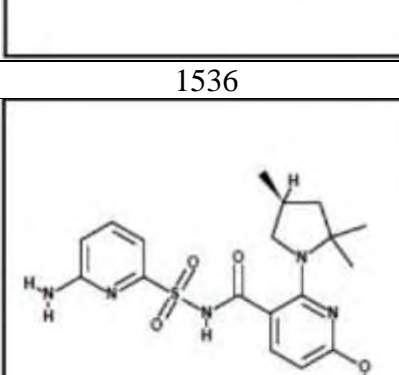
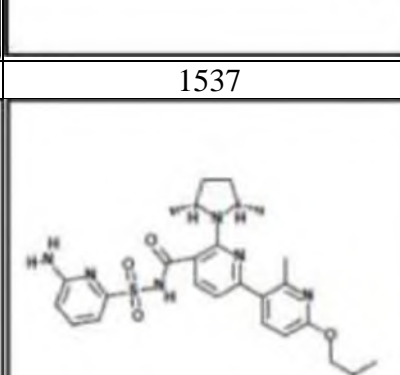
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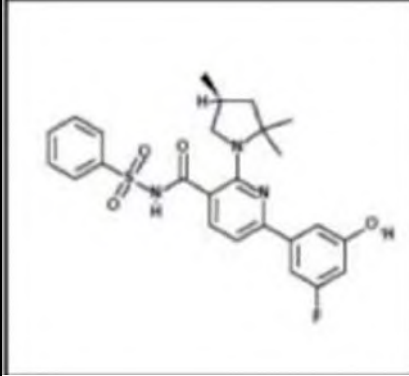
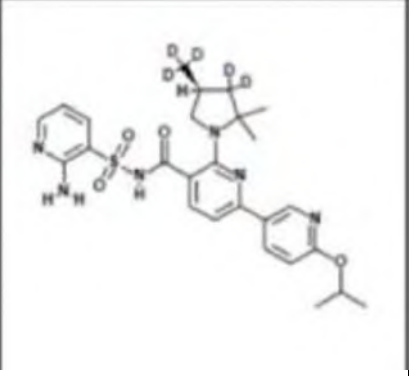
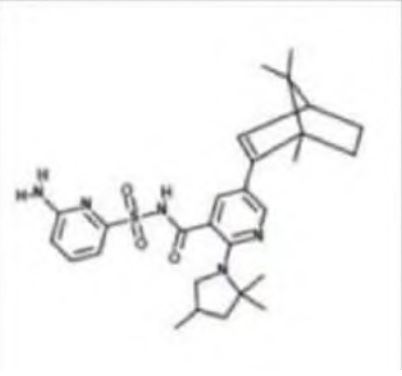
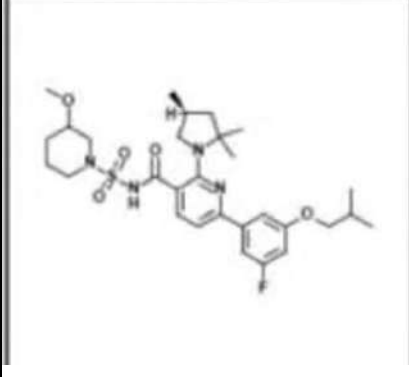
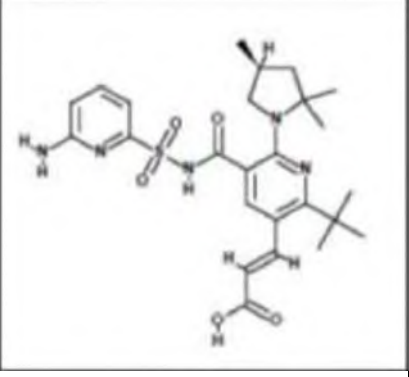
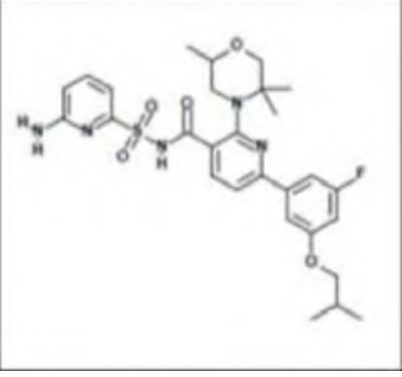
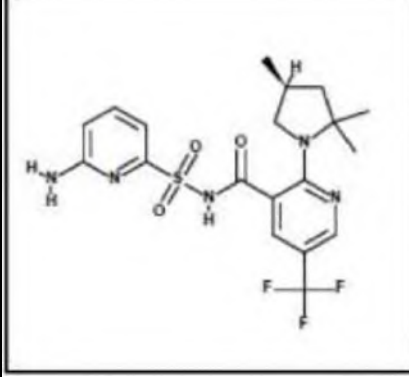
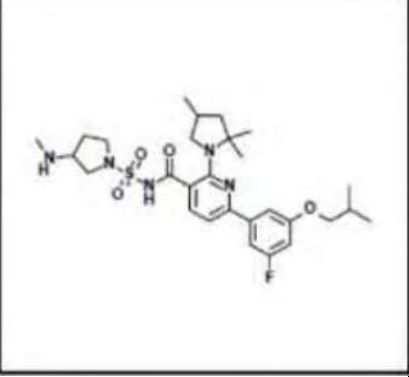
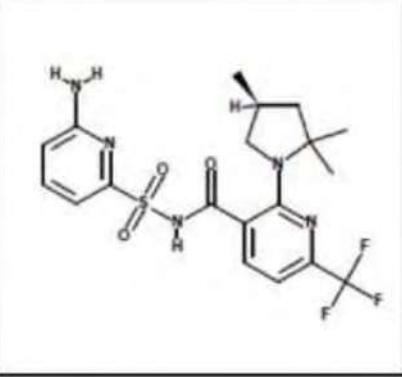
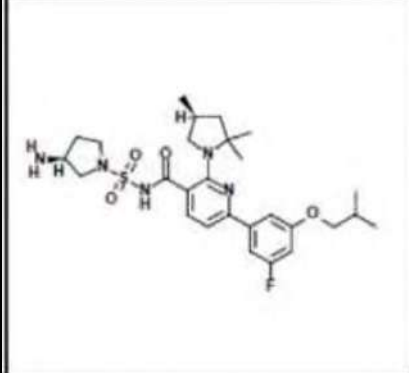
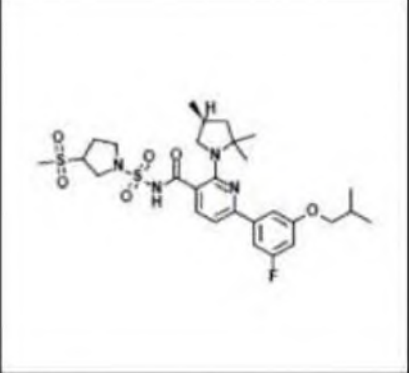
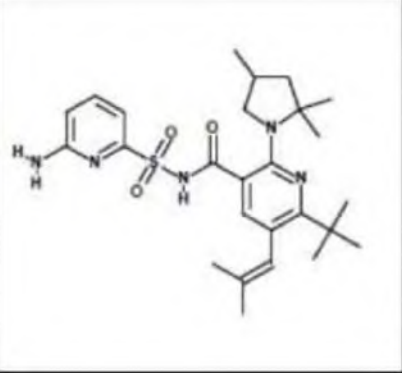
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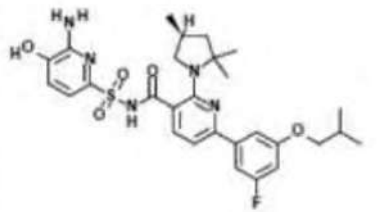
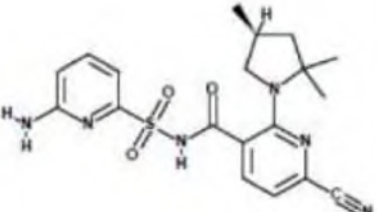
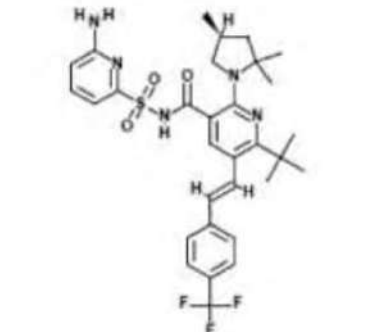
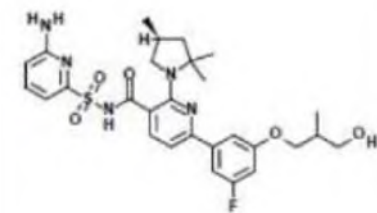
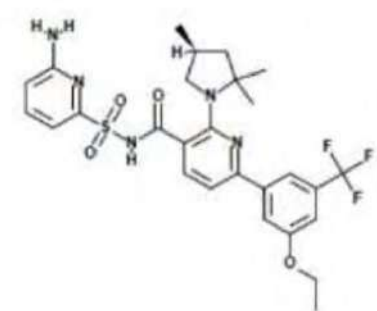
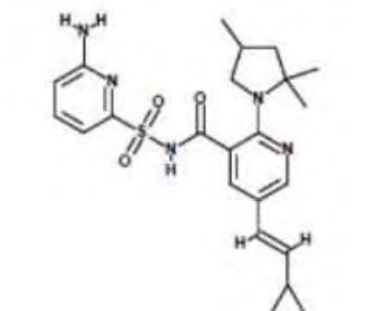
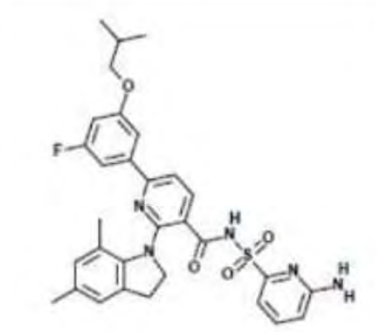
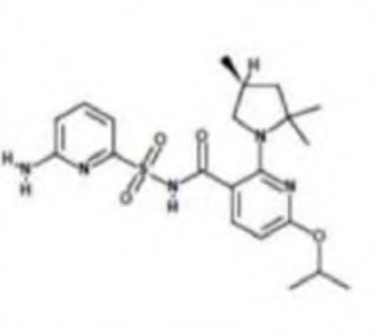
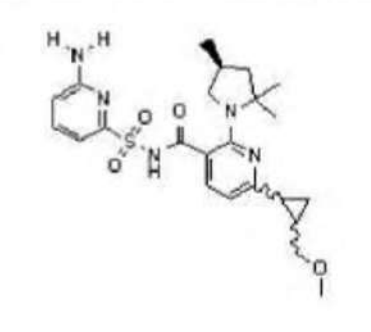
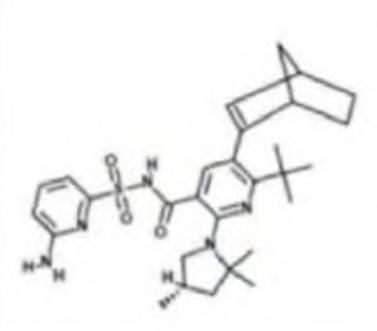
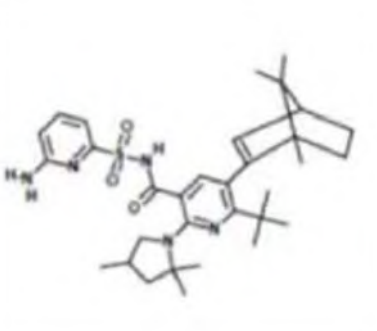
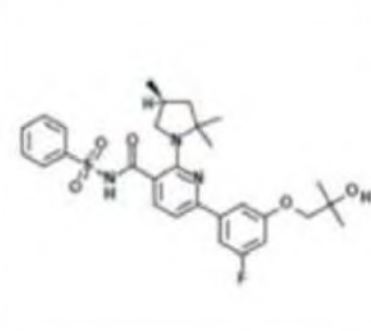
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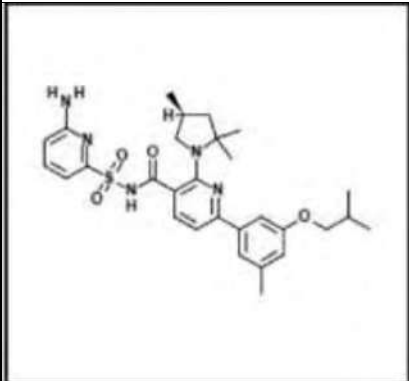
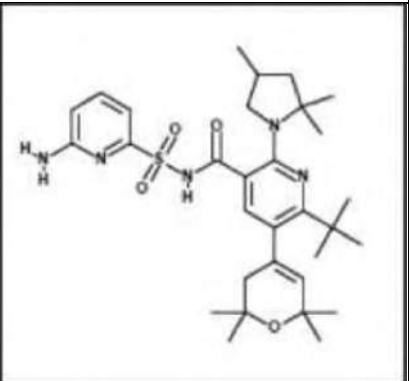
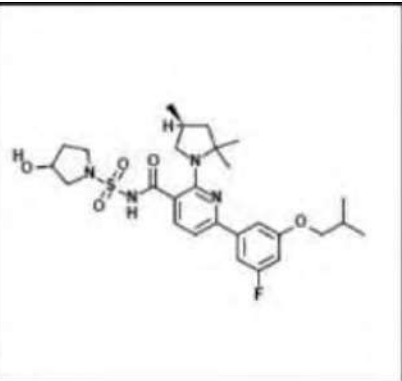
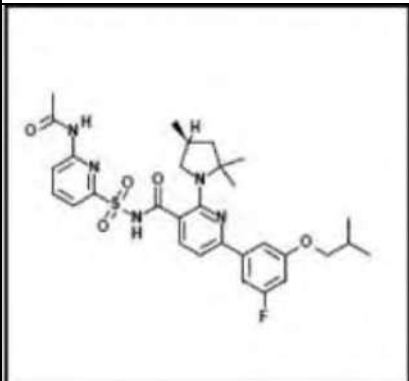
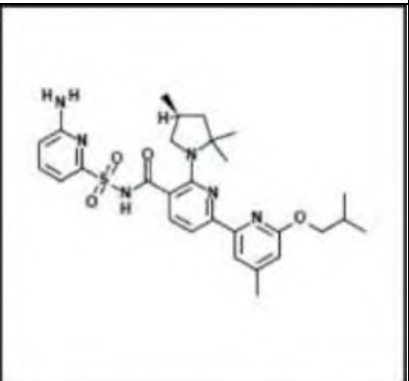
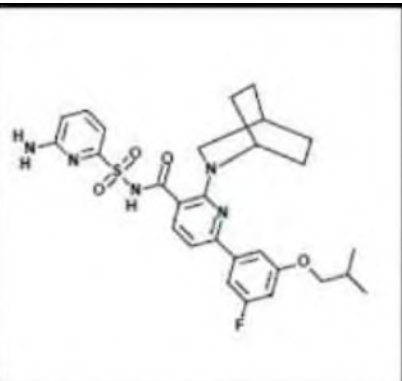
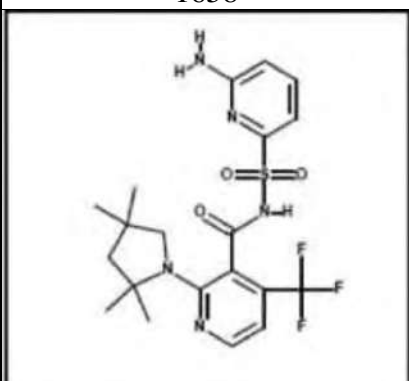
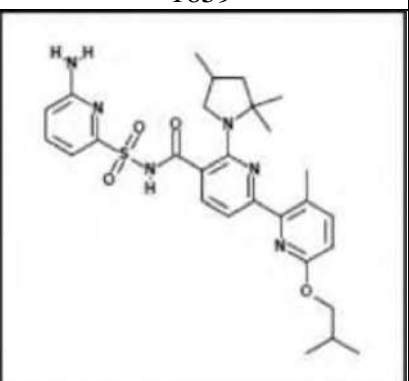
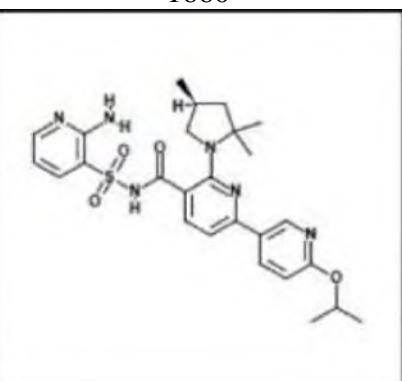
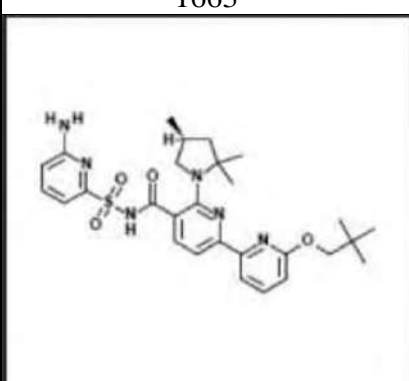
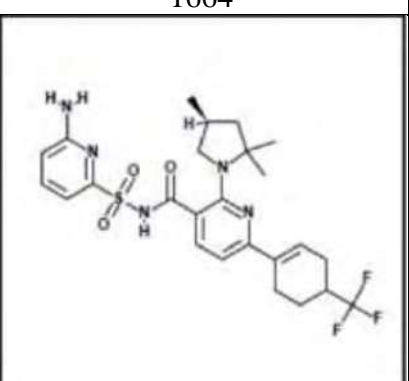
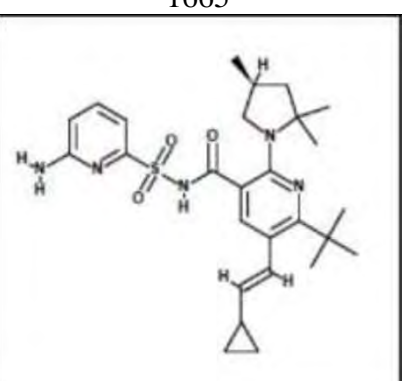
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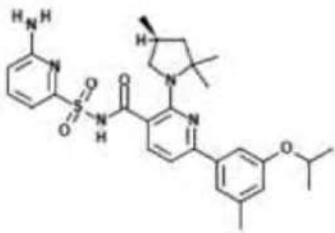
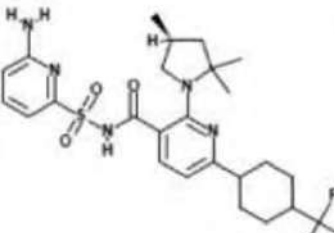
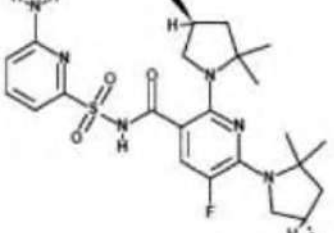
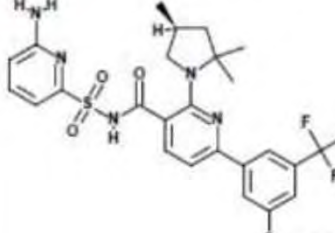
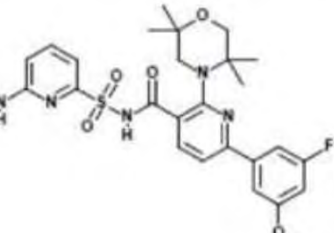
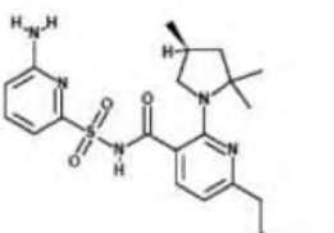
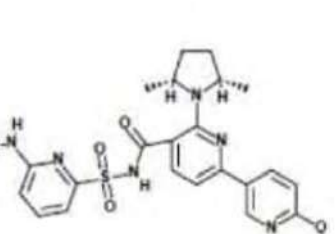
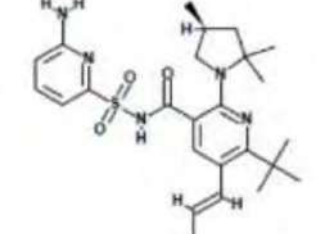
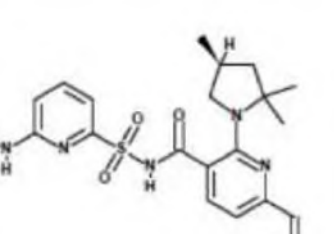
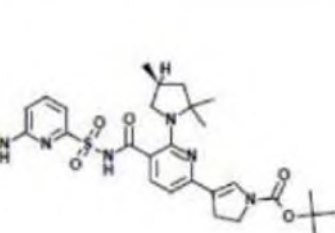
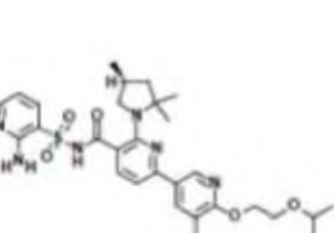
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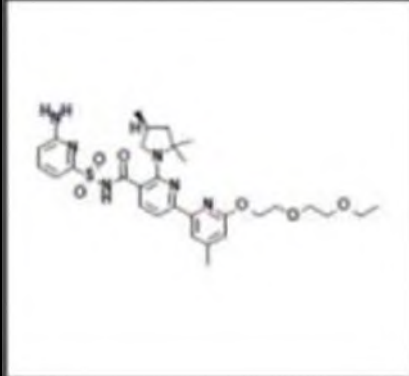
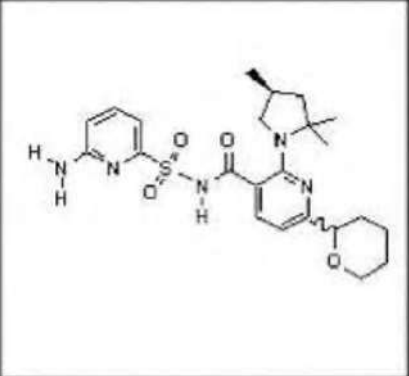
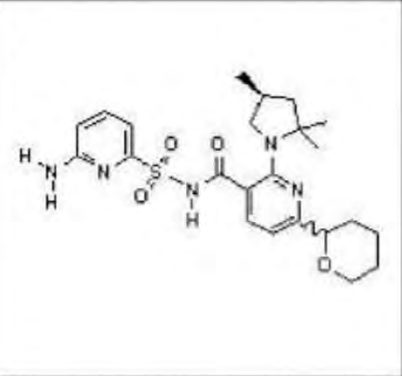
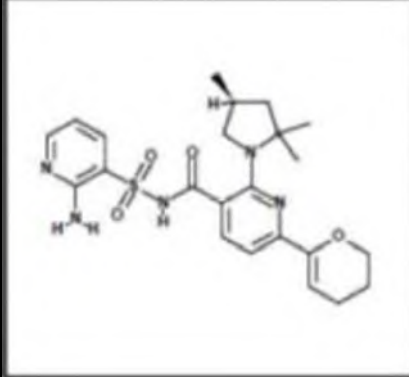
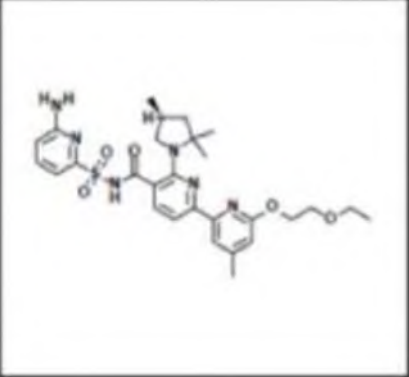
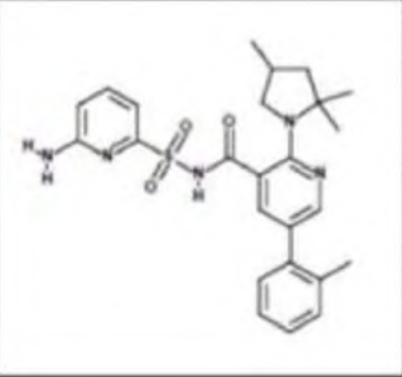
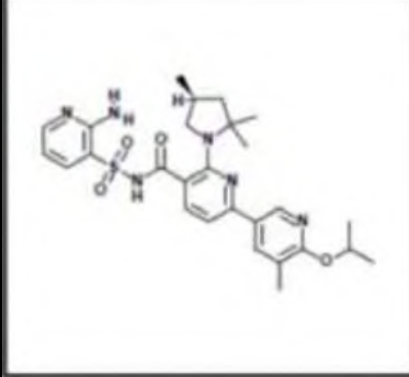
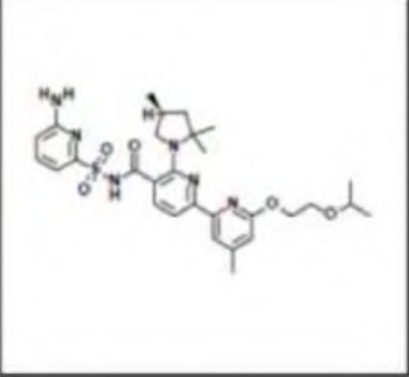
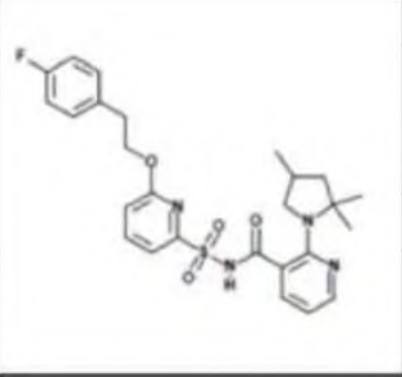
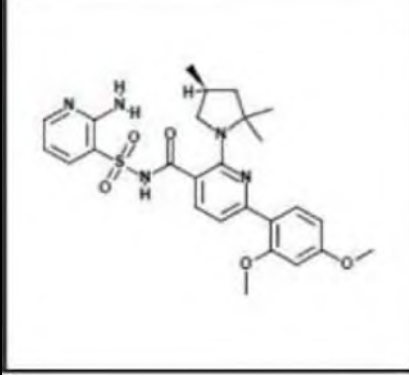
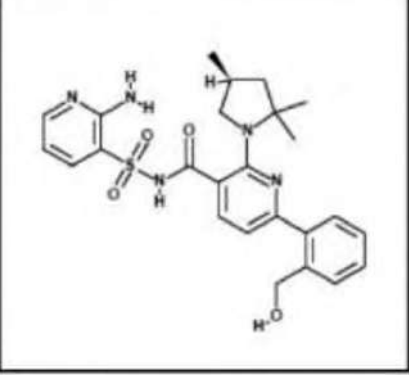
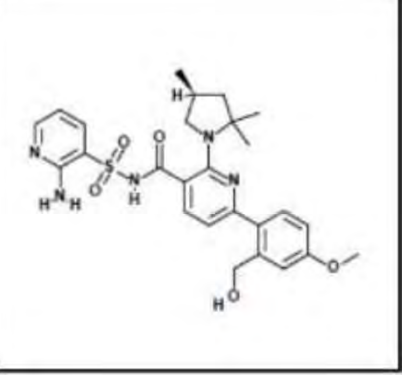
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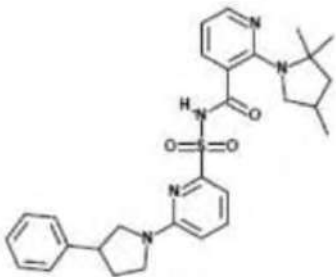
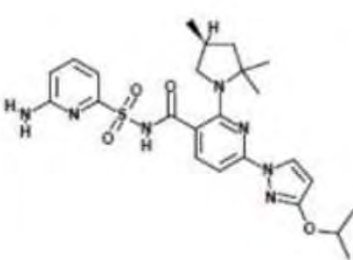
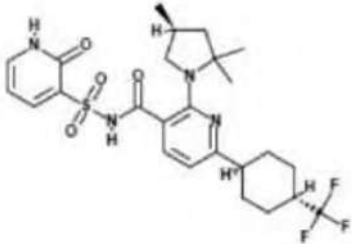
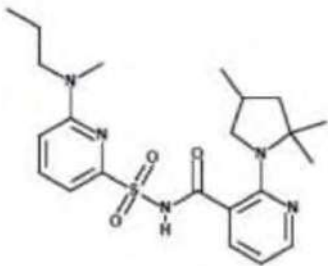
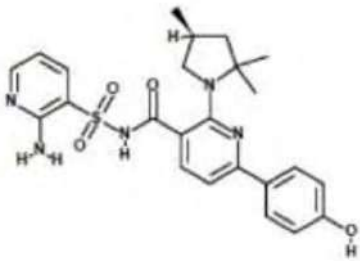
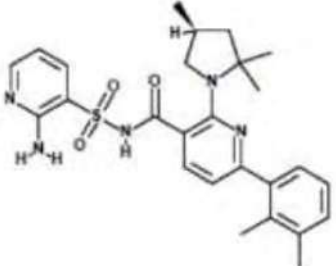
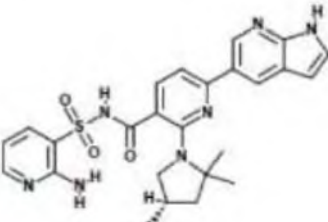
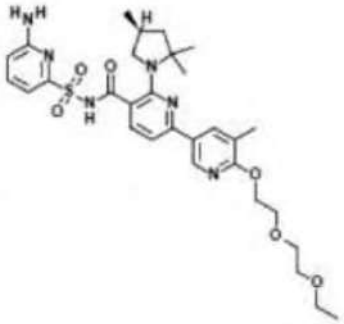
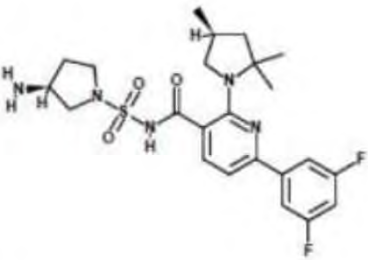
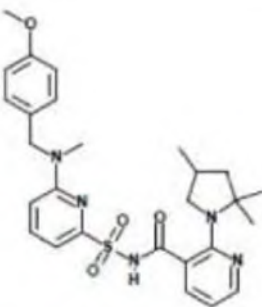
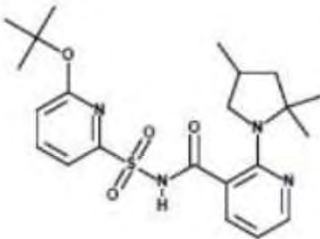
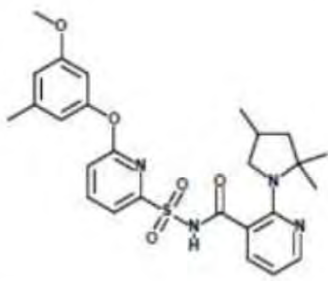
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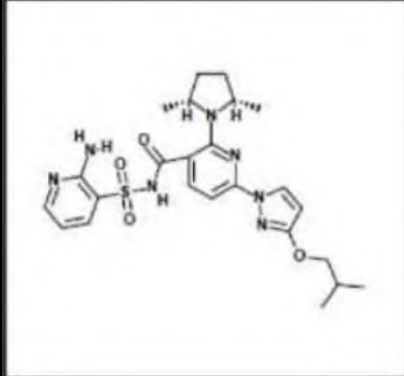
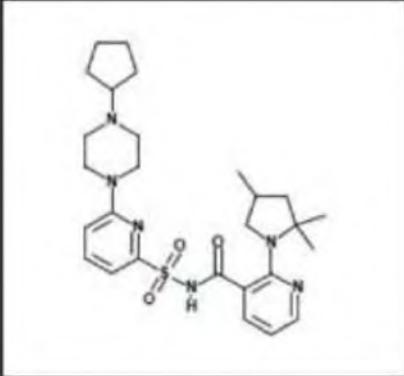
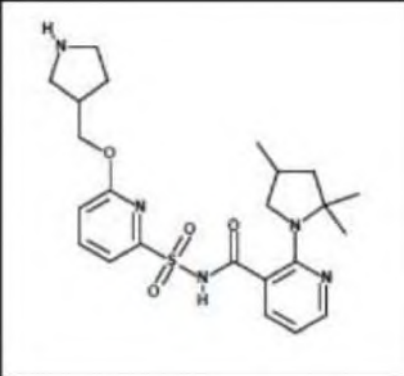
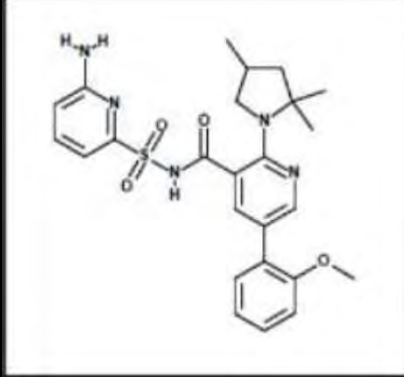
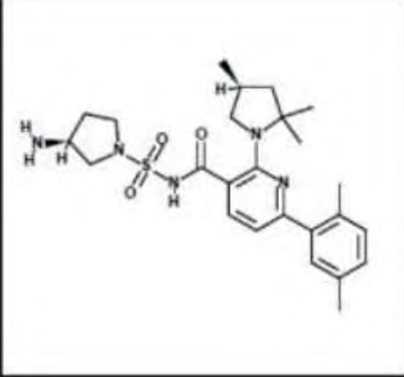
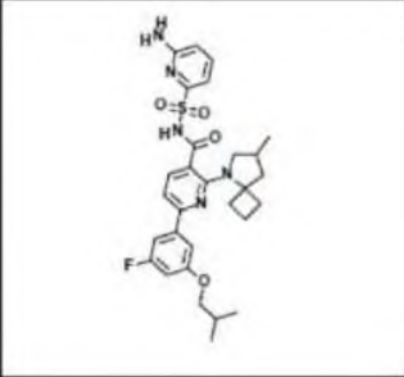
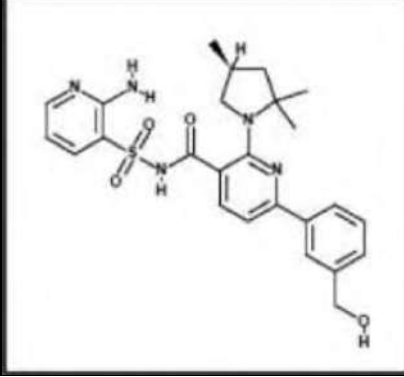
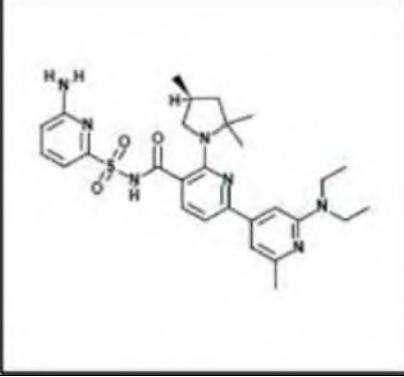
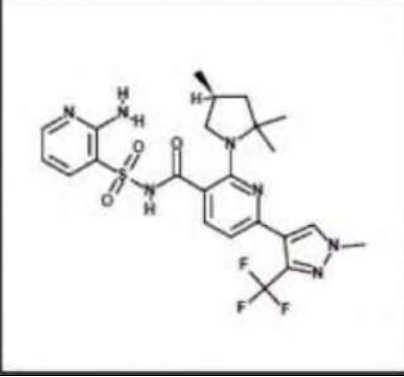
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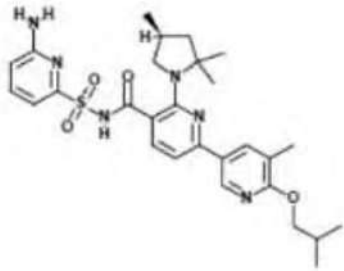
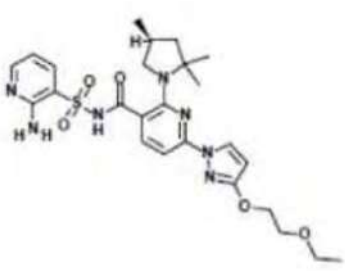
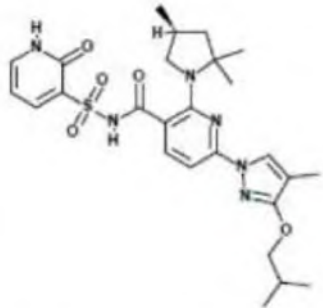
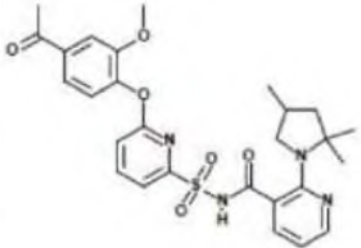
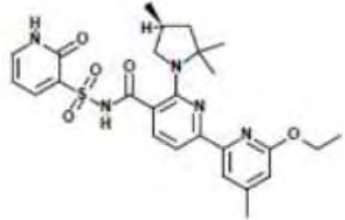
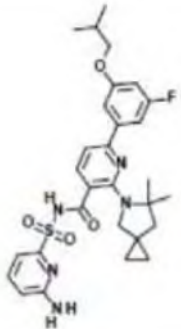
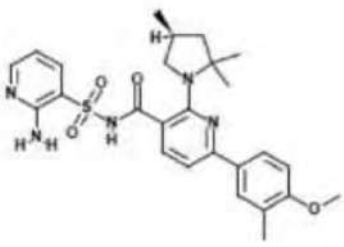
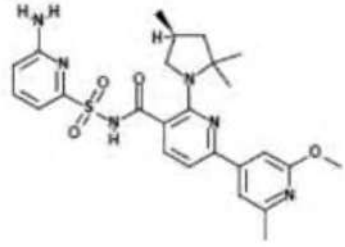
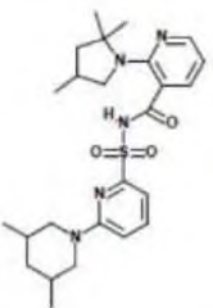
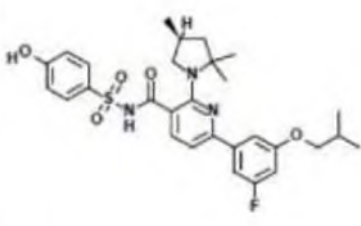
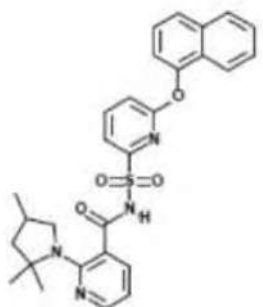
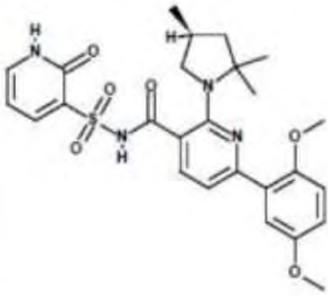
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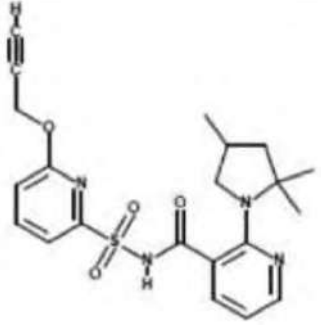
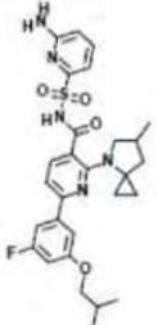
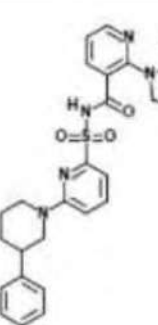
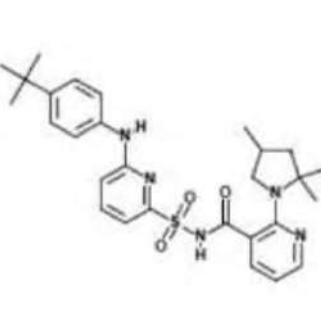
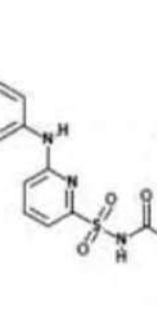
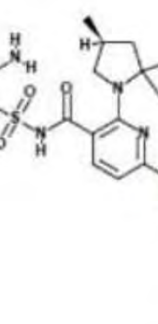
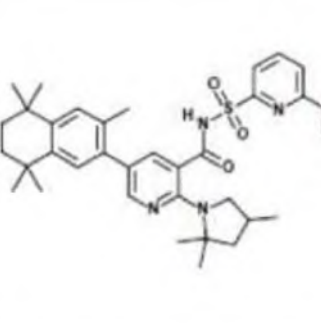
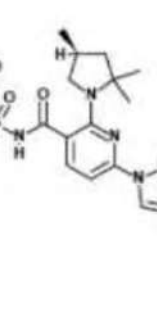
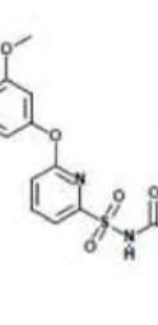

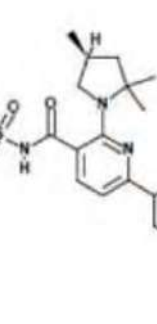
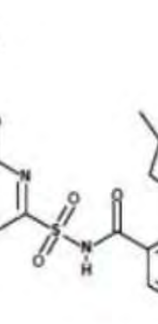
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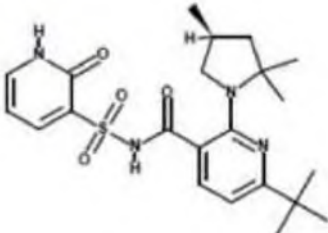
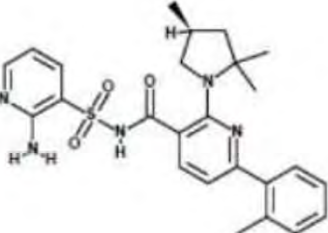
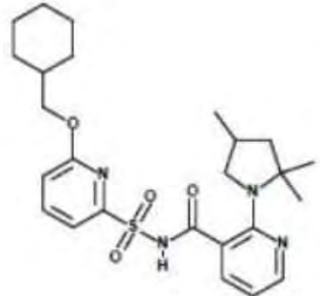
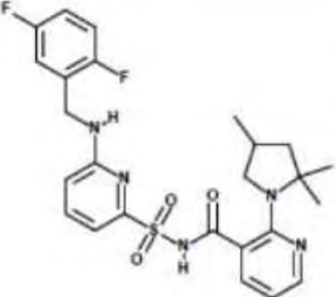
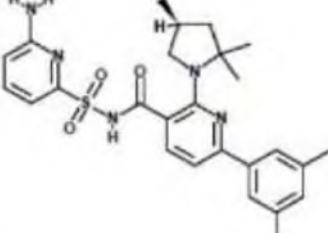
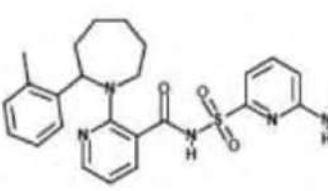
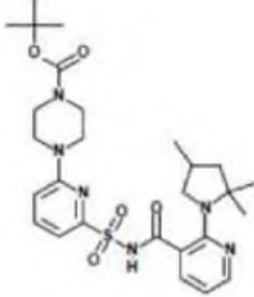
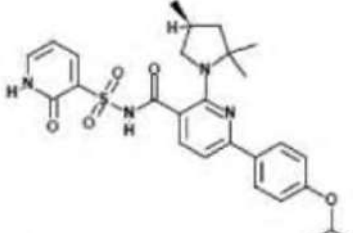
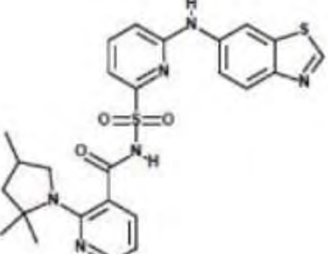
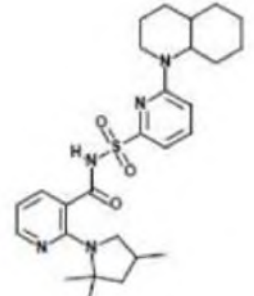
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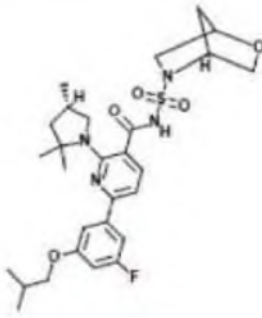
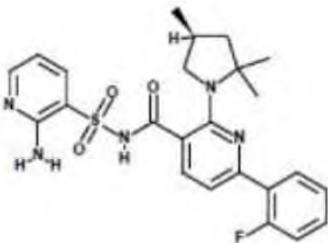
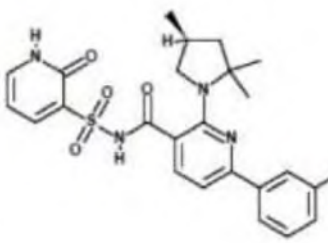
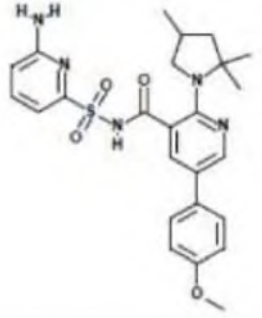
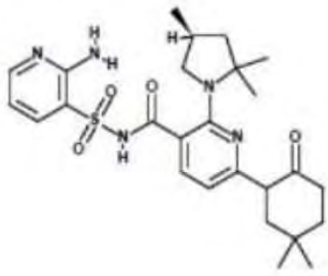
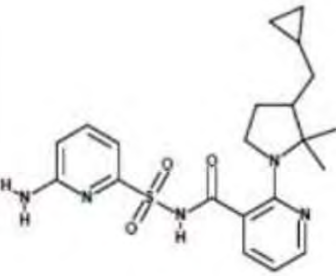
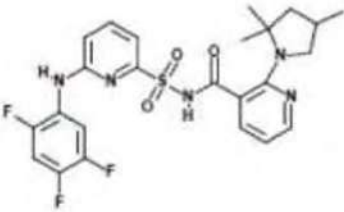
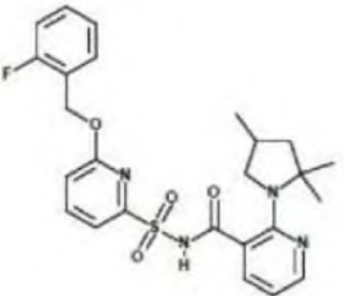
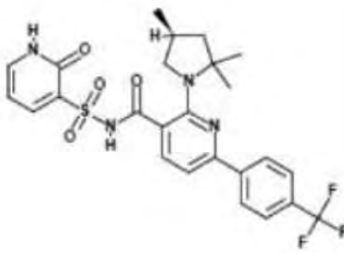
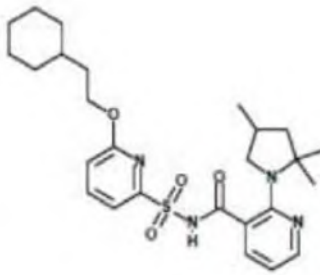
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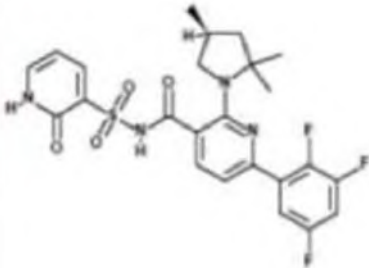
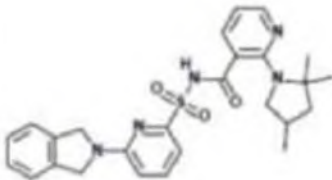
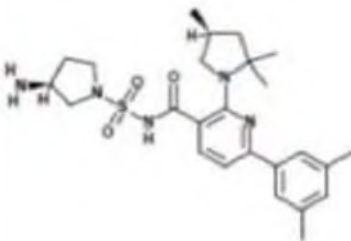
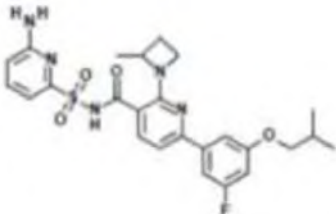
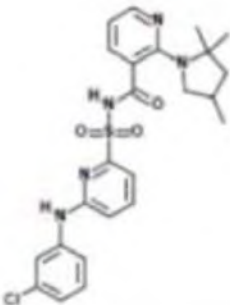
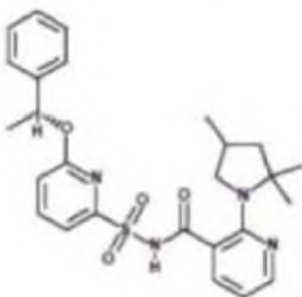
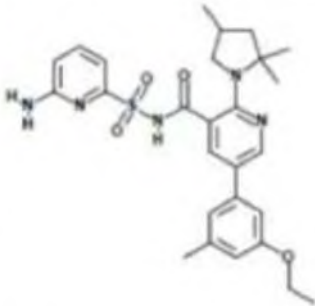
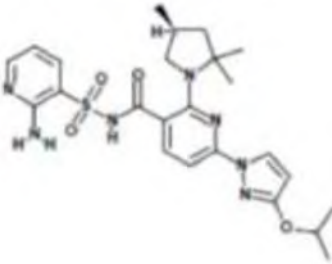
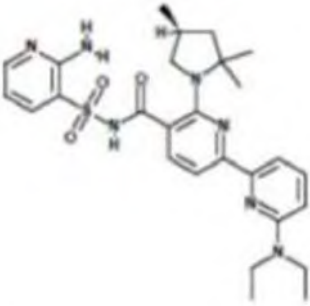
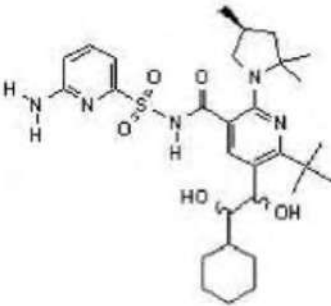
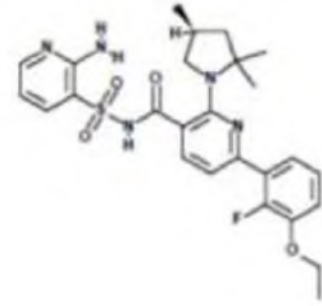
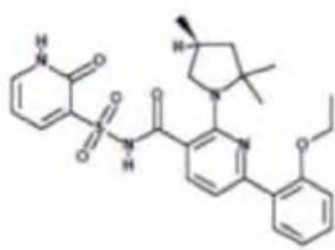
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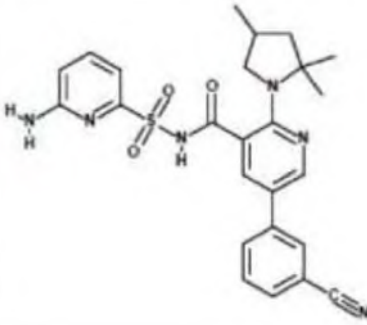
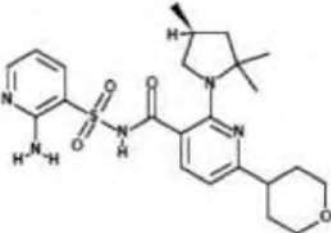
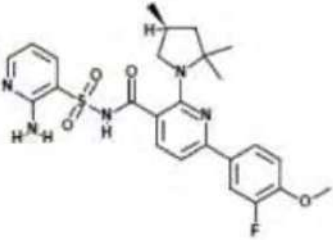
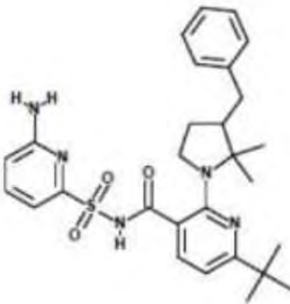
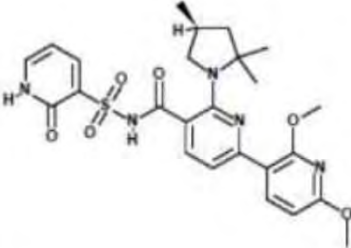
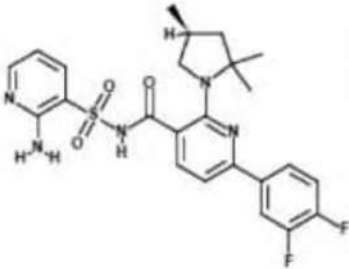
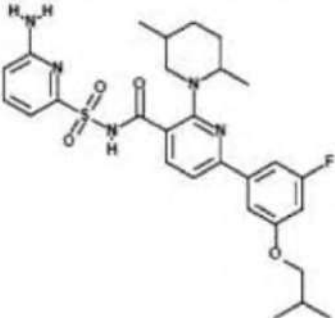
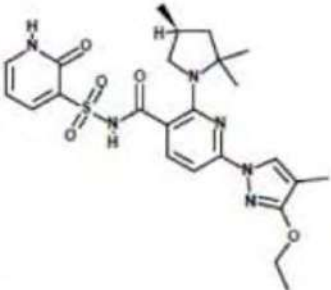
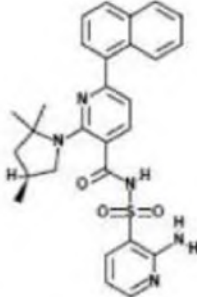
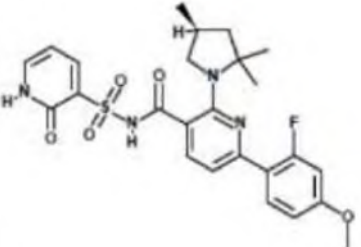
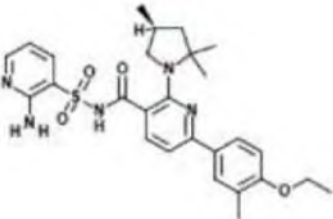
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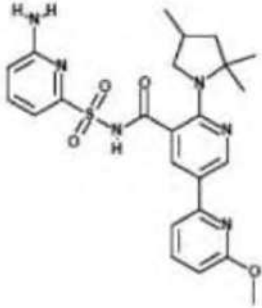
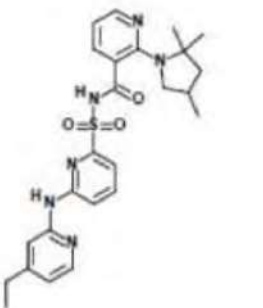
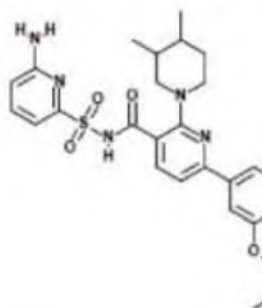
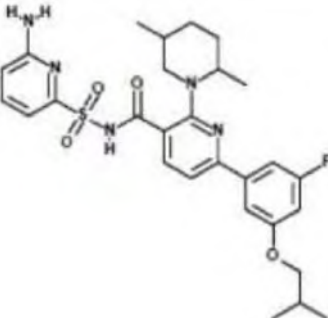
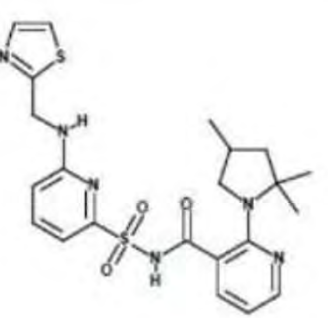
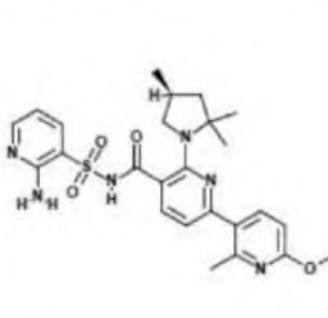
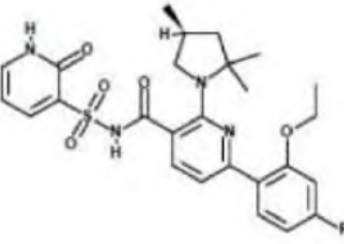
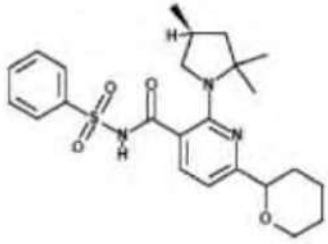
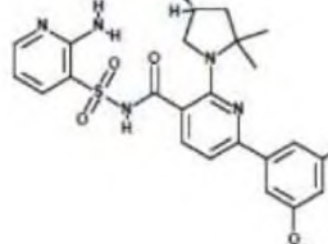
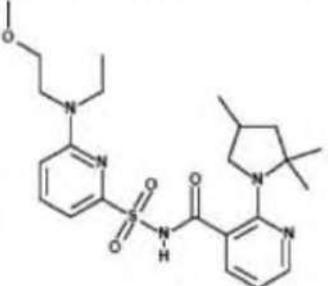
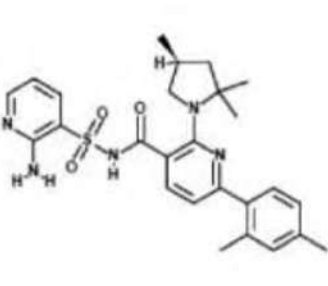
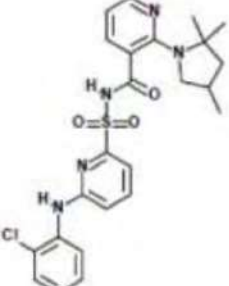
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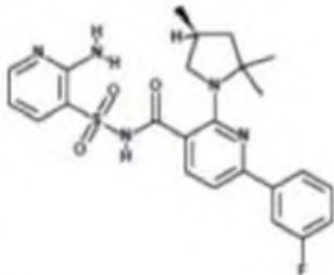
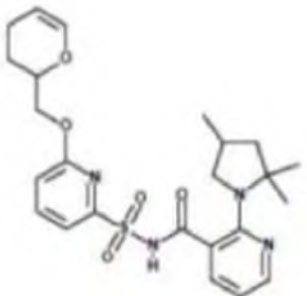
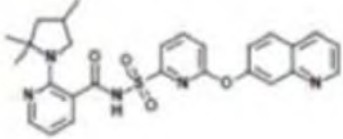
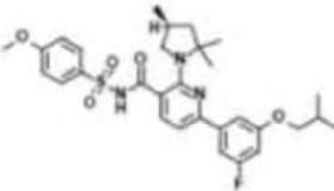
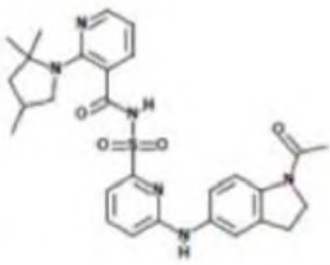
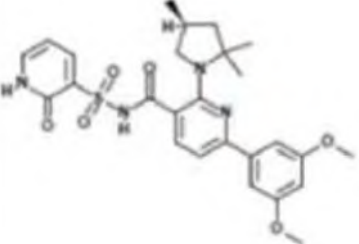
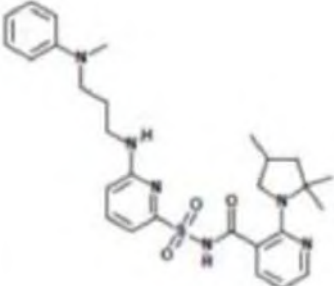
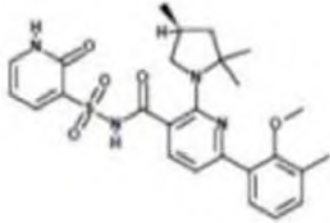
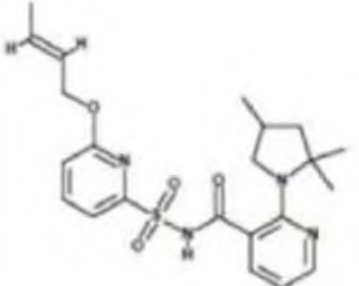
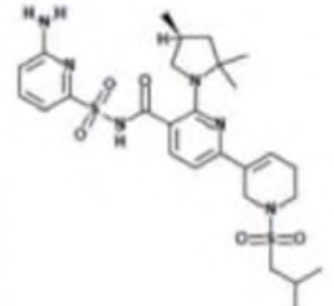
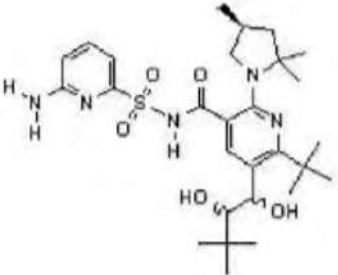
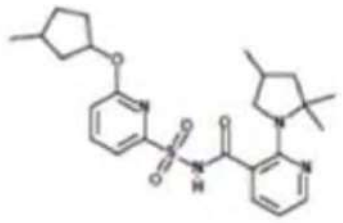
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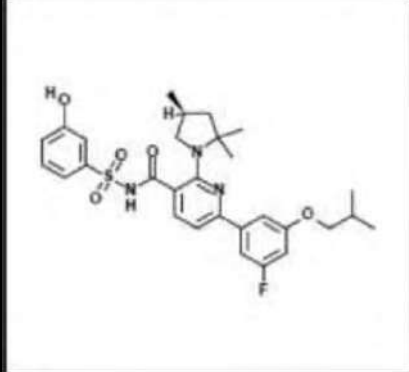
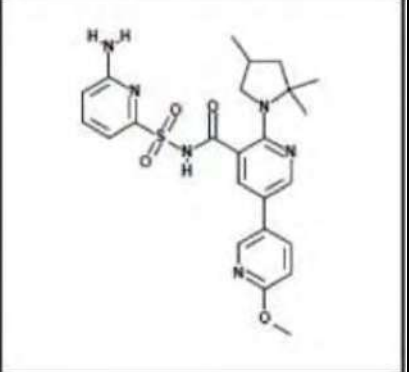
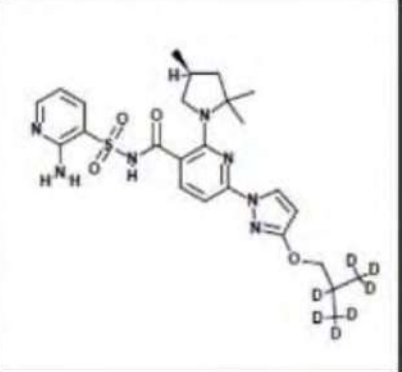
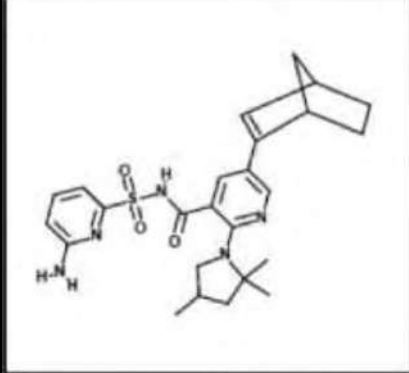
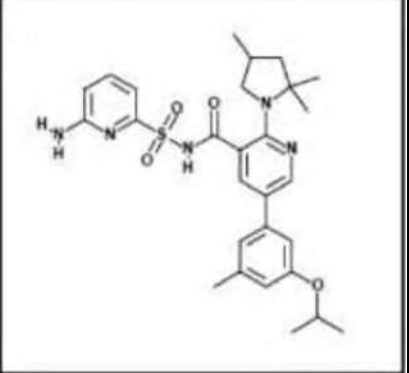
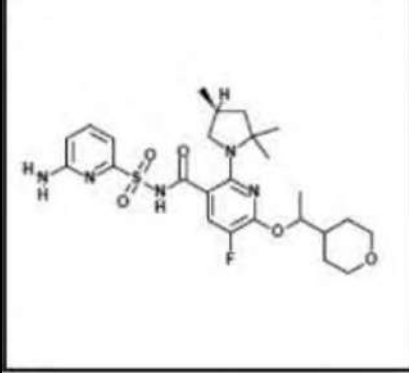
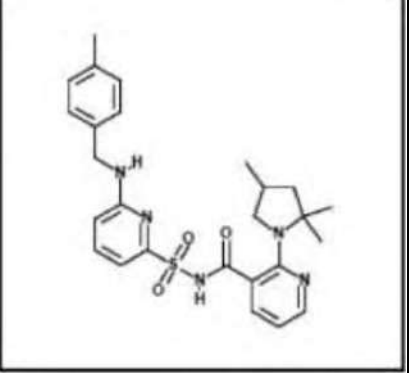
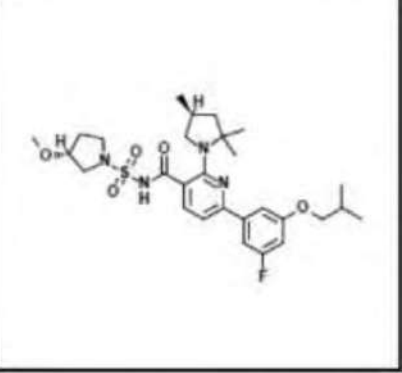
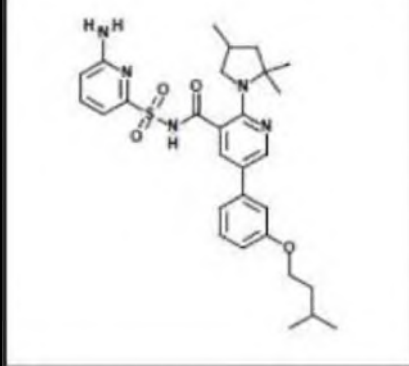
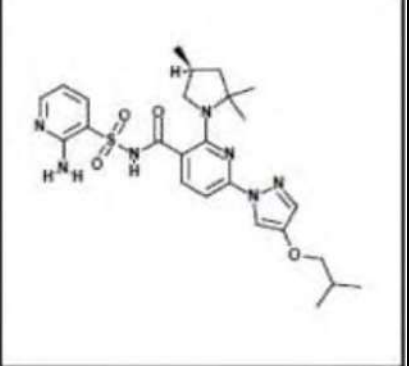
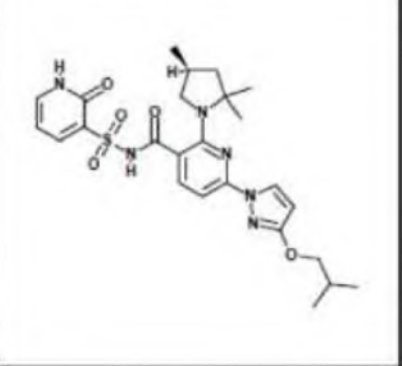
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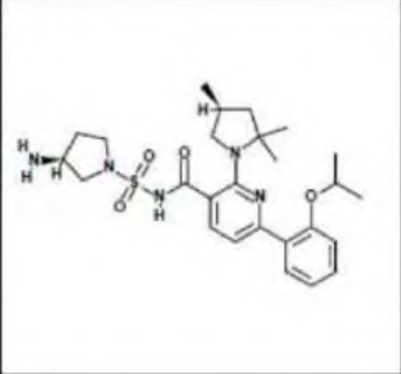
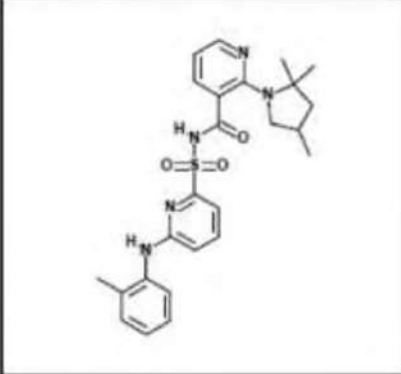
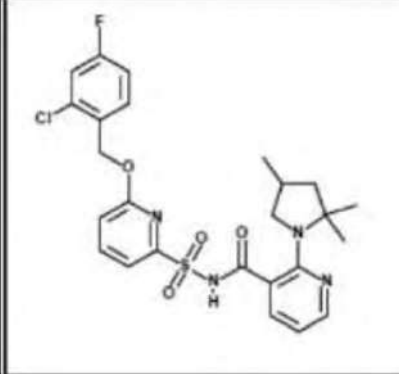
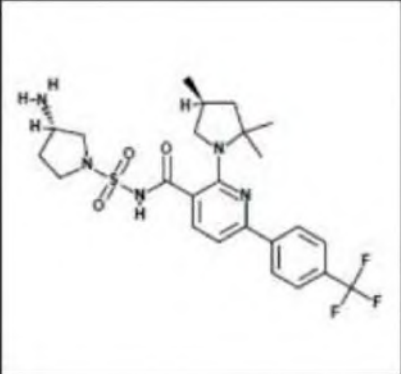
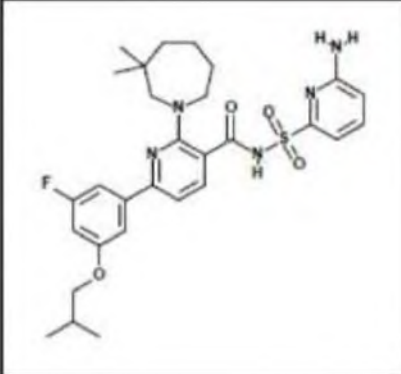
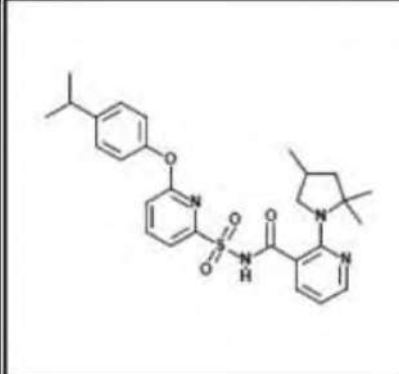
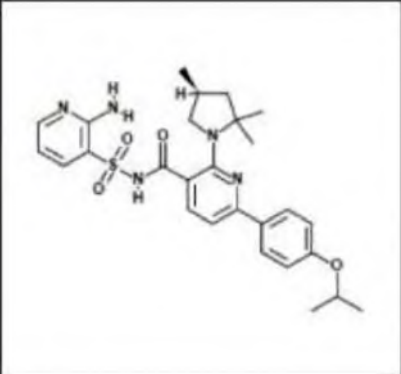
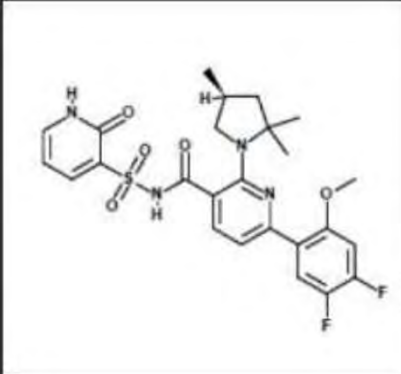
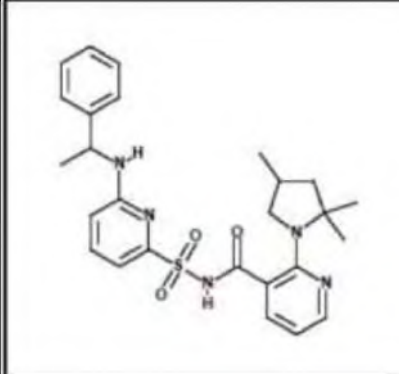
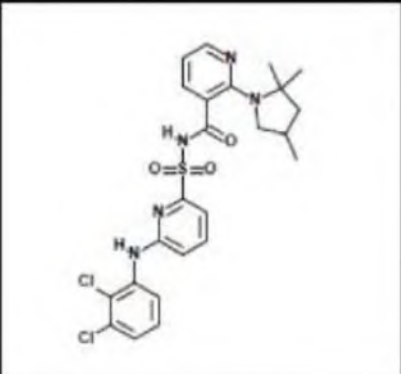
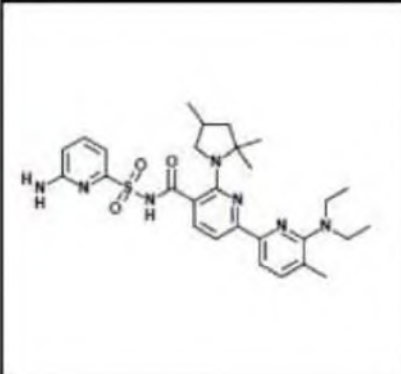
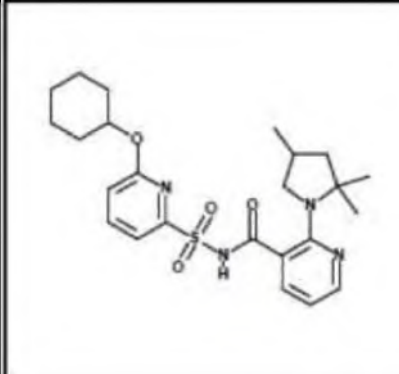
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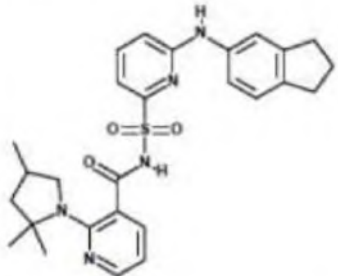
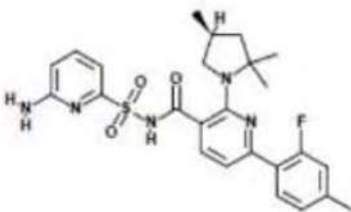
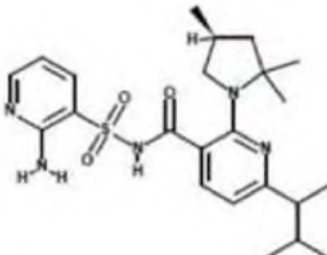
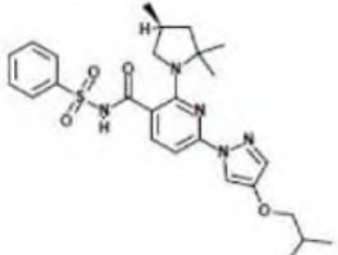
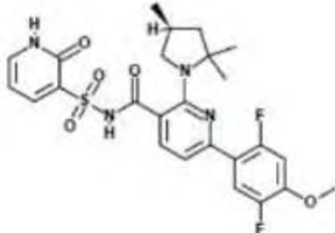
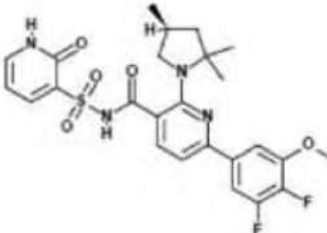
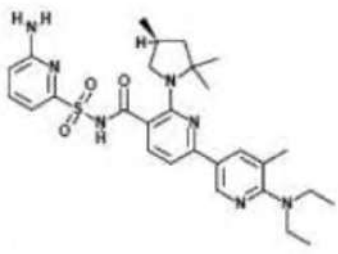
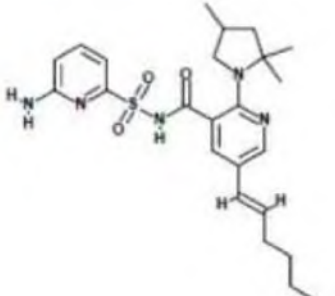
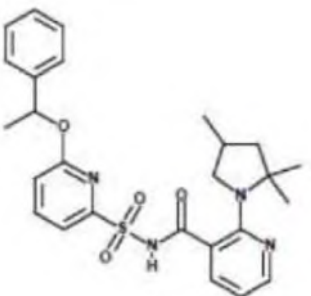
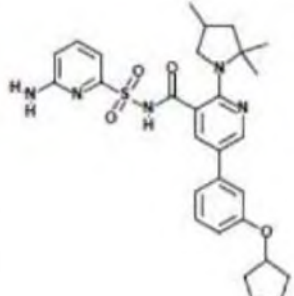
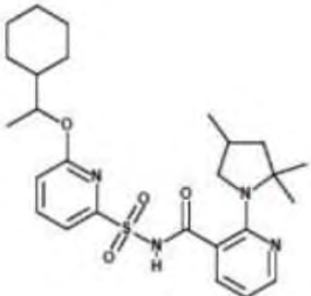
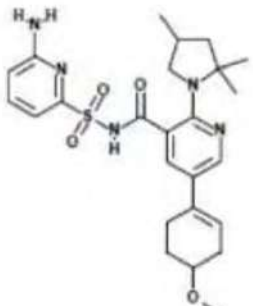
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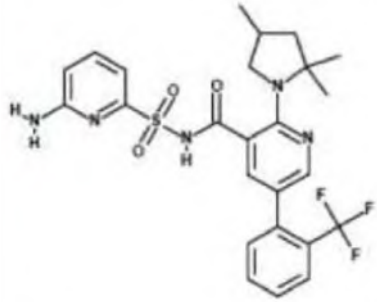
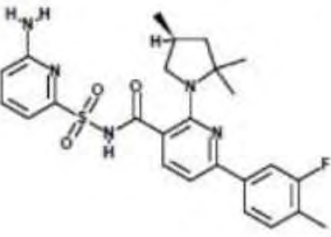
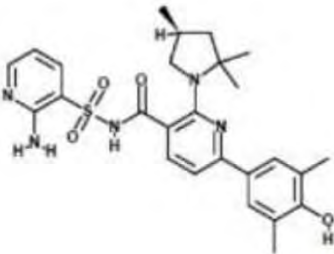
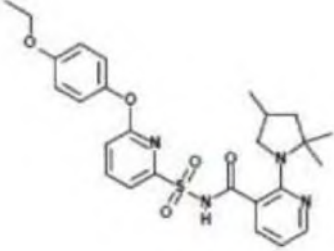
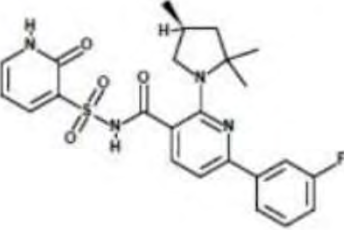
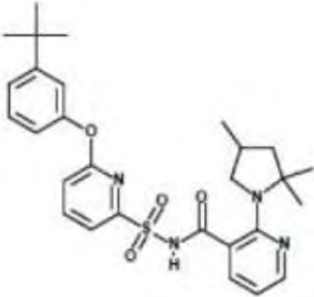
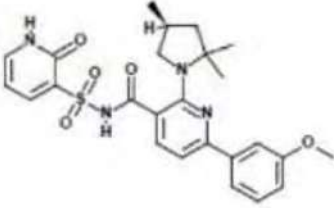
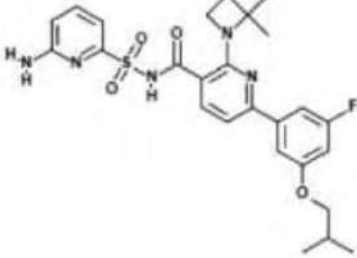
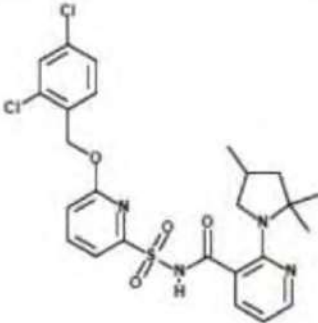
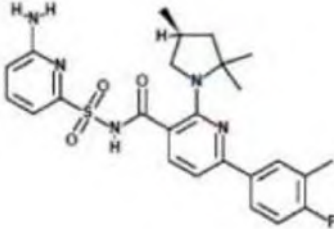
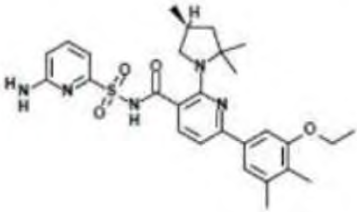
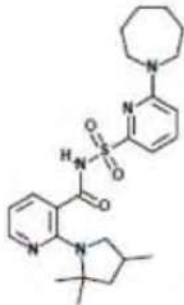
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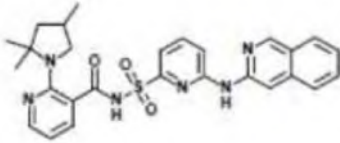
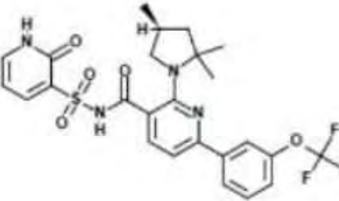
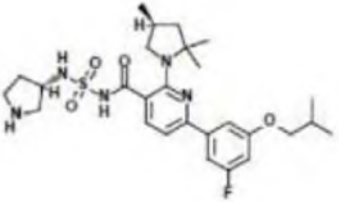
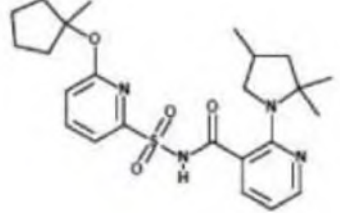
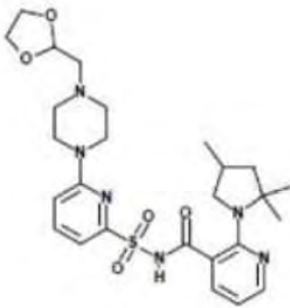
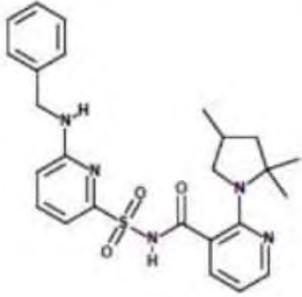
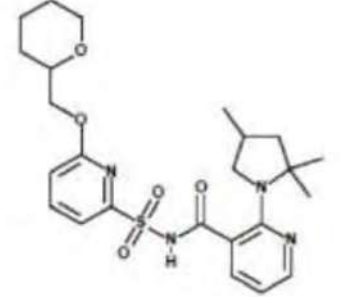
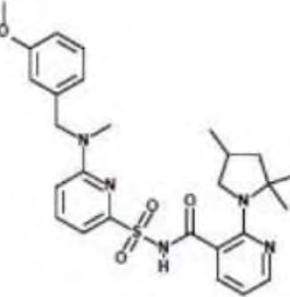
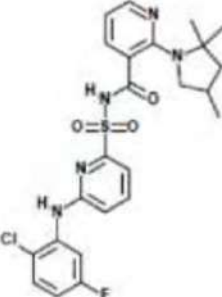
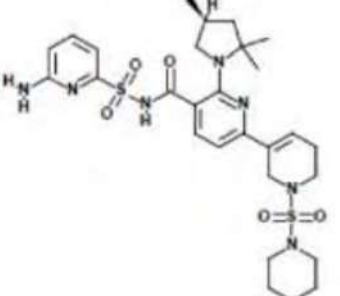
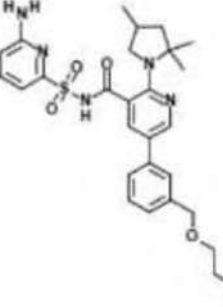
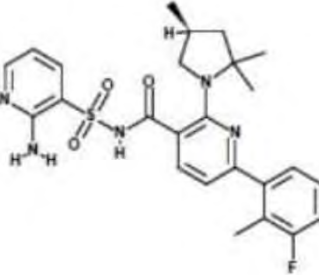
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1885	1886	1887
		
1888	1889	
		
1891	1892	1893
		
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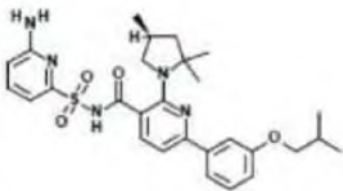
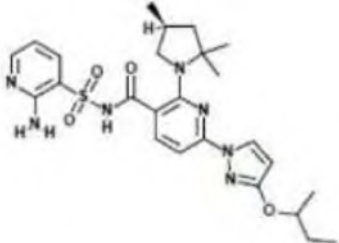
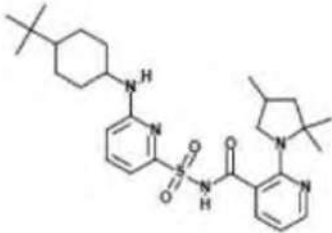
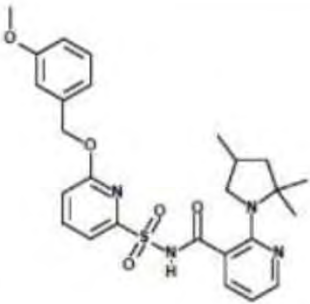
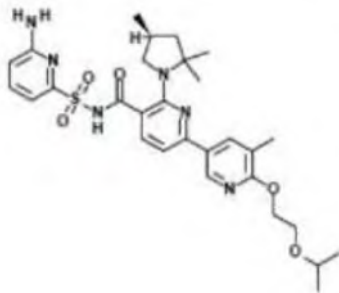
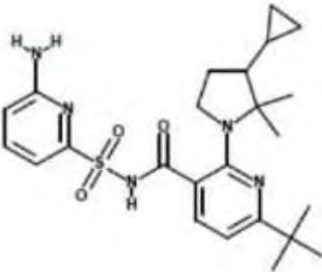
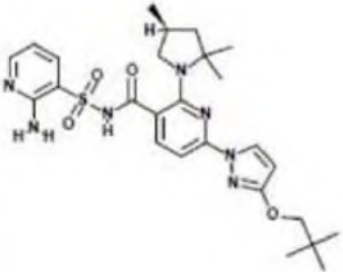
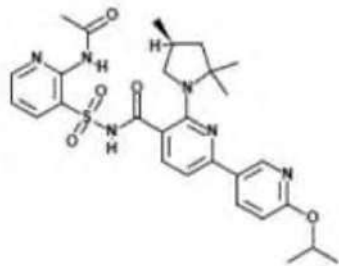
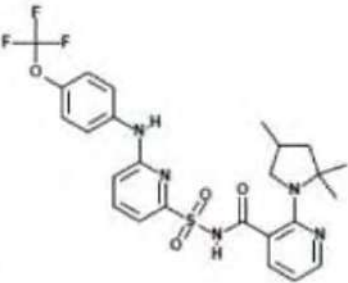
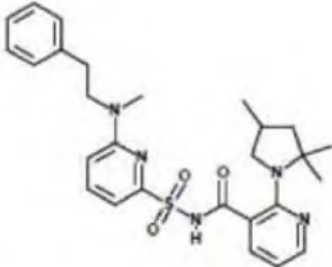
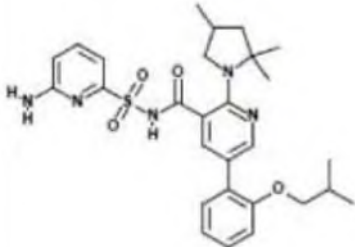
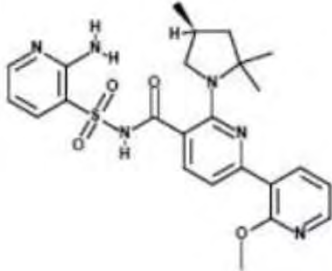
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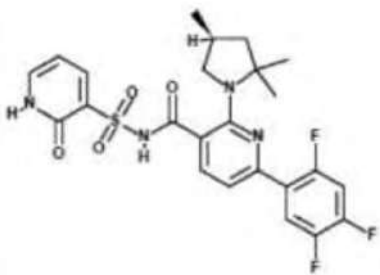
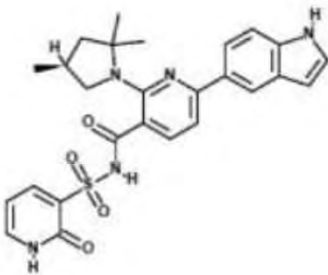
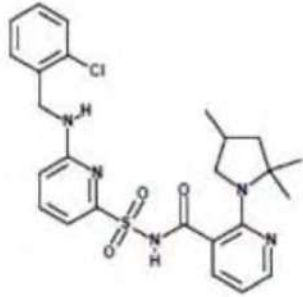
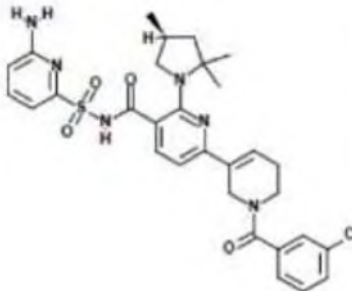
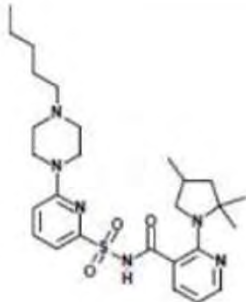
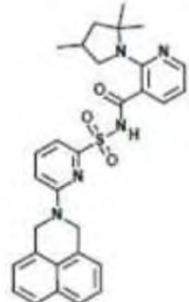
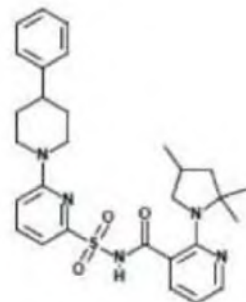
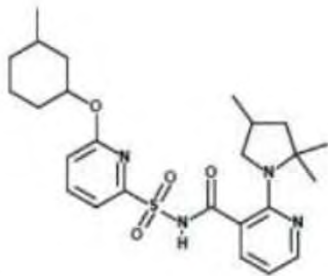
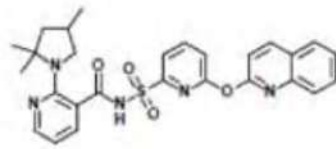
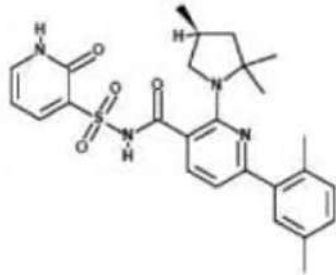
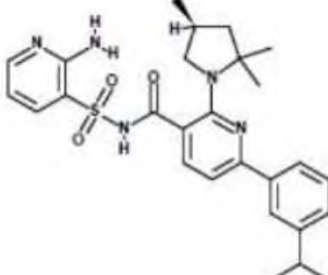
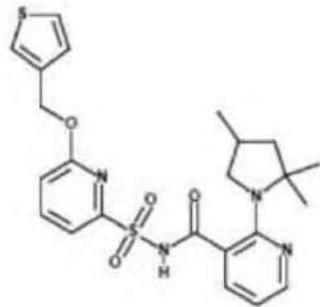
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1930	1931	1932
		

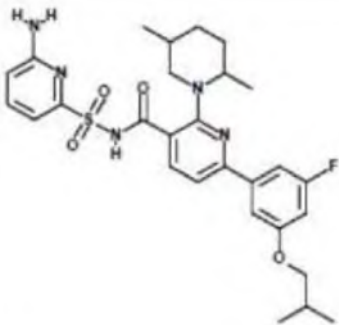
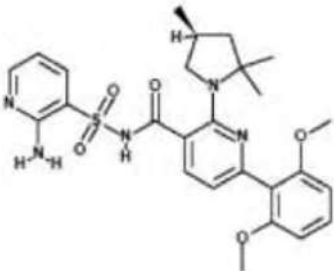
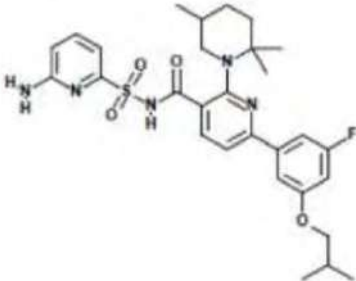
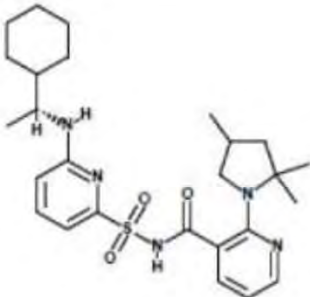
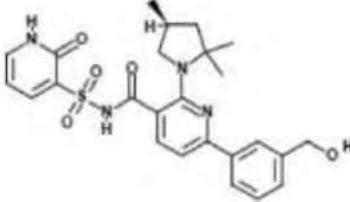
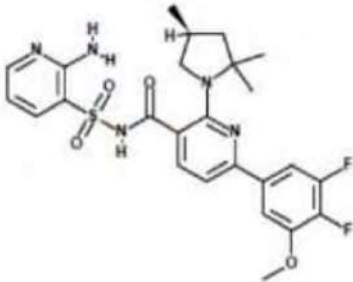
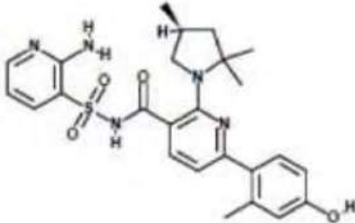
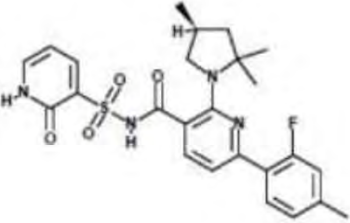
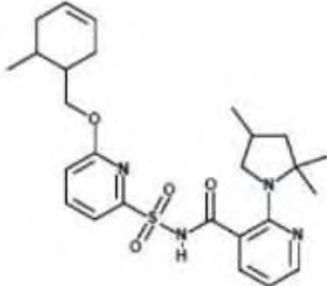
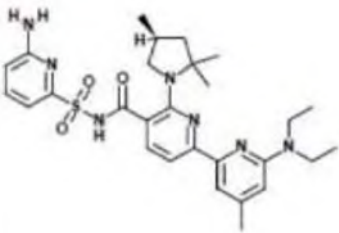
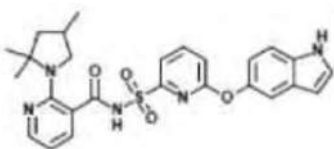
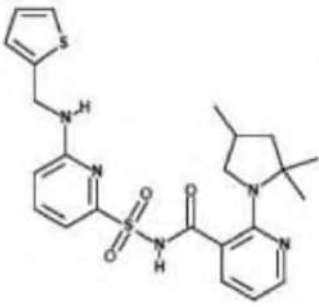
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1939	1940	1941
		
1942	1943	1944
		

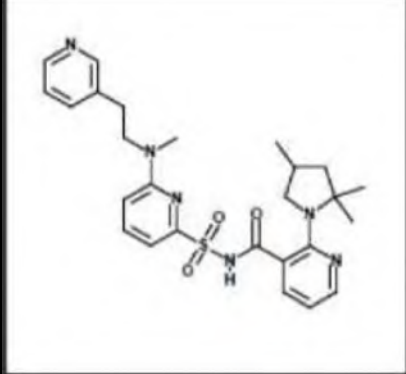
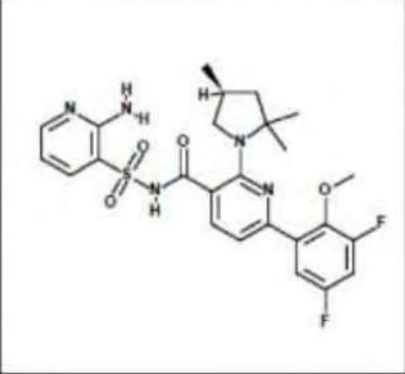
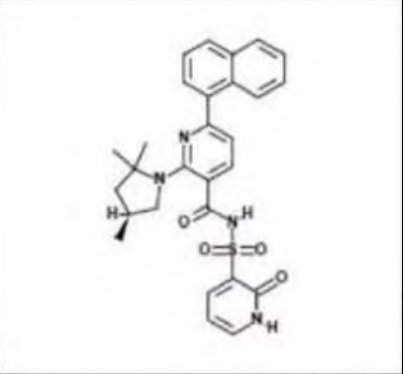
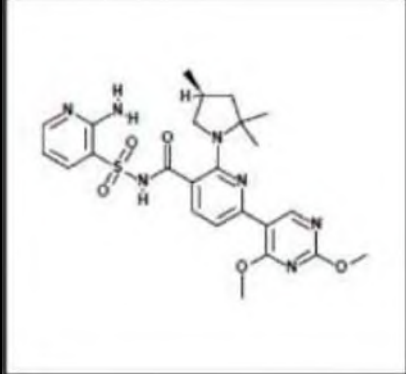
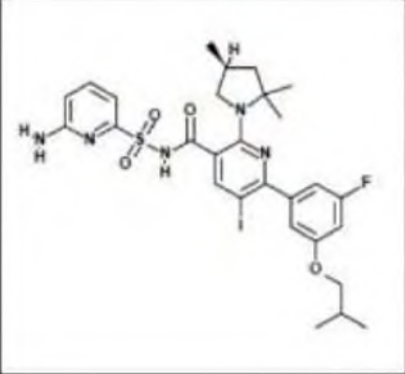
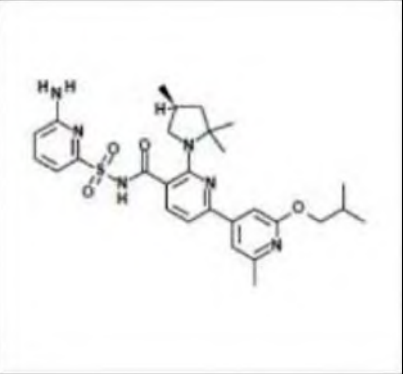
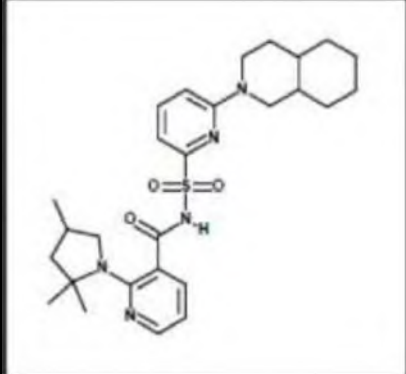
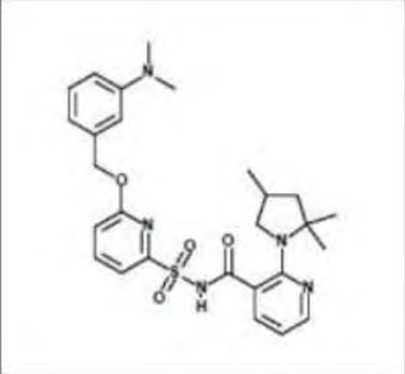
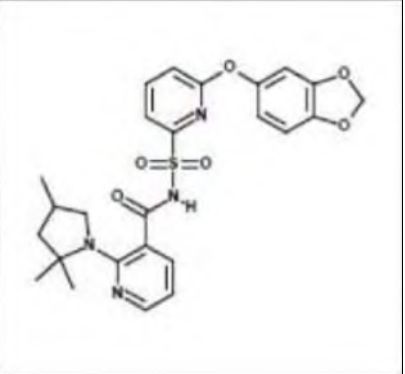
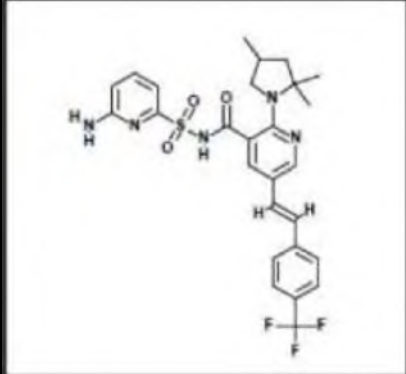
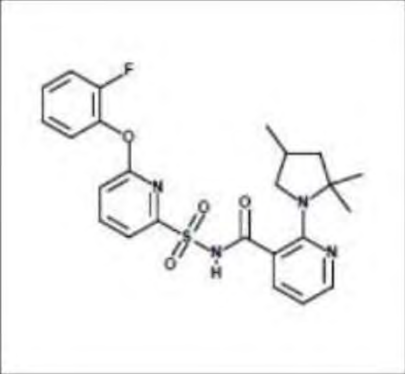
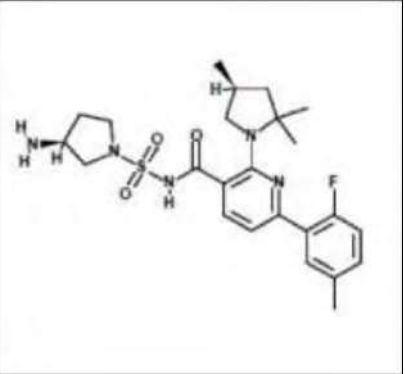
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1954	1955	1956

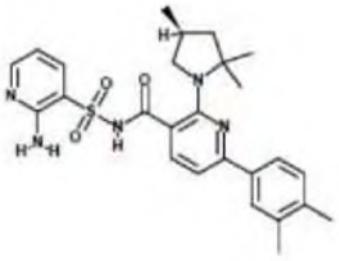
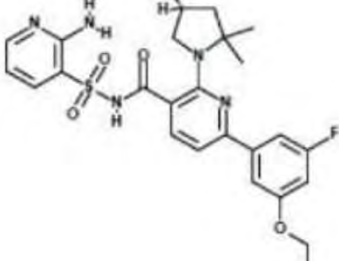
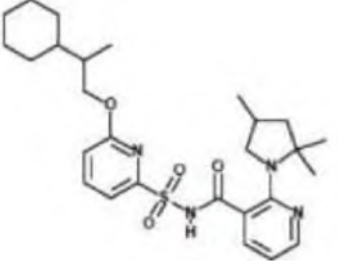
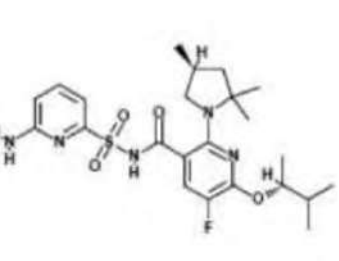
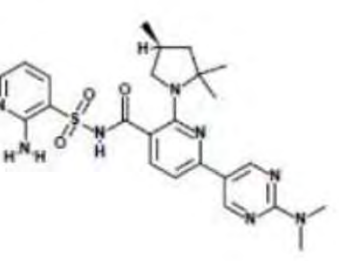
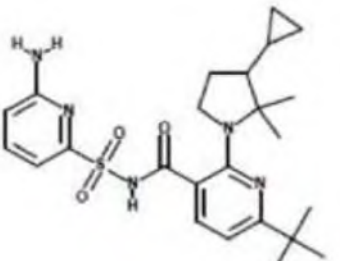
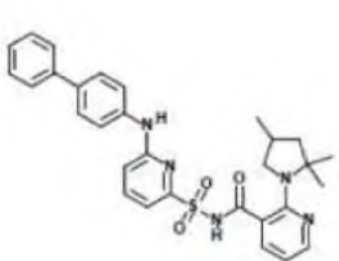
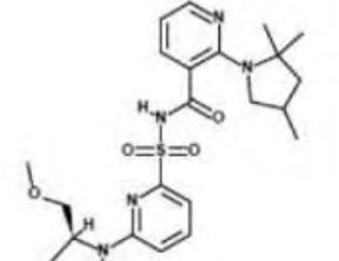
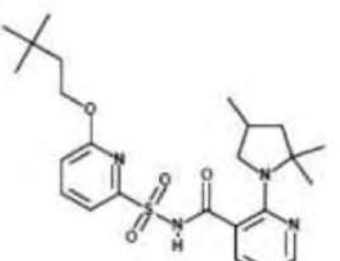
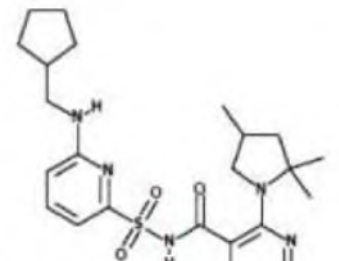
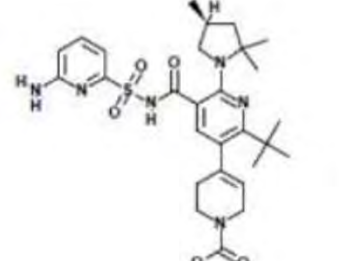
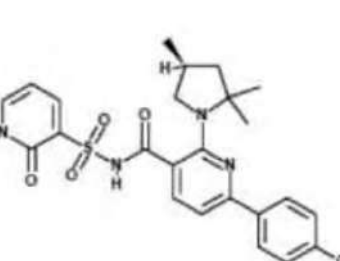
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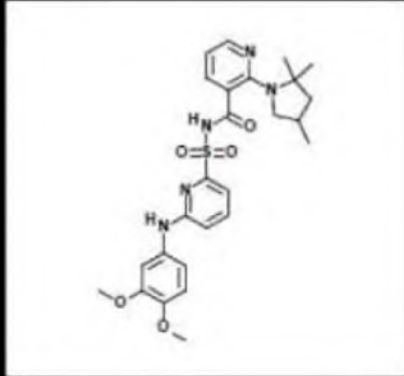
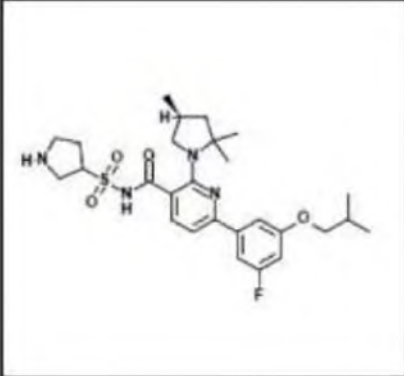
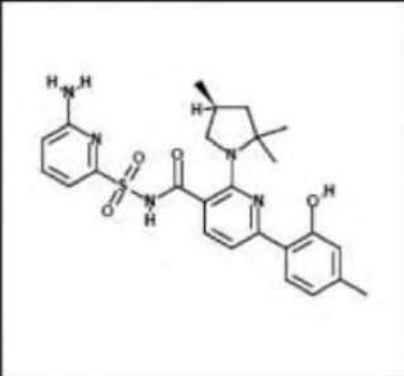
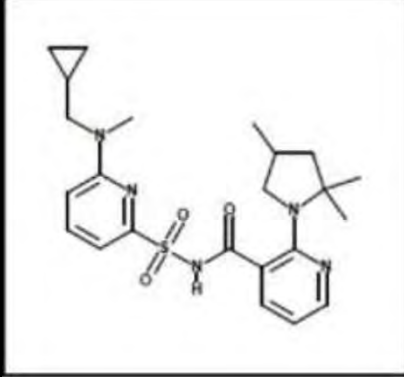
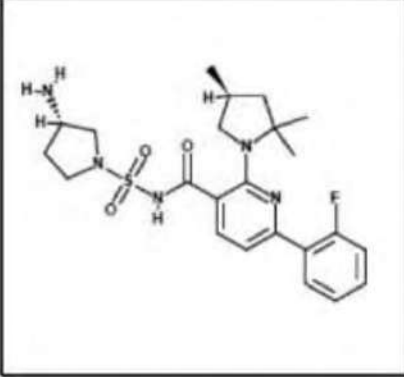
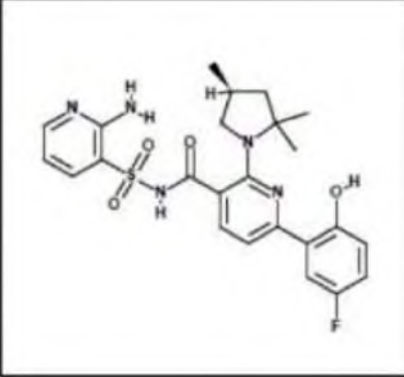
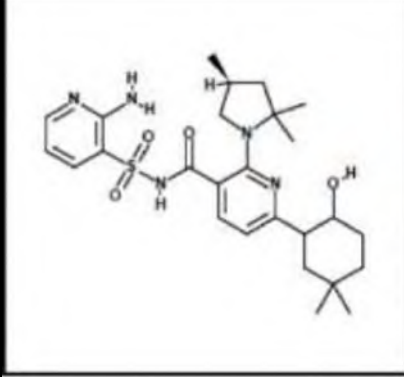
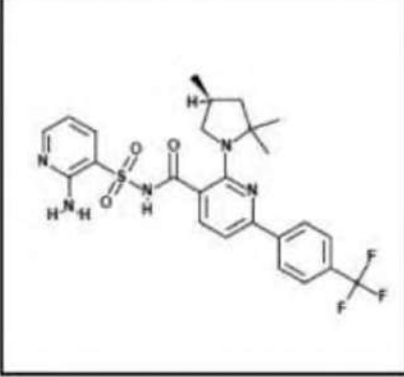
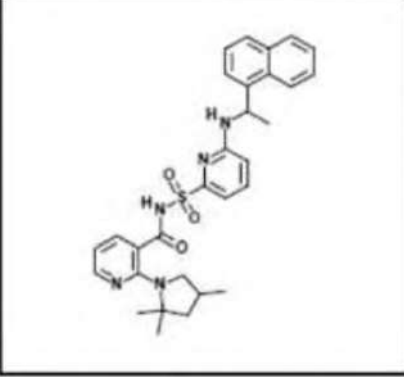
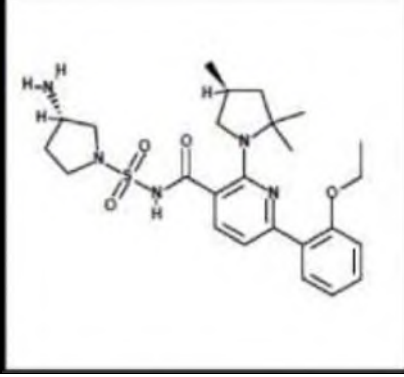
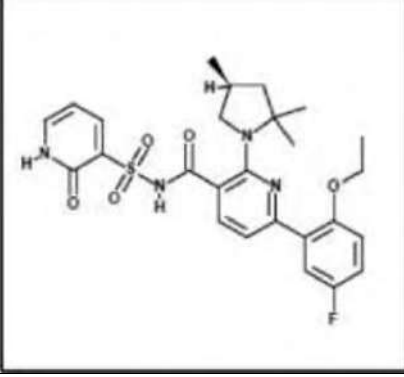
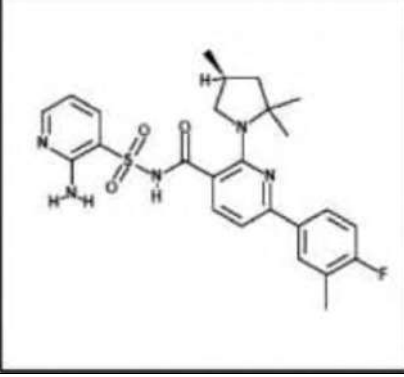
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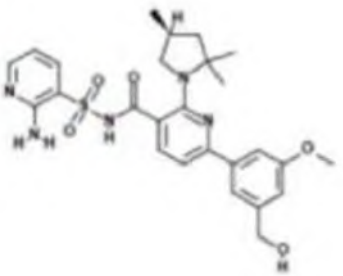
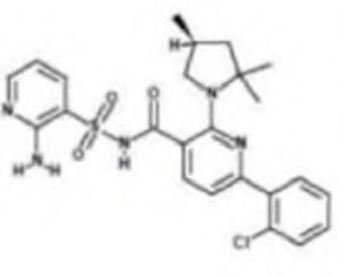
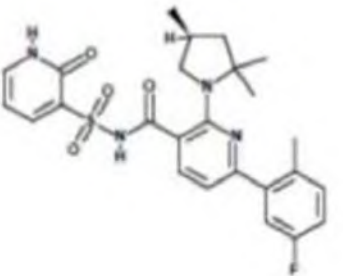
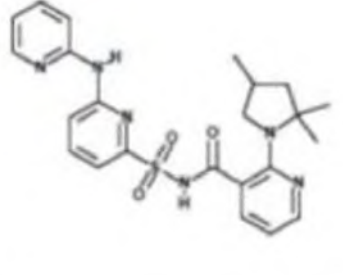
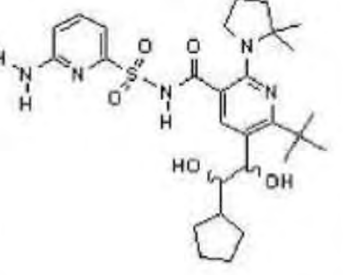
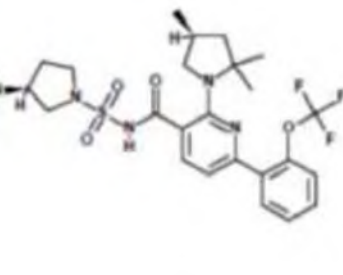
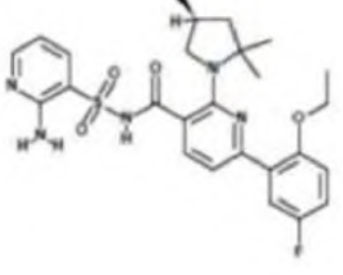
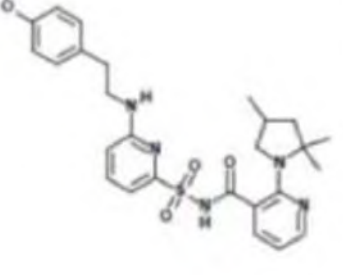
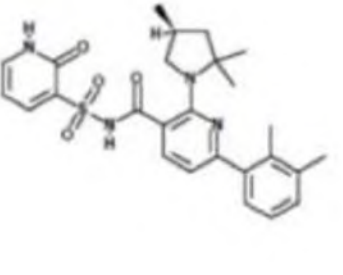
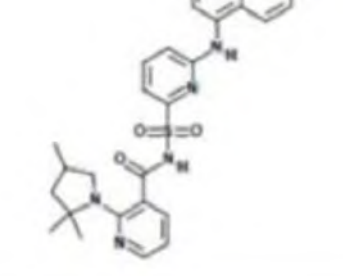
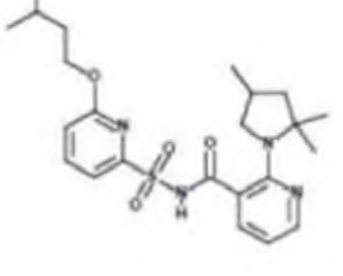
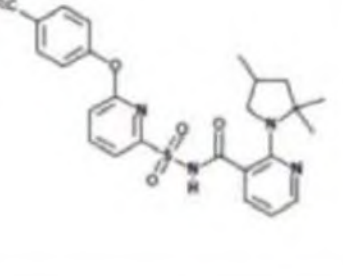
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2014	2015	2016
		

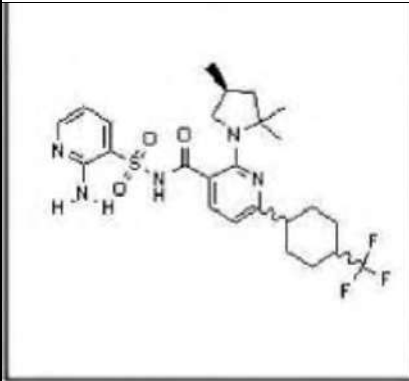
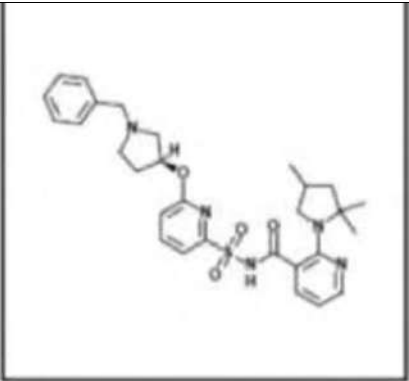
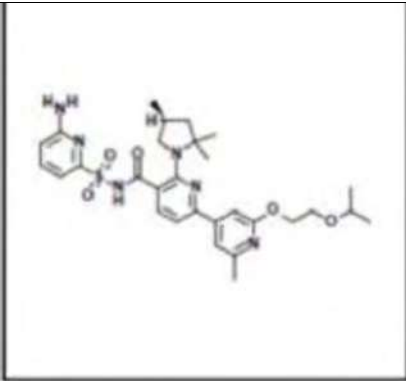
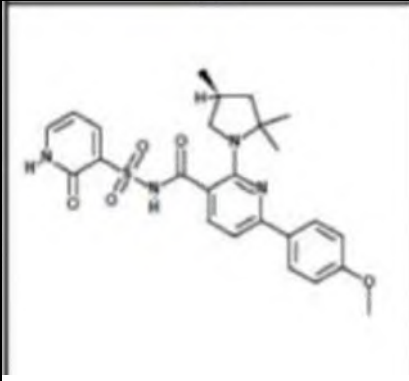
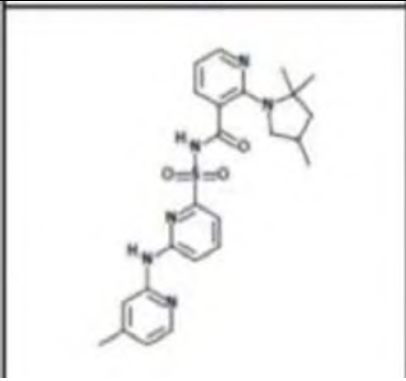
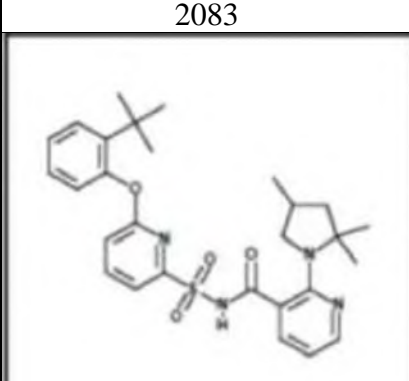
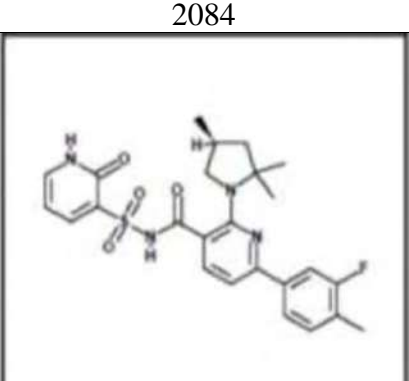
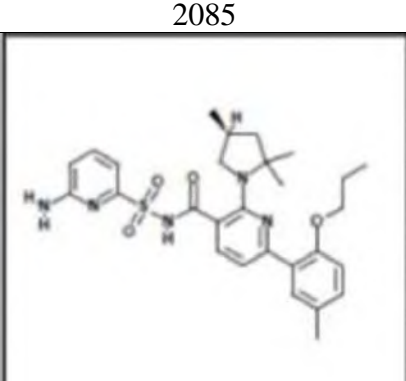
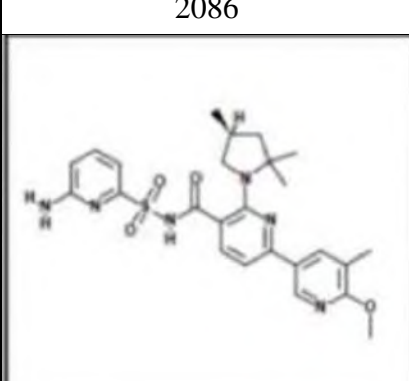
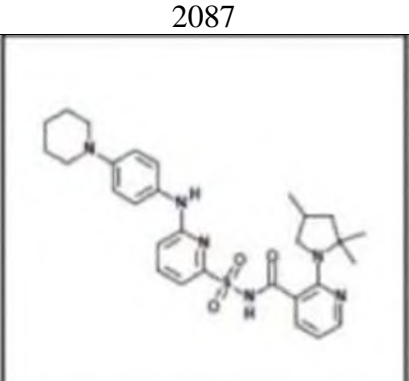
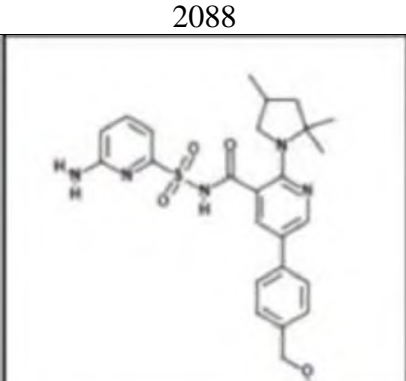
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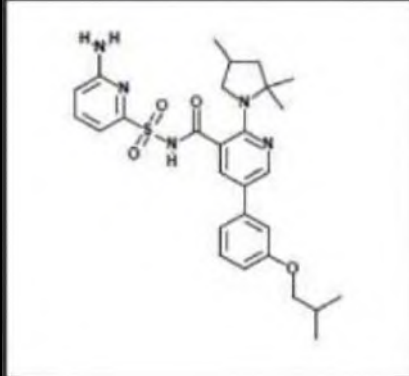
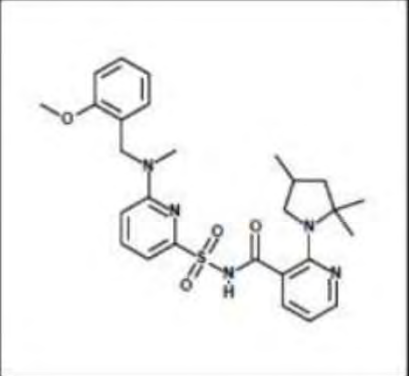
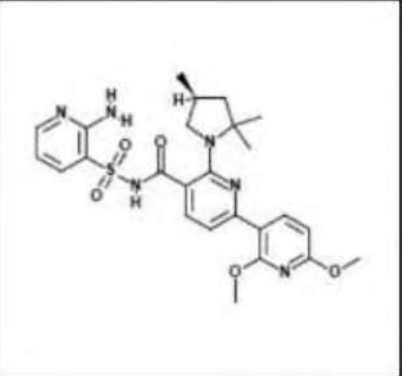
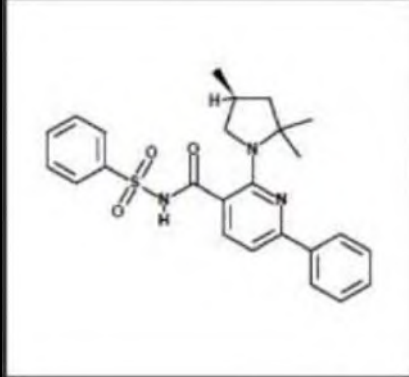
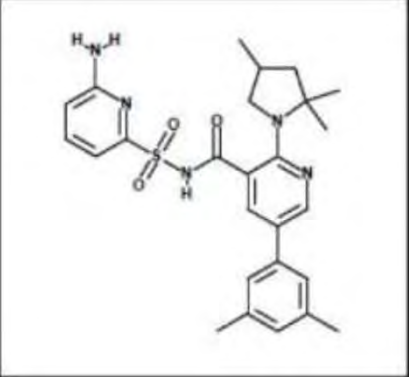
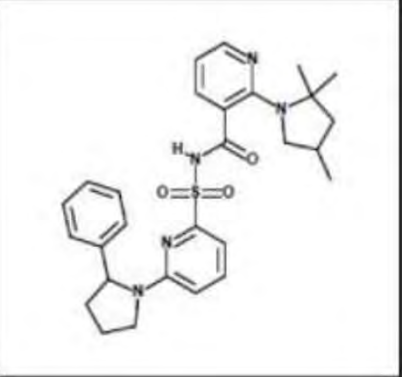
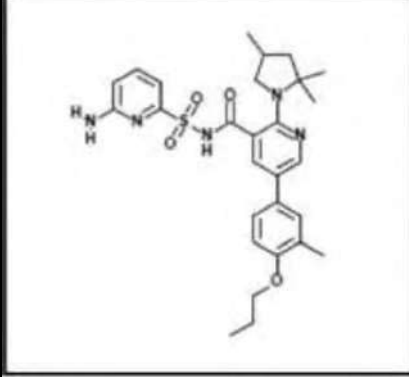
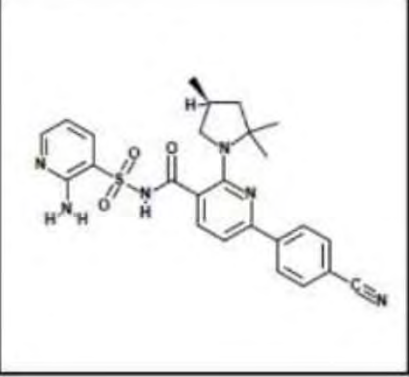
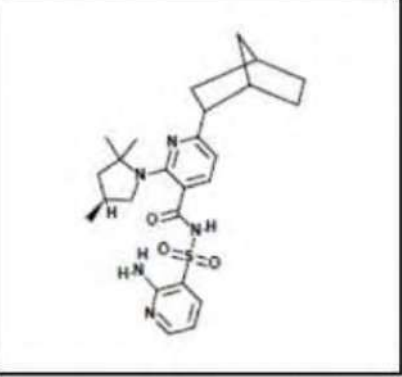
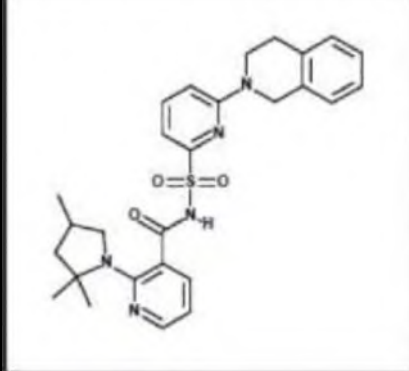
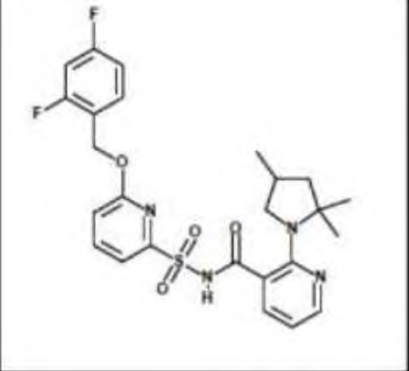
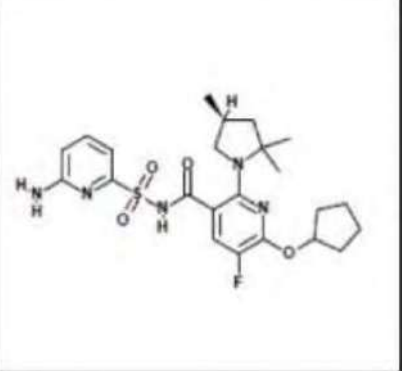
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2038		2040

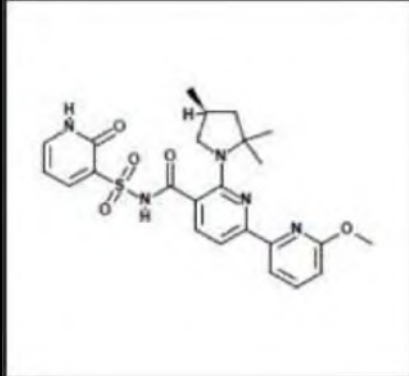
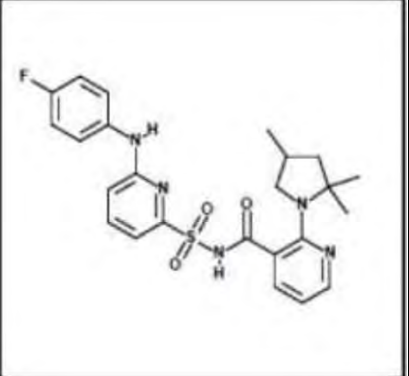
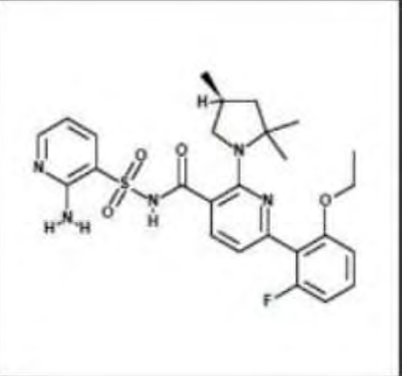
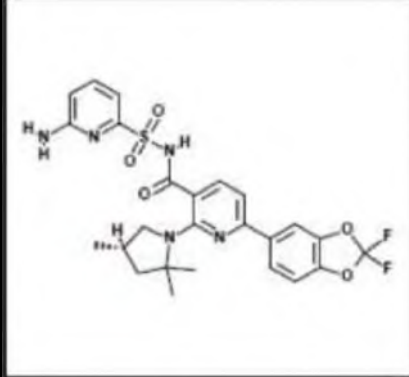
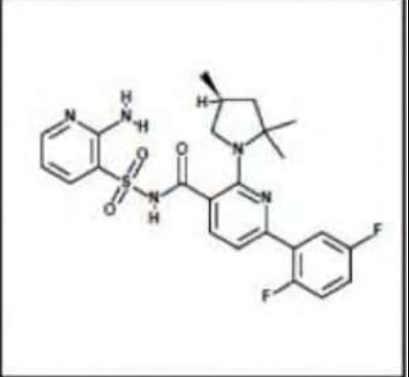
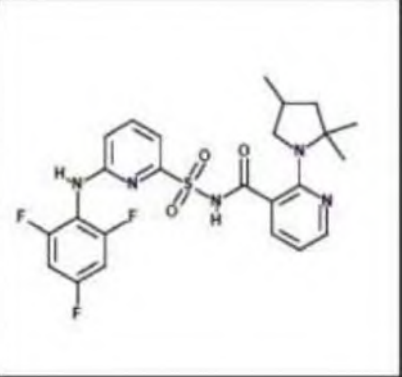
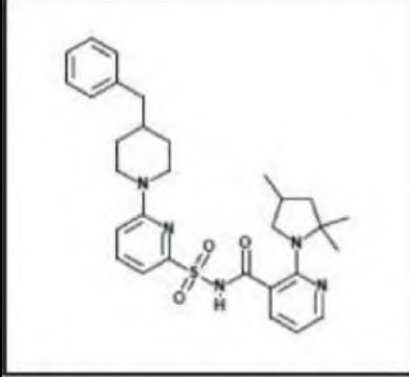
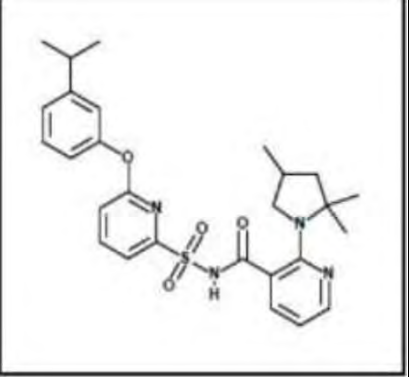
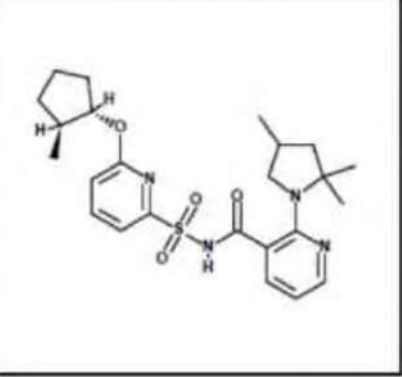
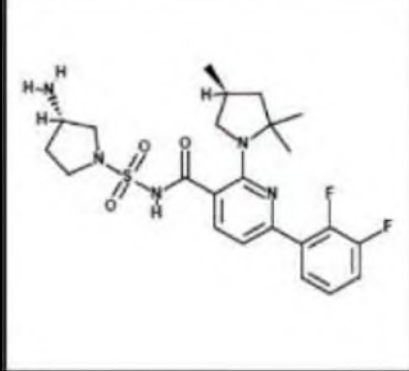
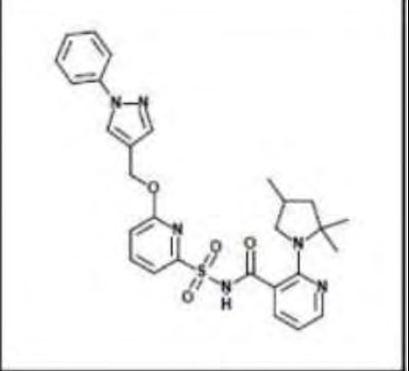
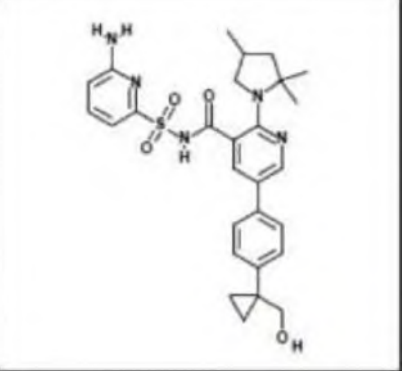
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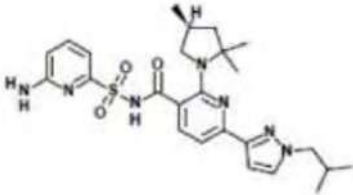
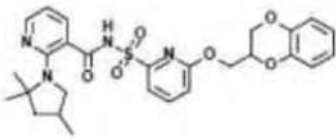
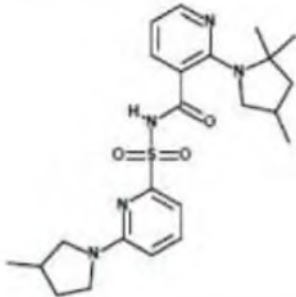
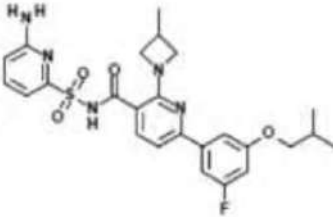
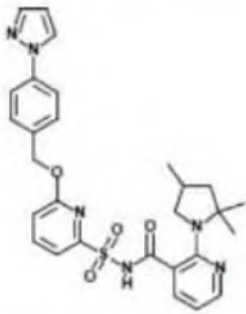
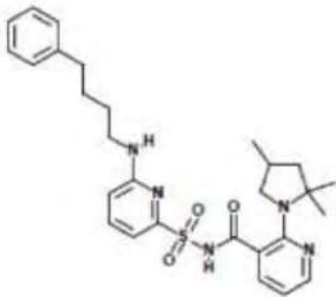
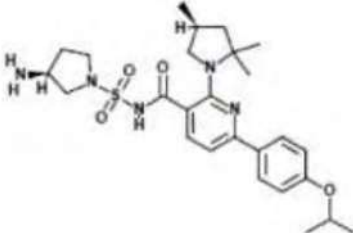
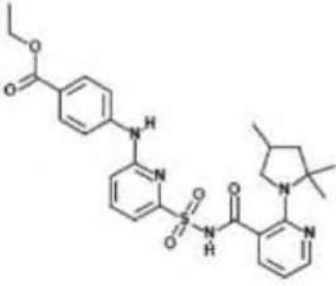
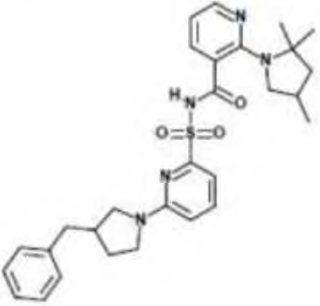
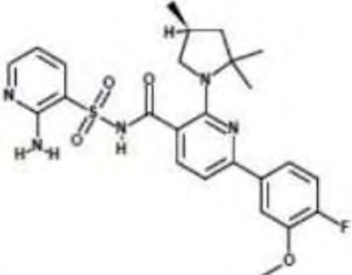
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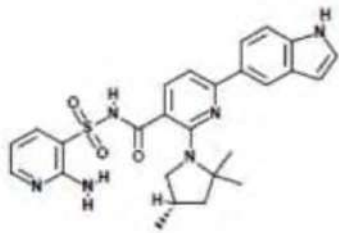
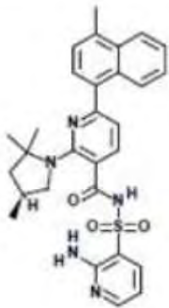
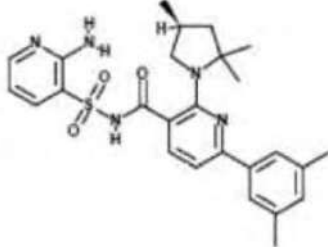
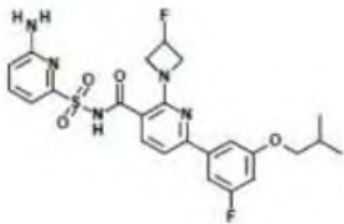
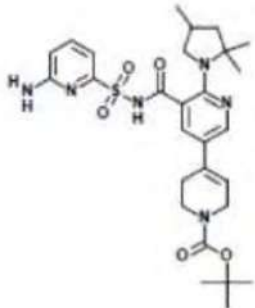
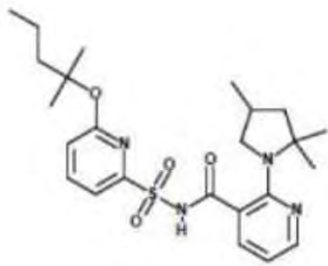
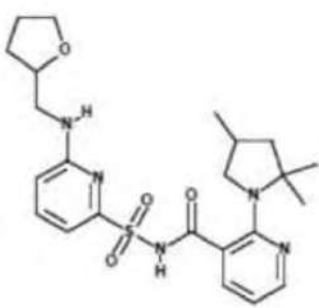
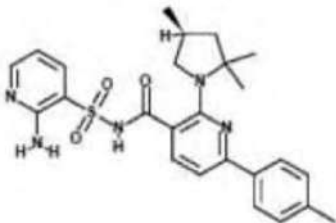
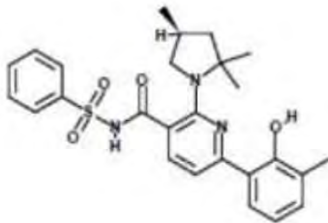
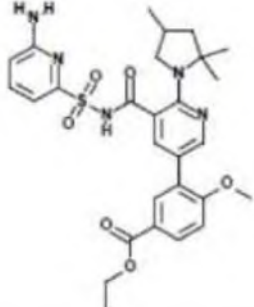
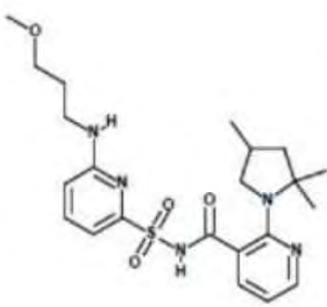
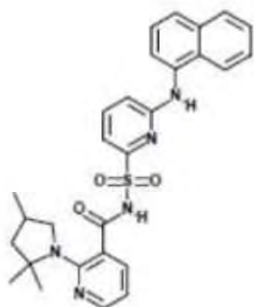
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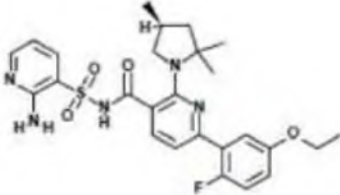
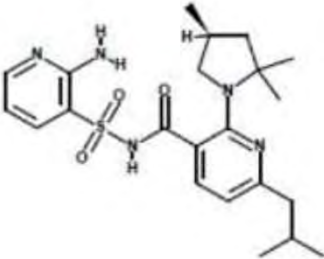
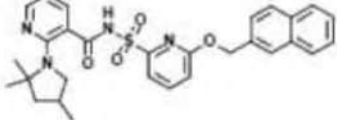
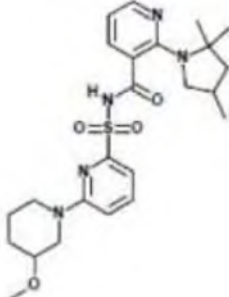
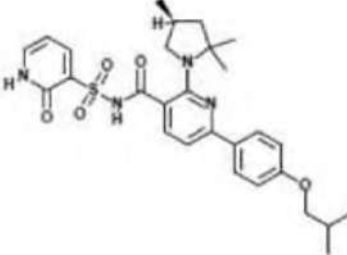
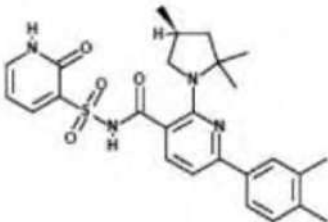
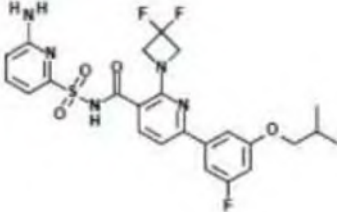
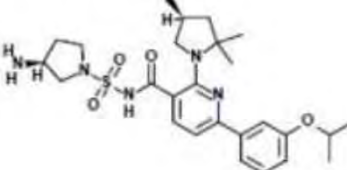
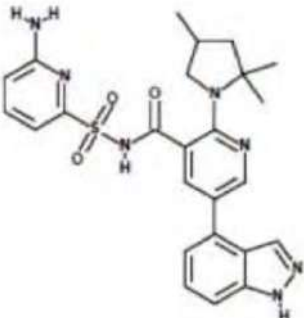
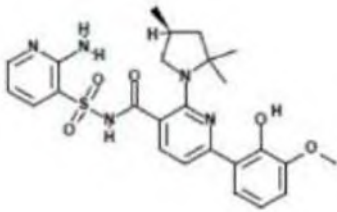
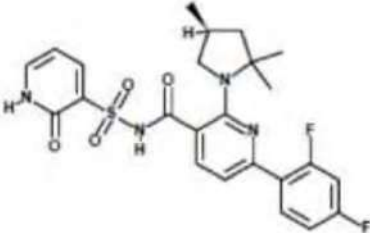
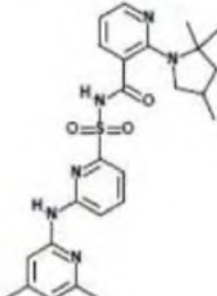
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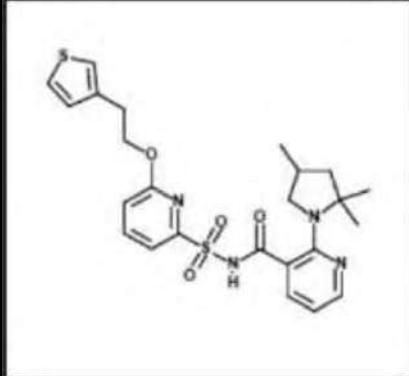
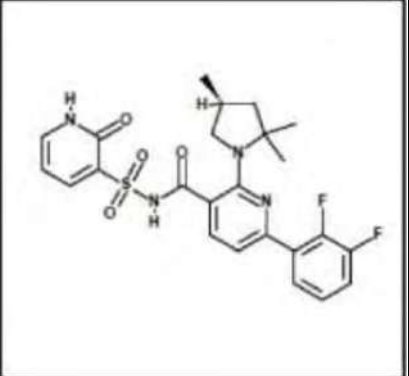
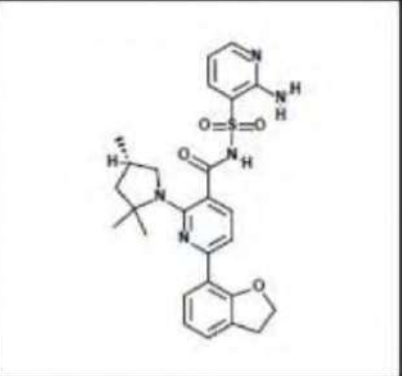
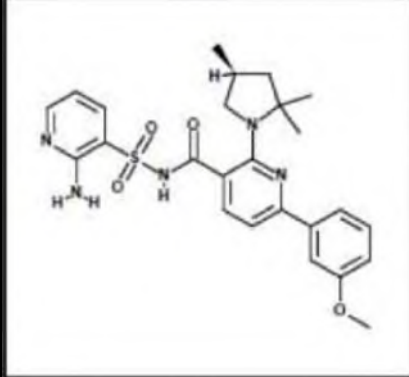
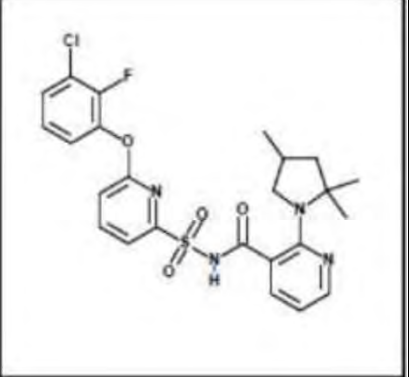
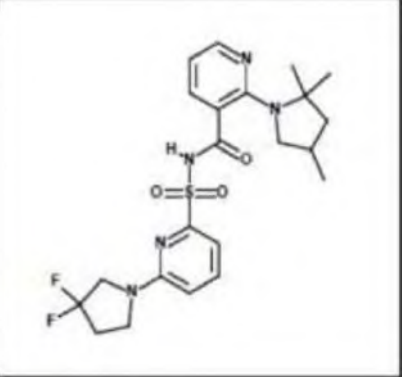
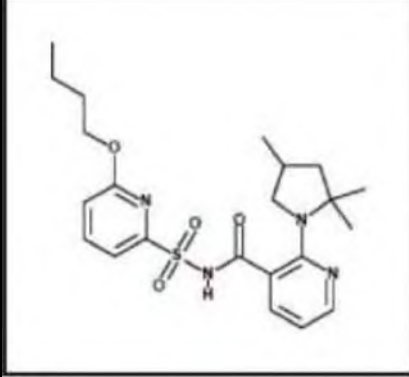
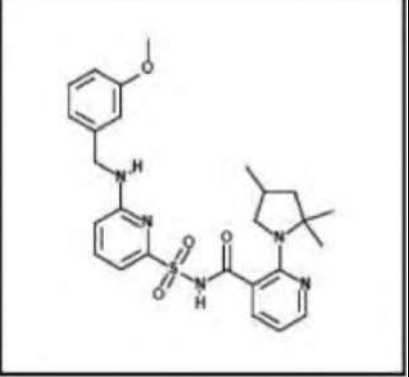
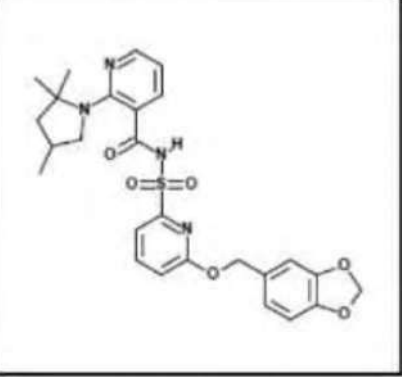
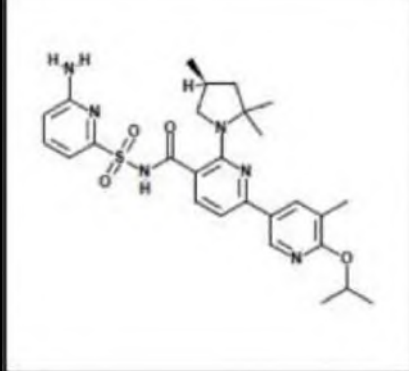
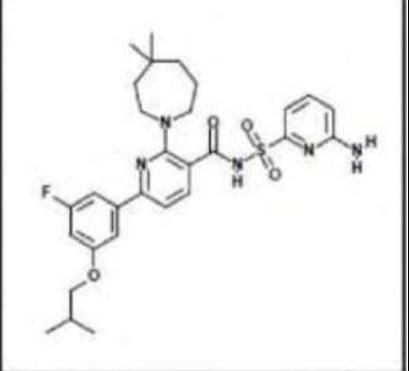
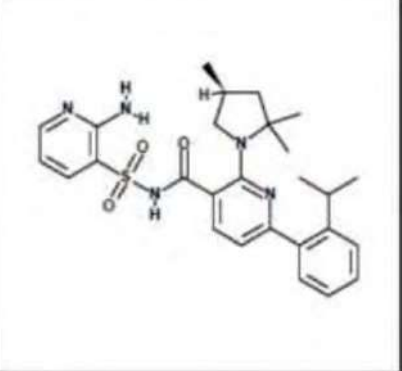
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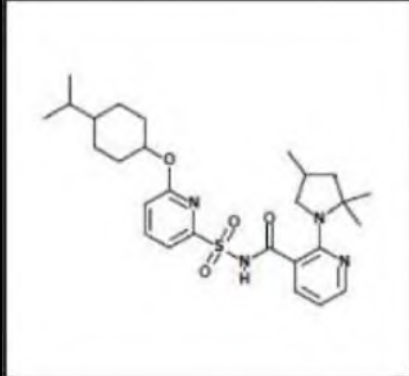
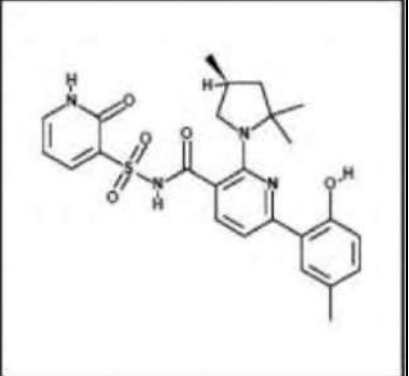
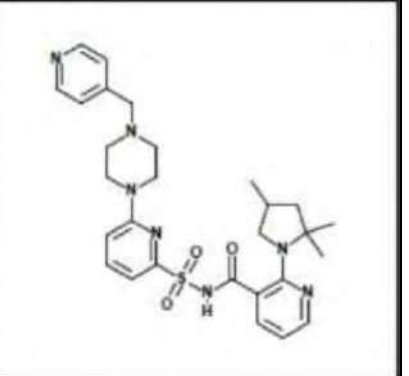
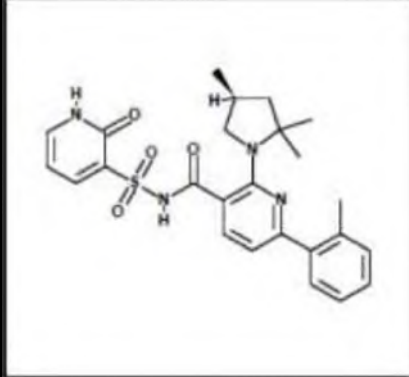
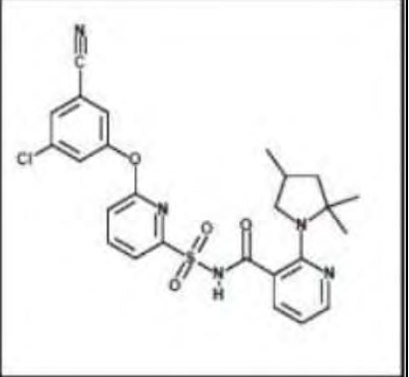
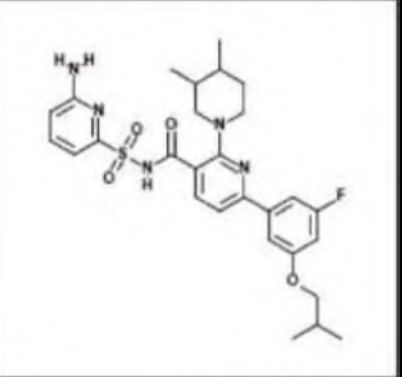
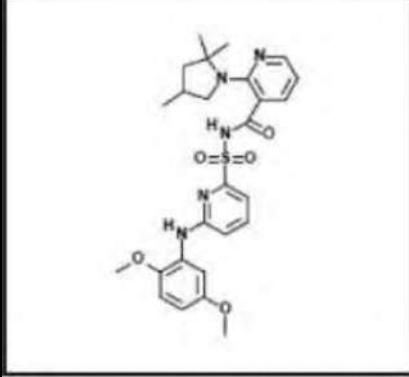
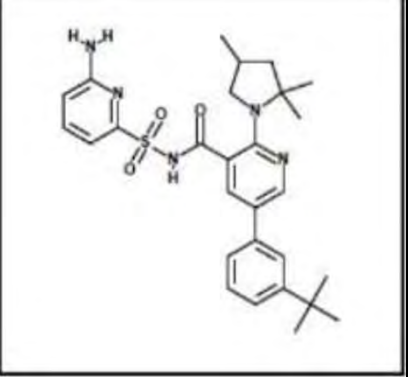
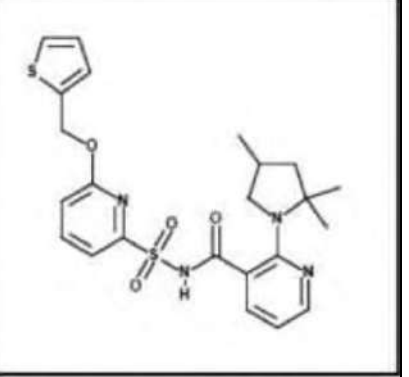
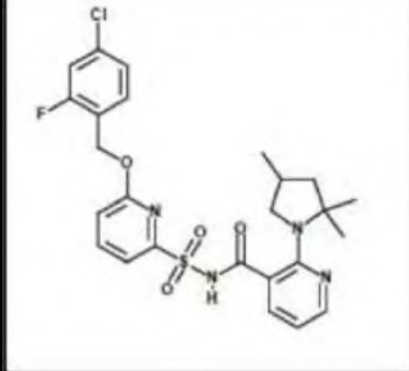
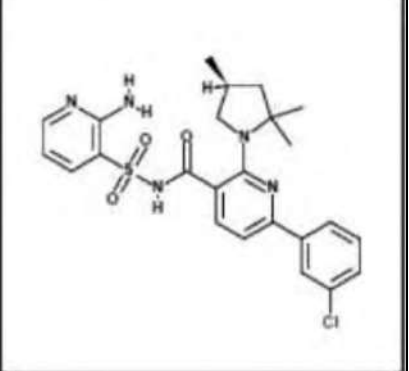
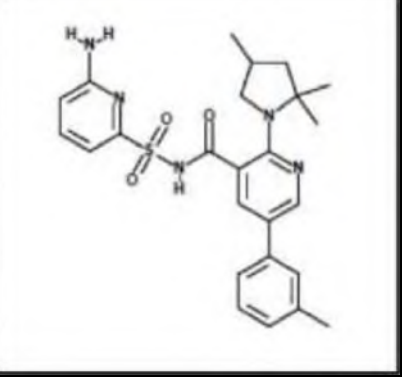
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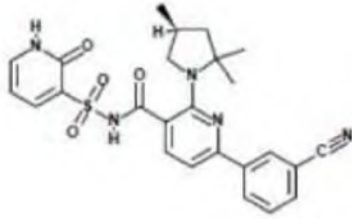
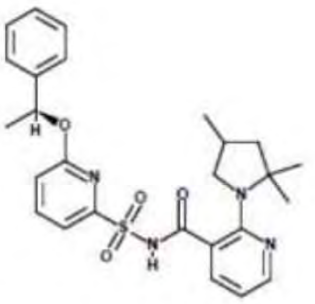
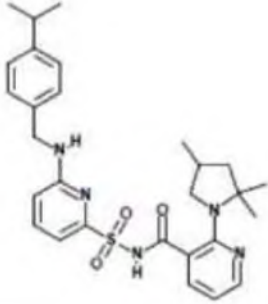
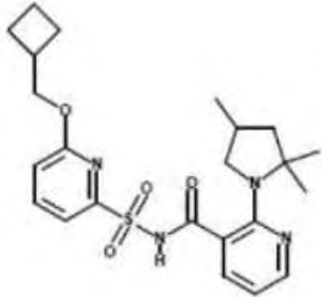
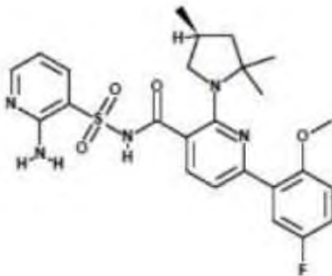
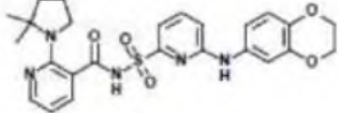
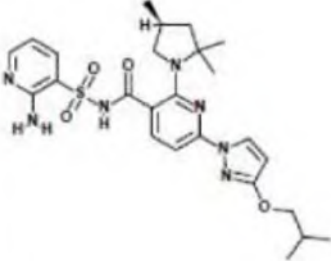
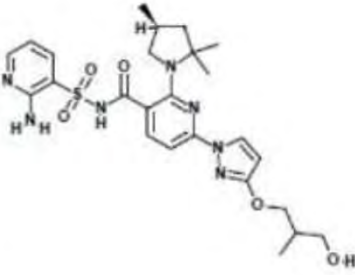
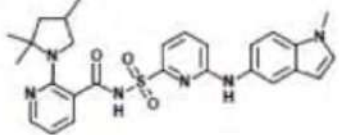
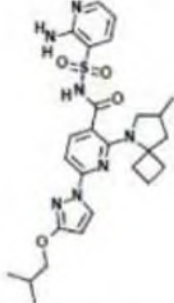
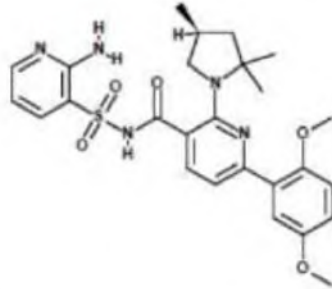
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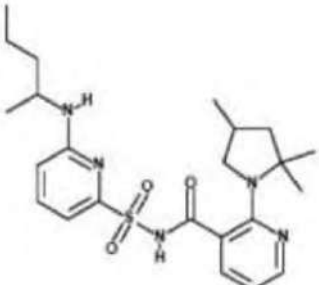
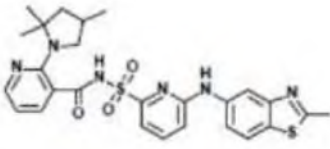
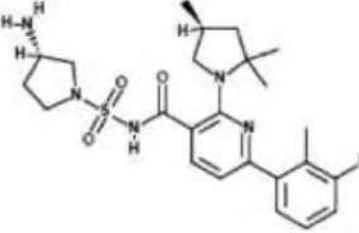
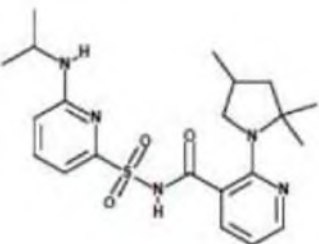
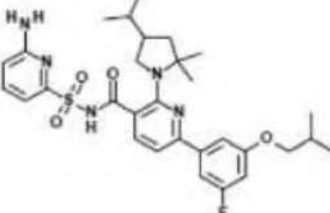
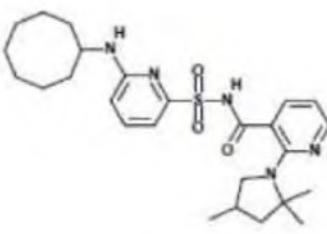
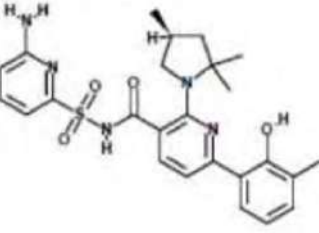
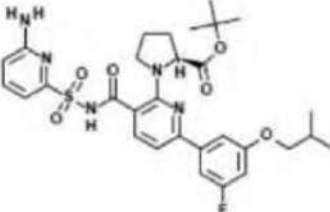
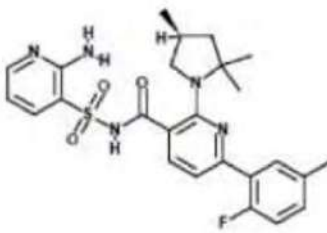
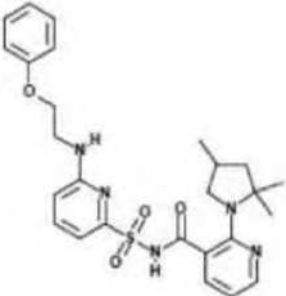
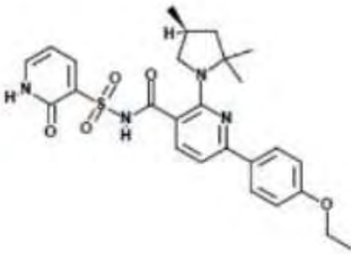
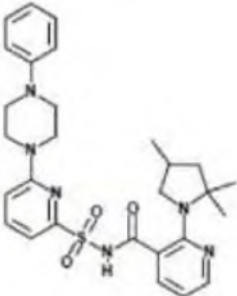
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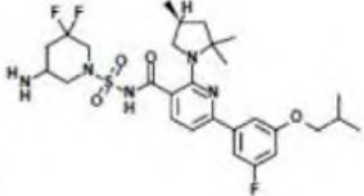
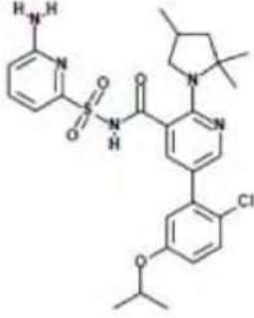
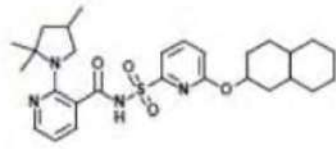
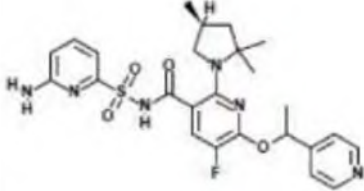
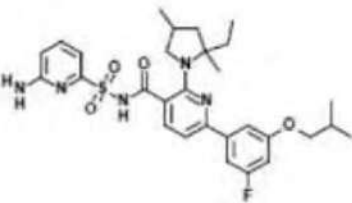
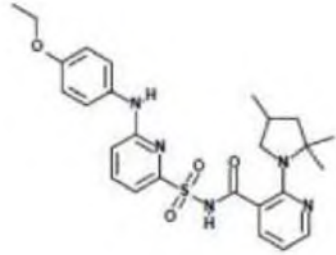
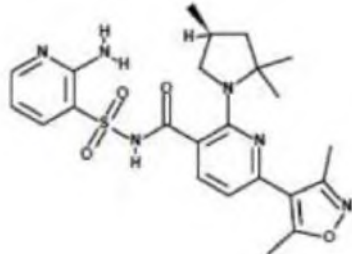
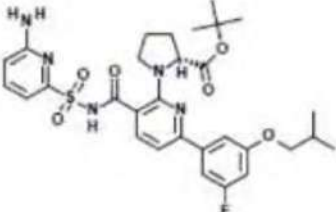
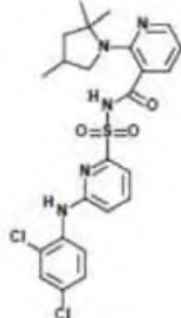
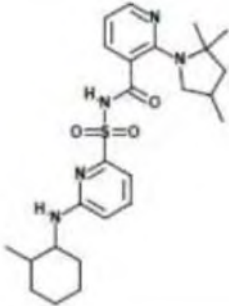
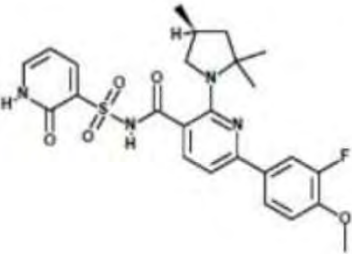
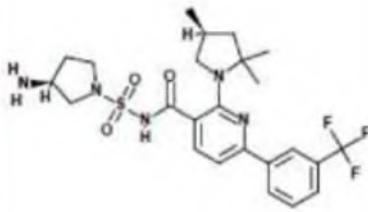
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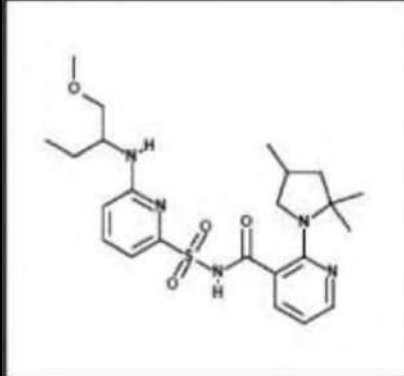
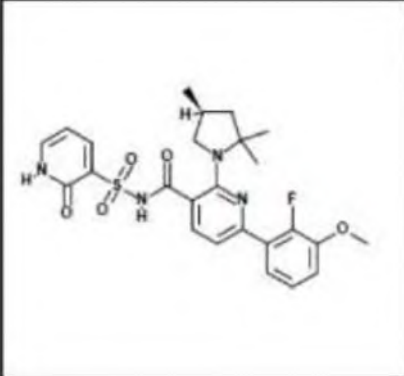
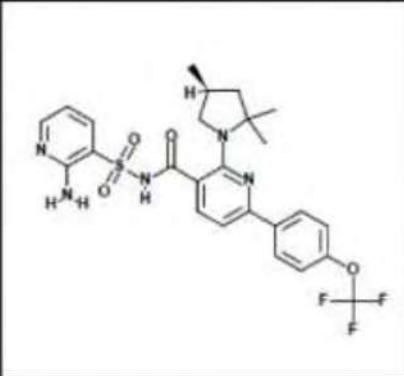
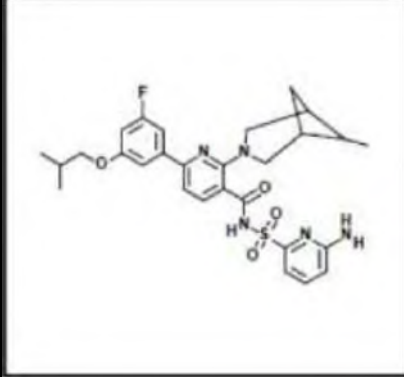
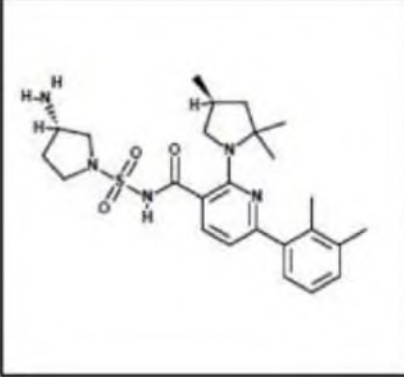
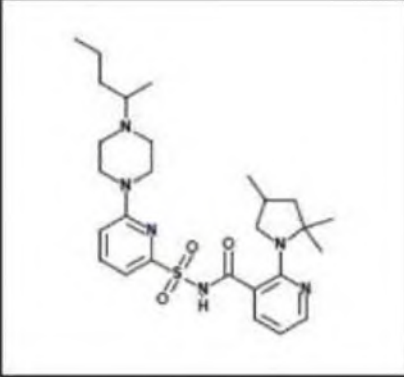
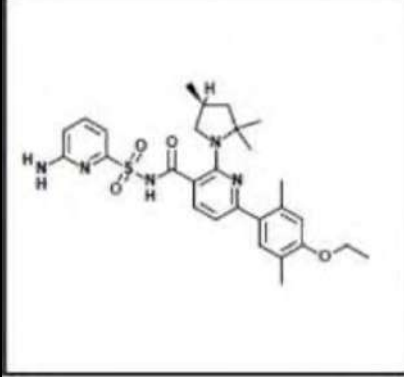
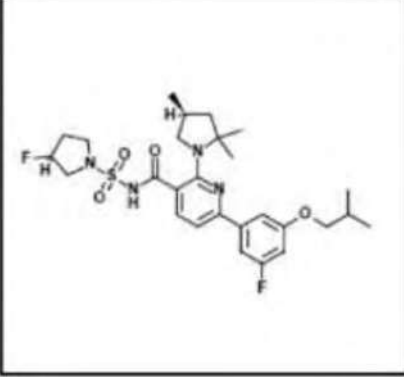
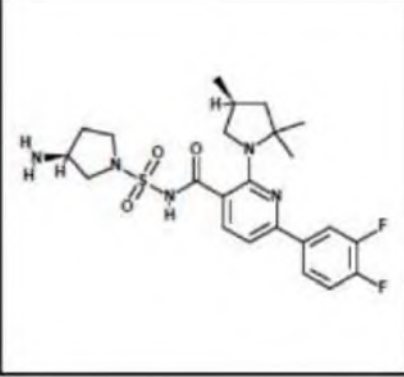
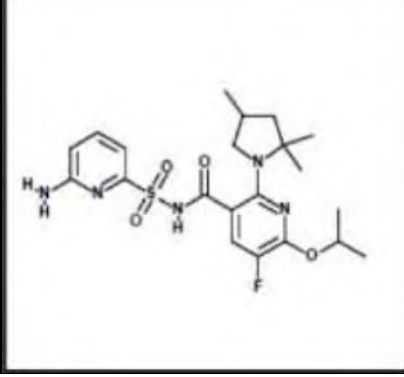
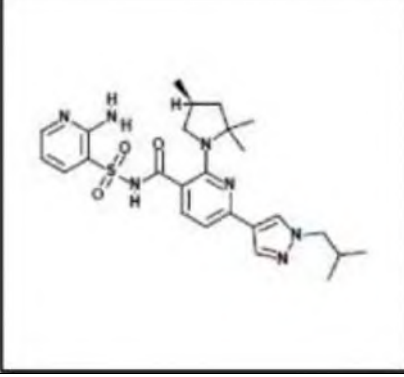
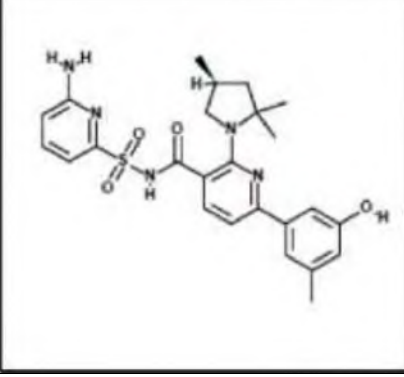
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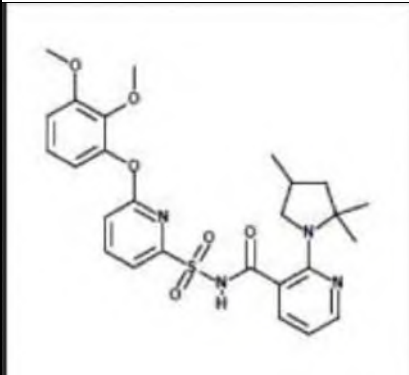
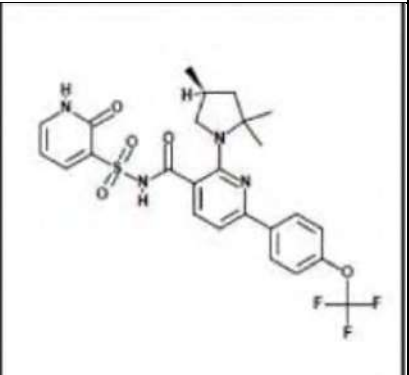
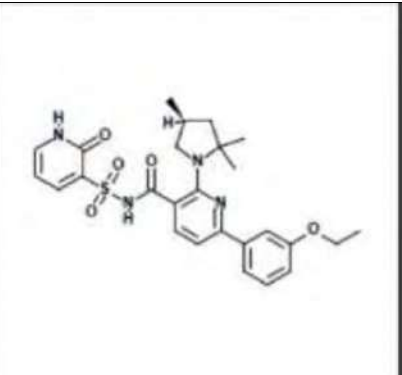
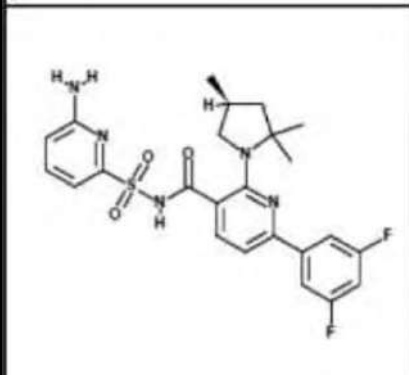
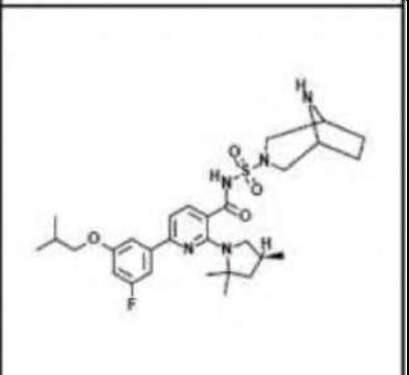
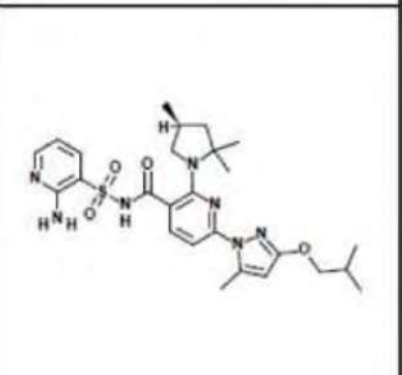
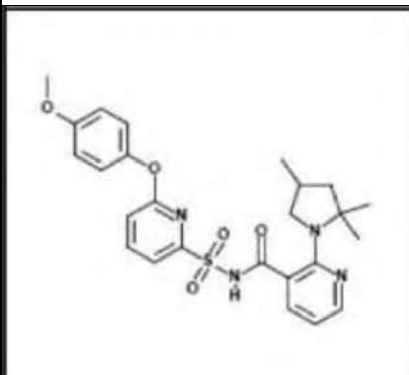
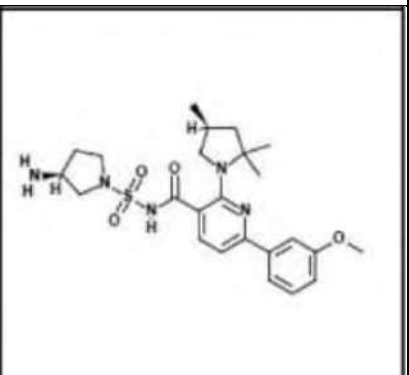
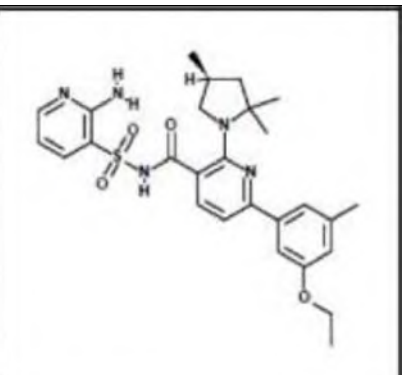
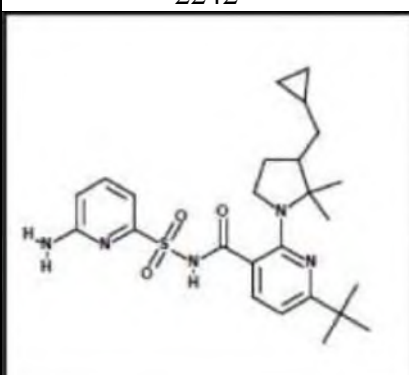
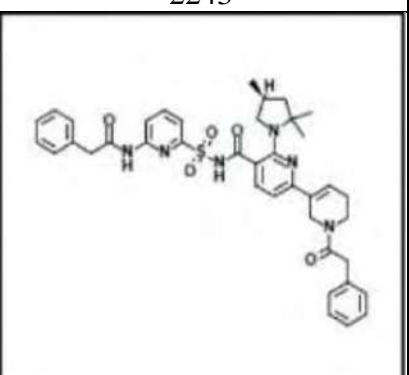
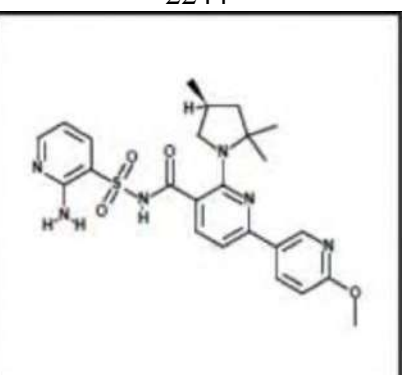
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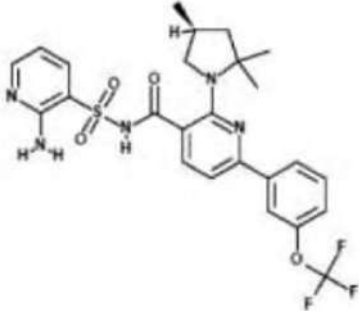
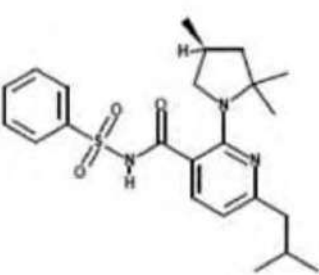
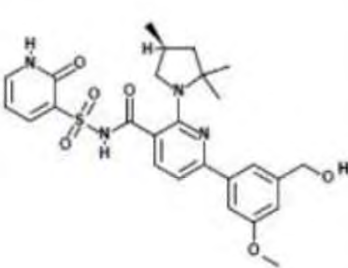
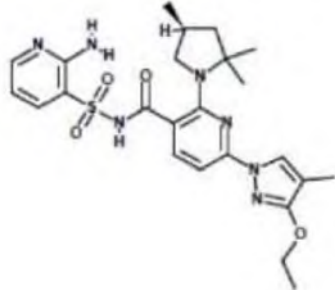
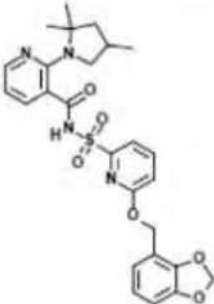
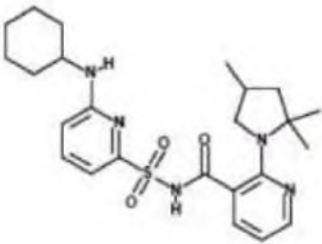
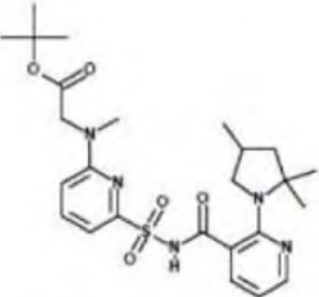
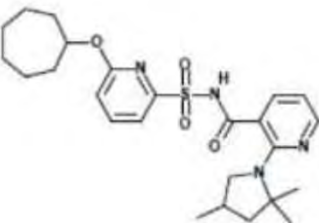
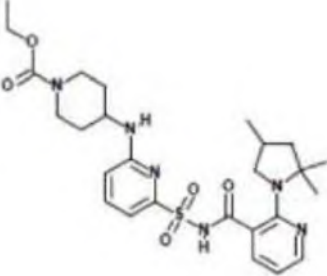
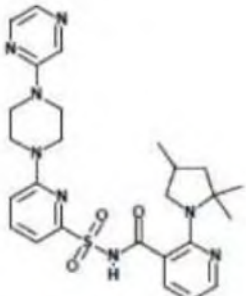
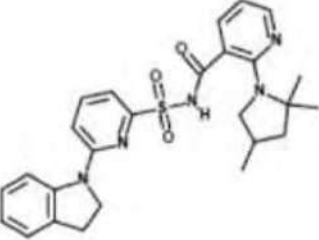
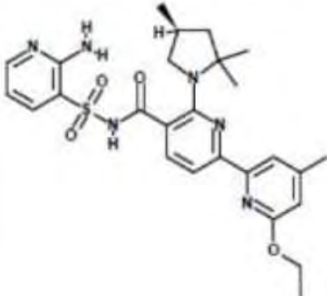
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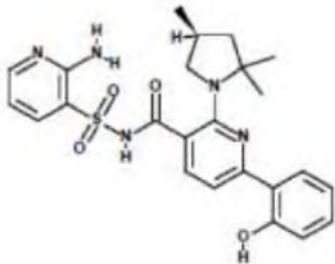
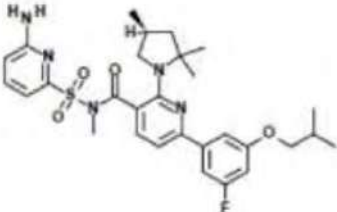
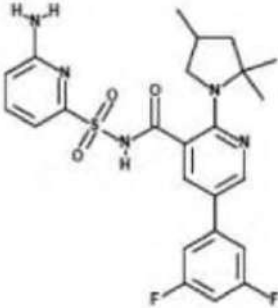
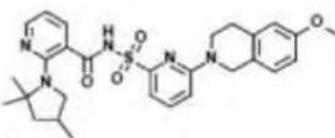
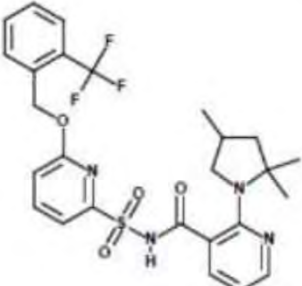
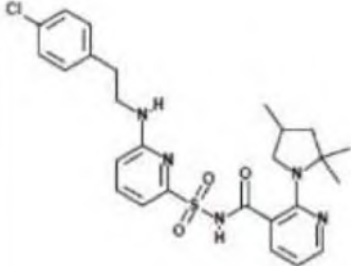
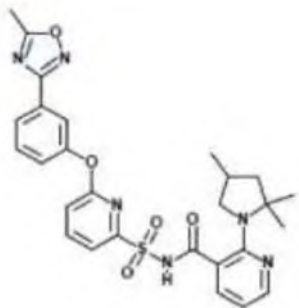
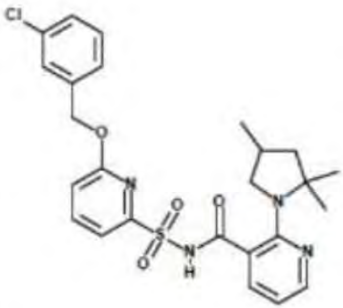
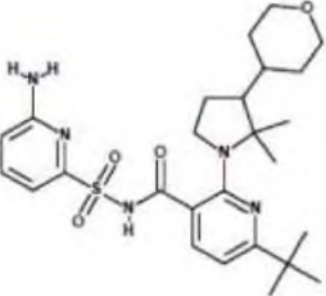
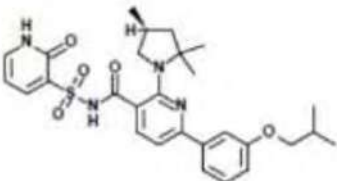
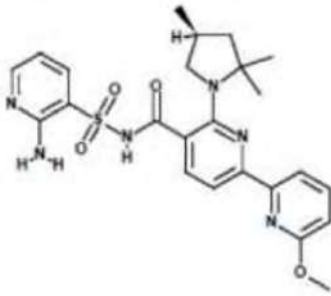
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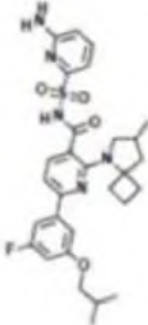
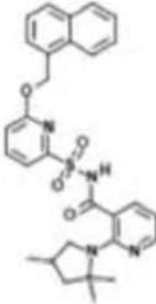
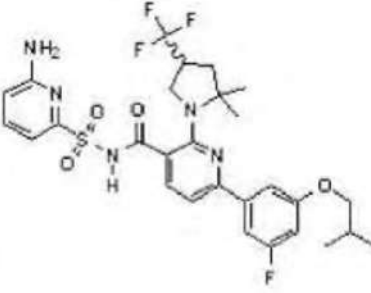
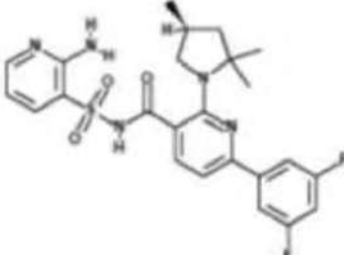
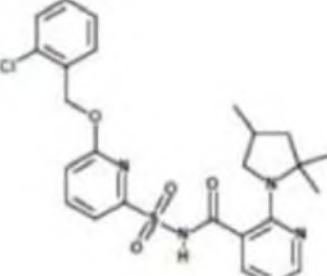
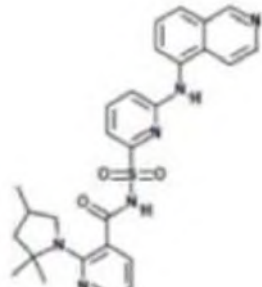
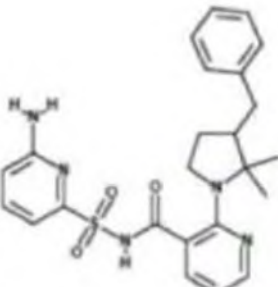
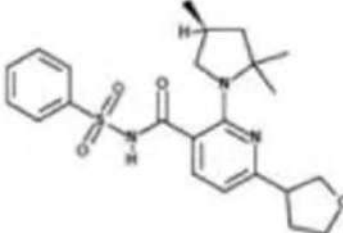
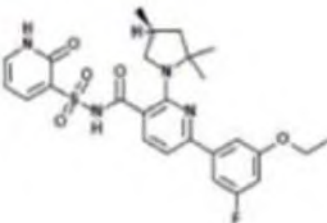
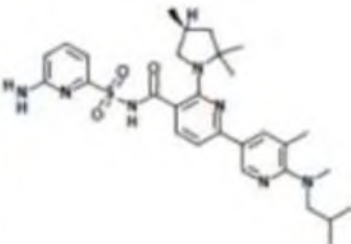
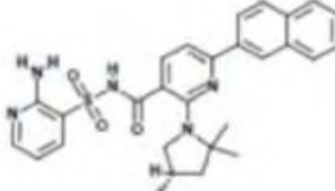
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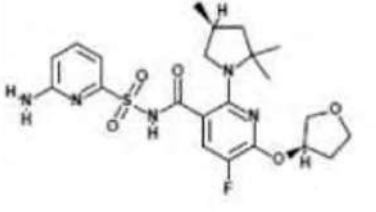
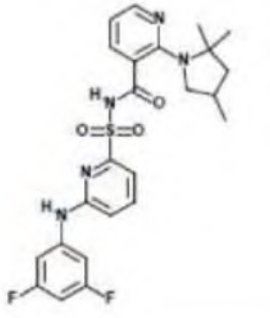
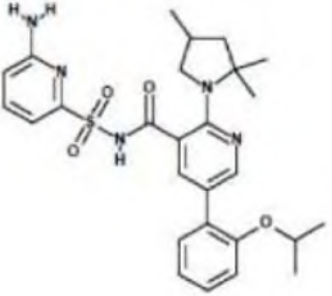
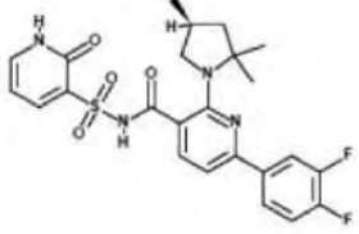
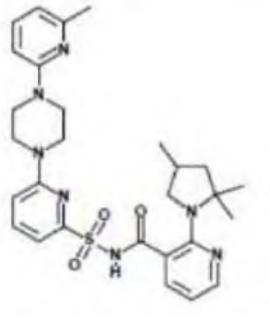
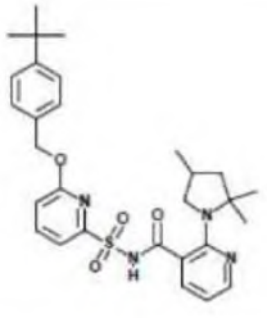
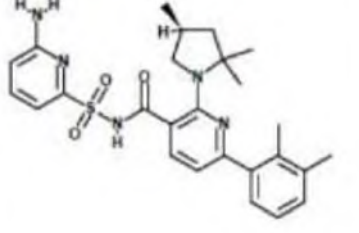
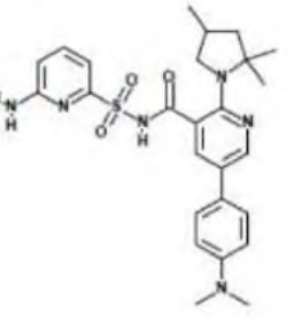
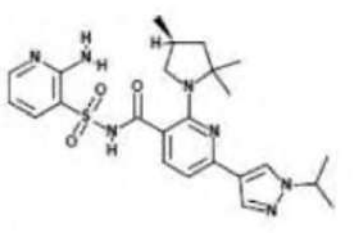
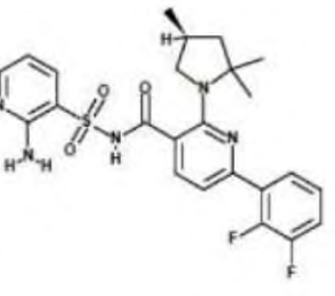
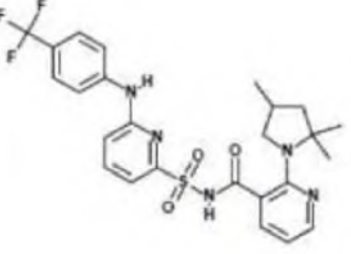
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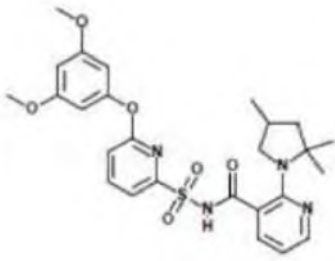
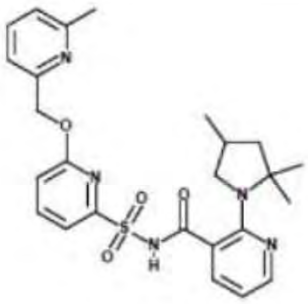
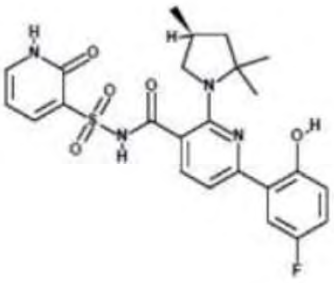
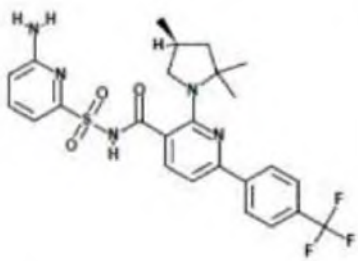
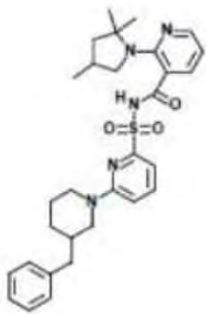
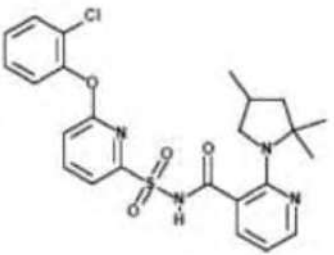
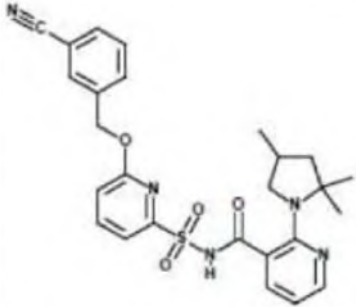
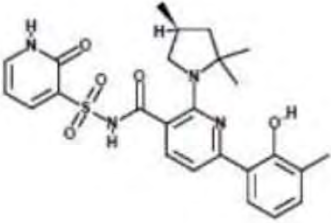
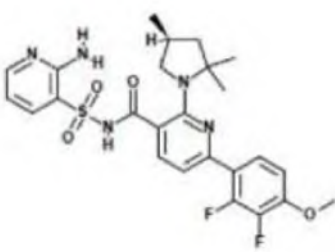
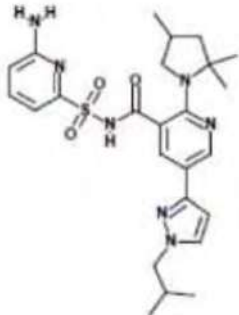
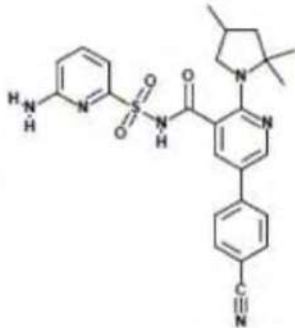
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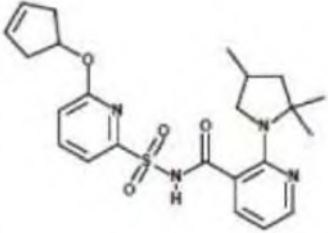
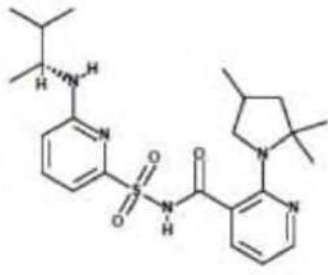
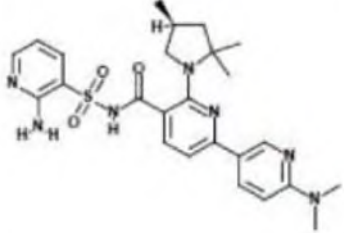
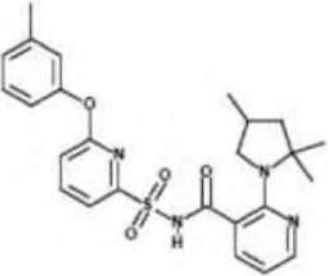
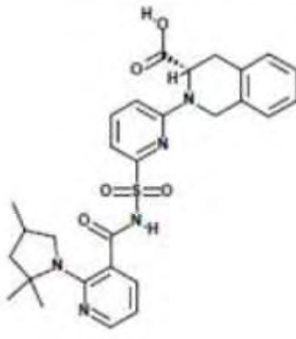
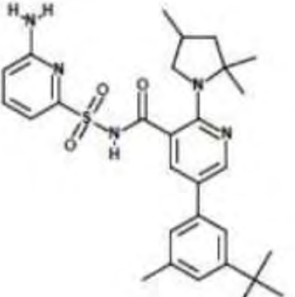
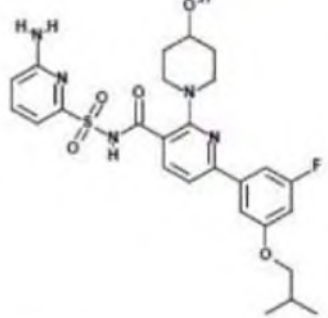
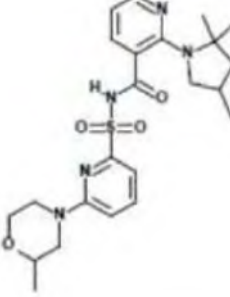
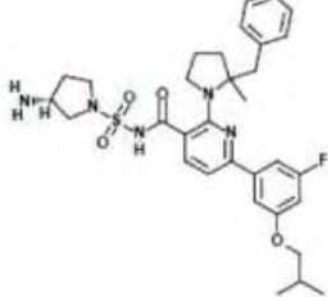
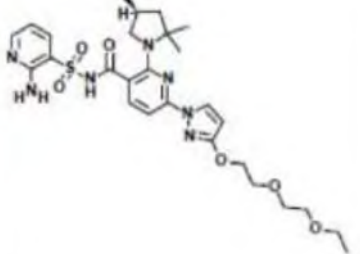
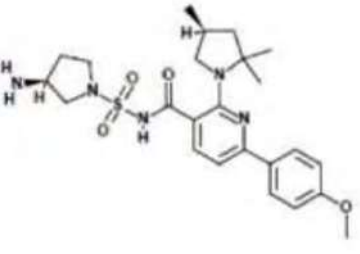
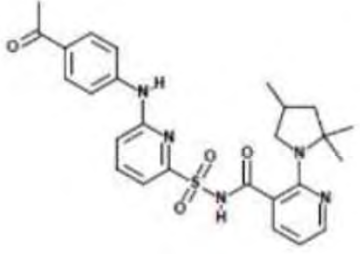
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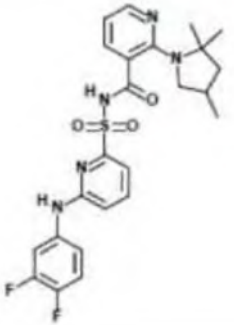
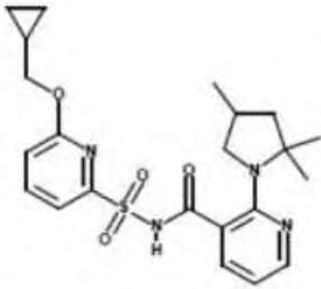
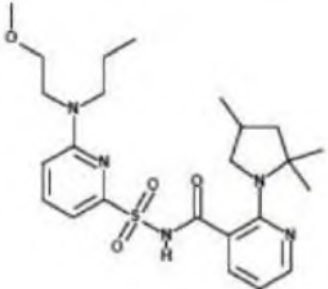
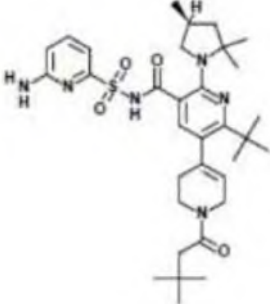
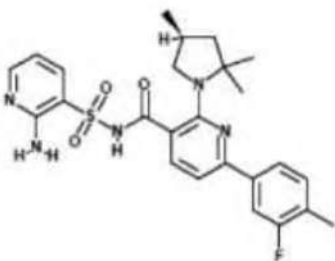
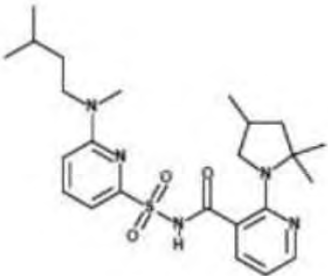
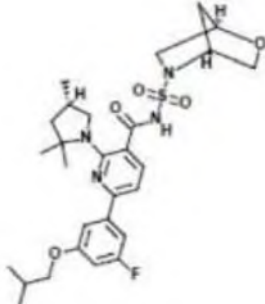
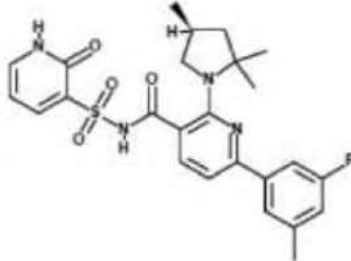
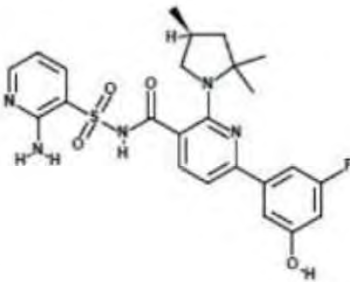
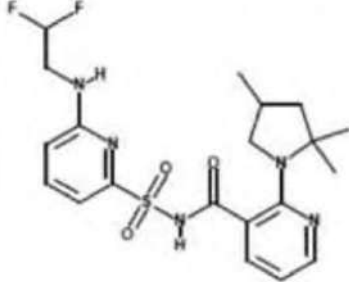
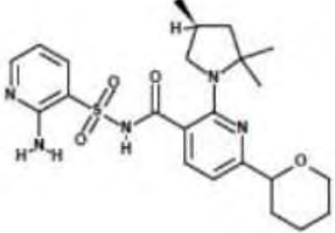
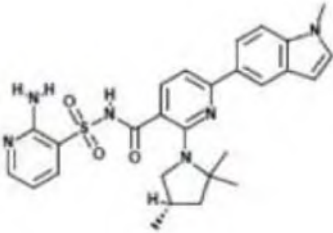
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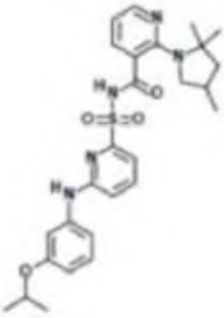
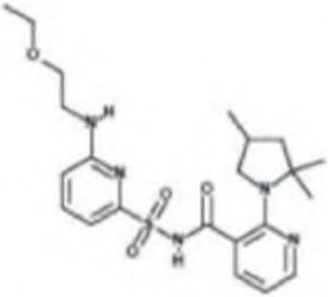
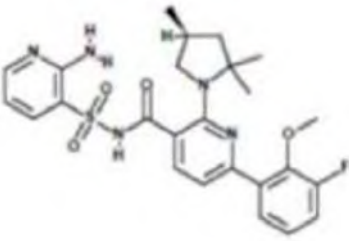
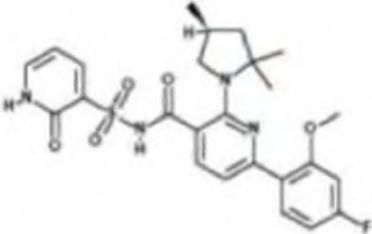
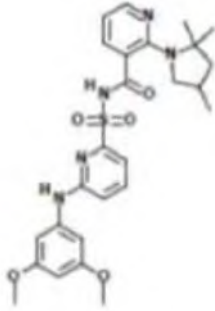
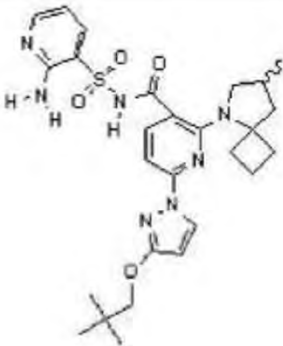
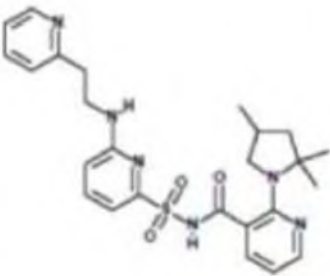
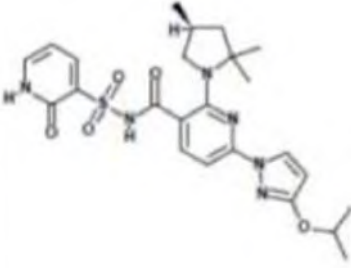
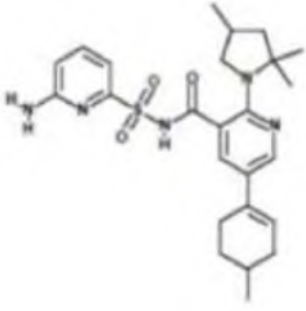
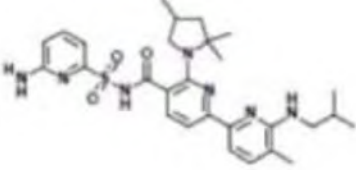
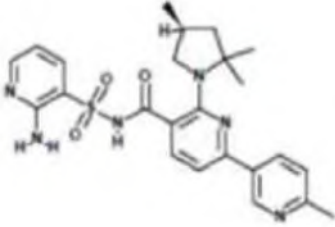
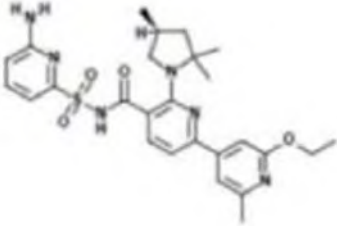
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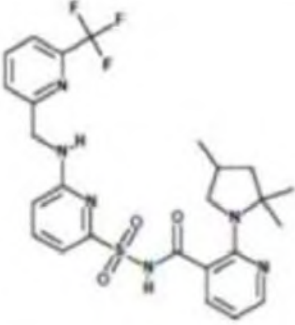
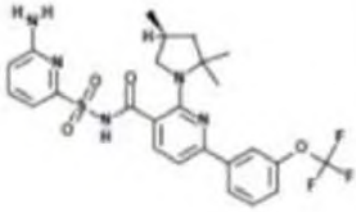
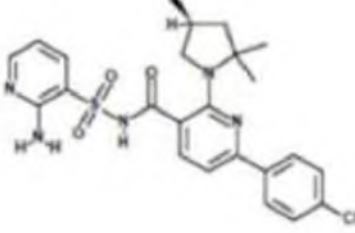
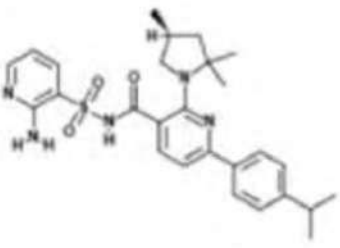
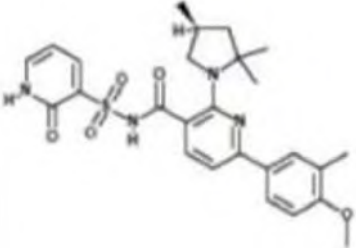
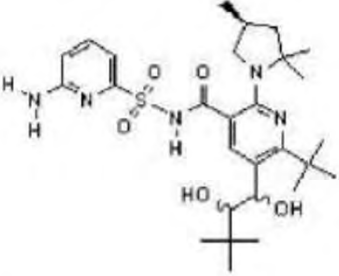
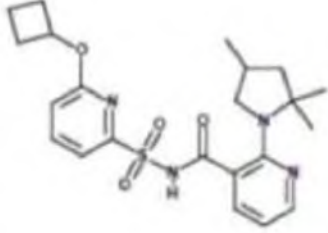
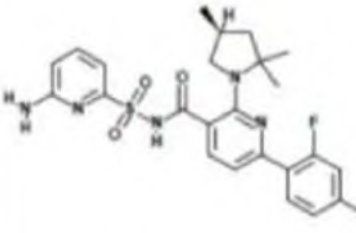
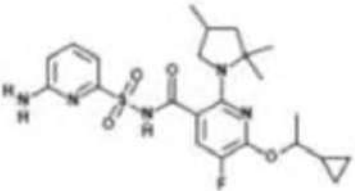
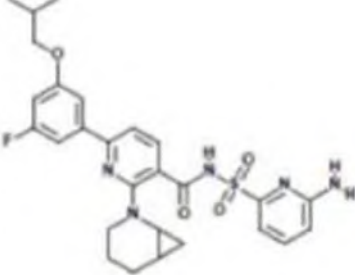
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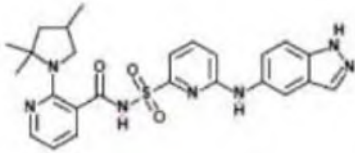
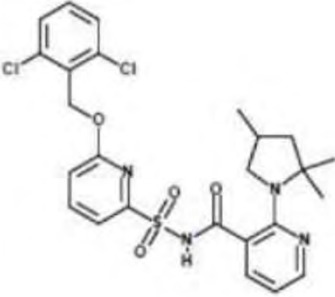
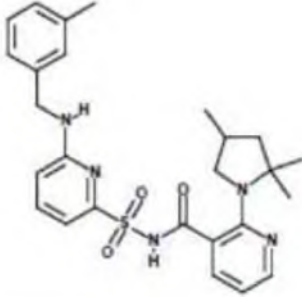
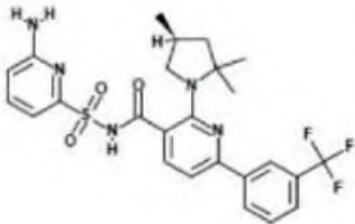
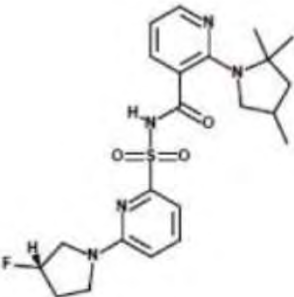
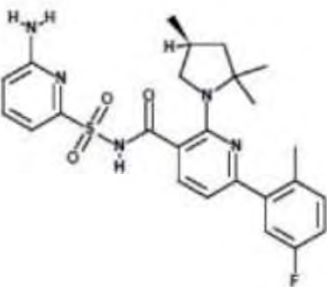
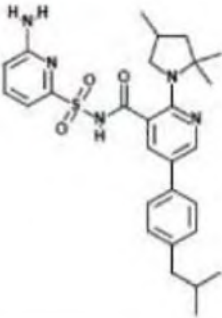
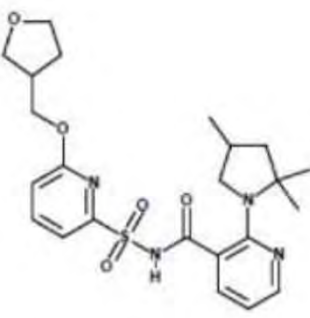
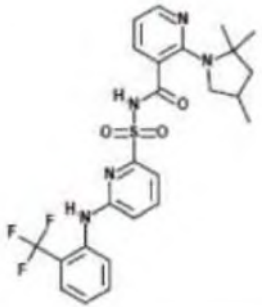
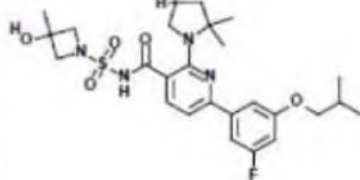
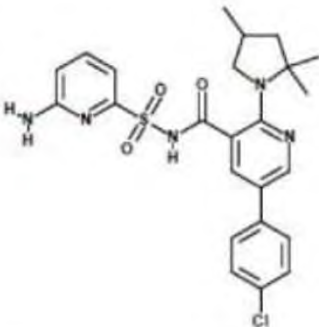
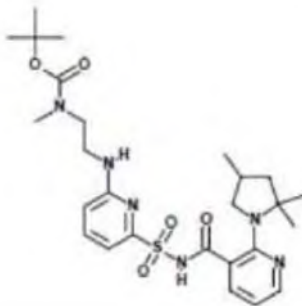
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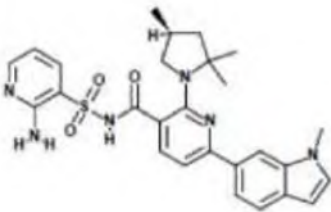
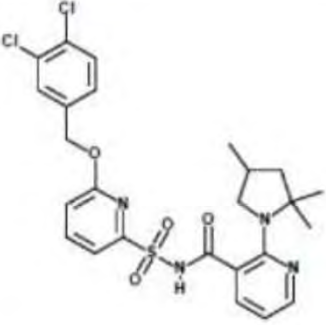
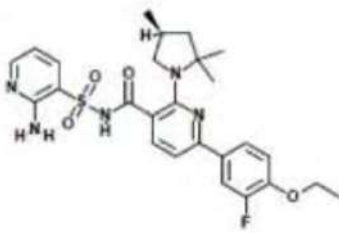
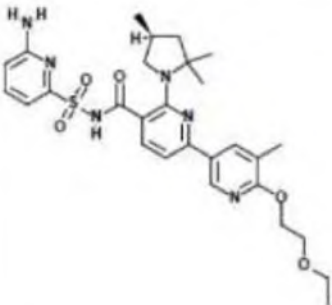
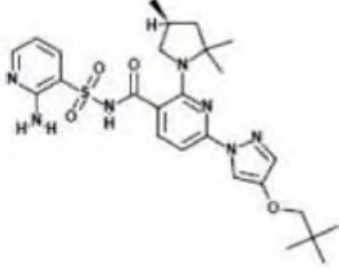
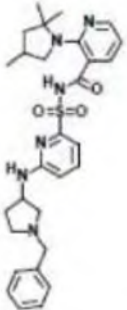
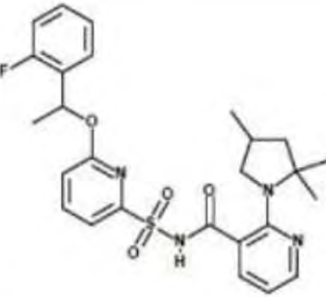
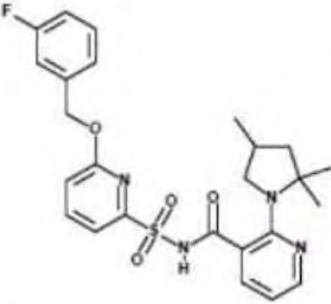
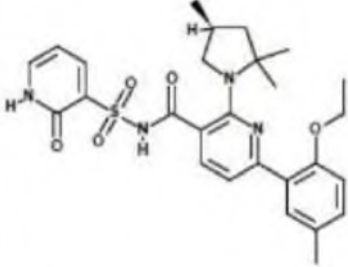
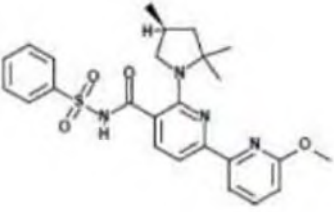
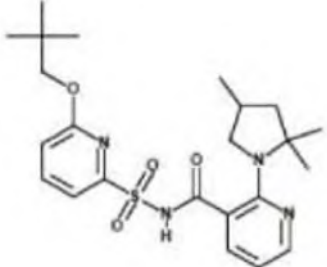
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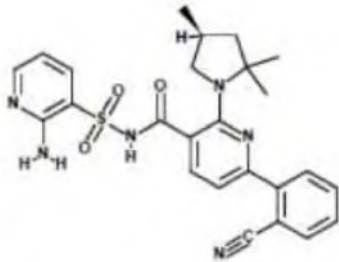
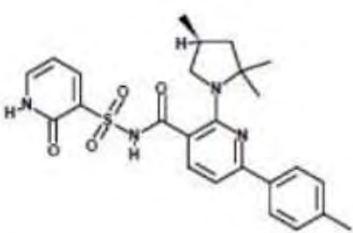
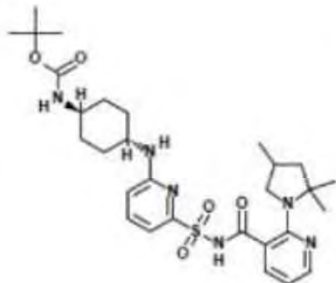
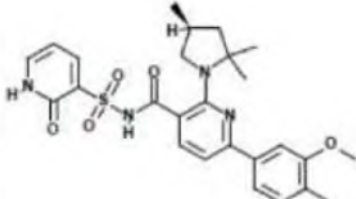
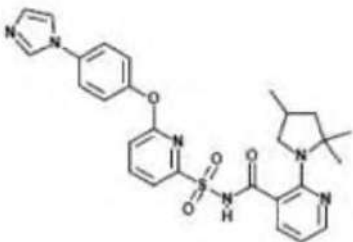
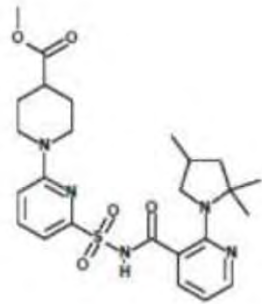
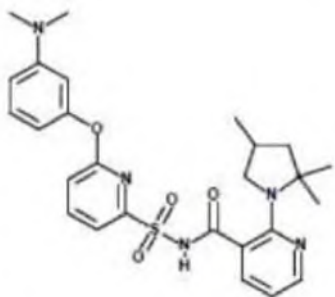
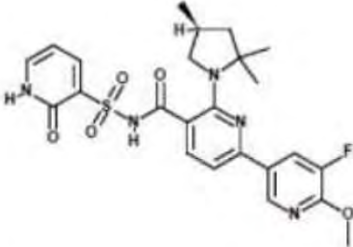
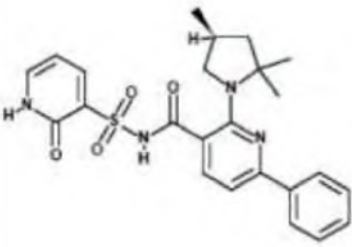
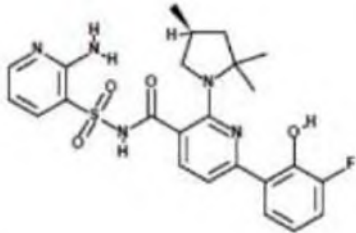
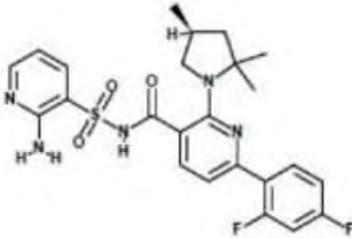
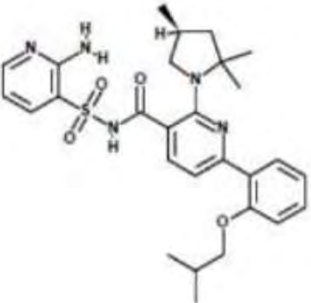
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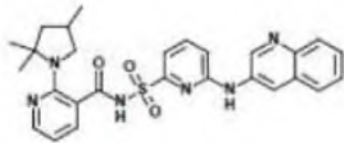
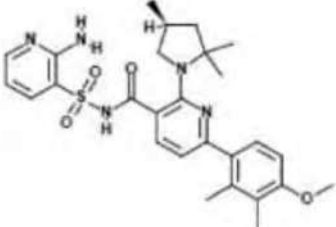
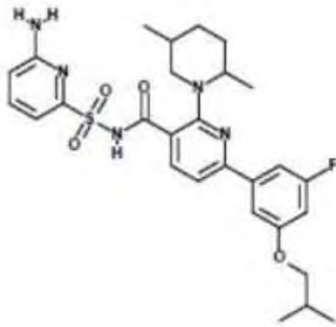
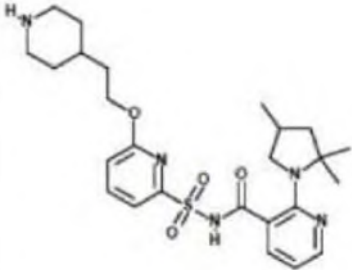
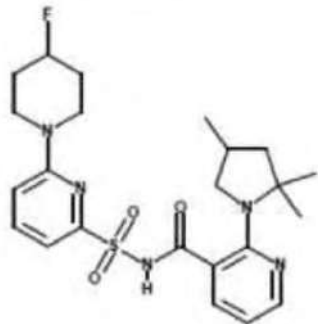
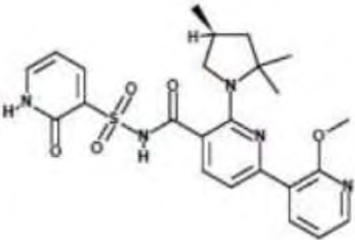
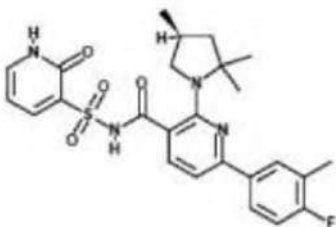
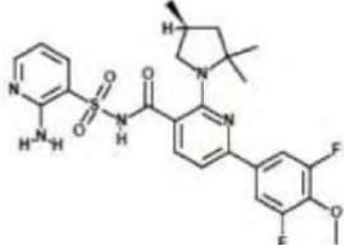
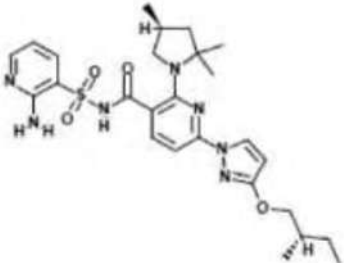
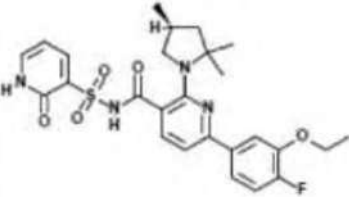
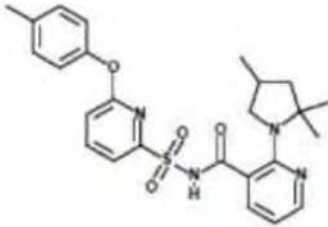
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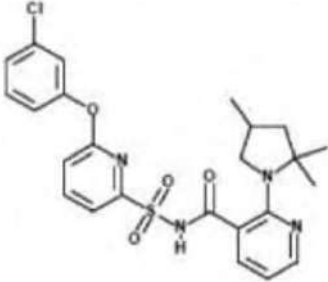
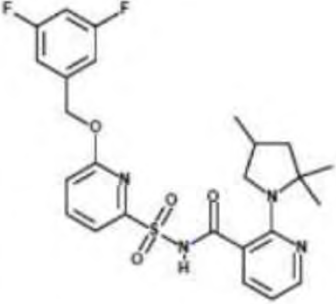
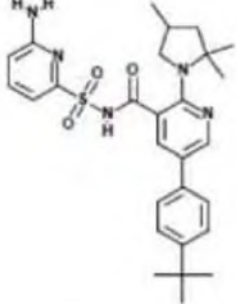
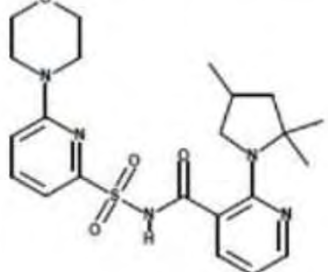
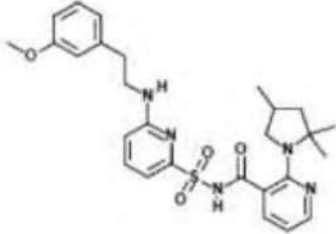
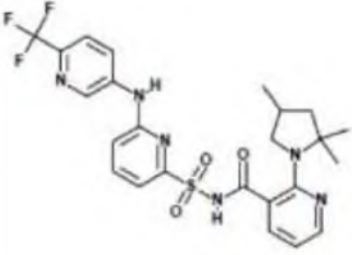
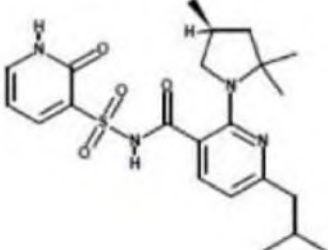
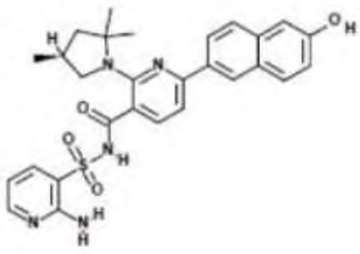
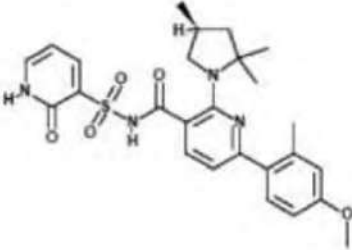
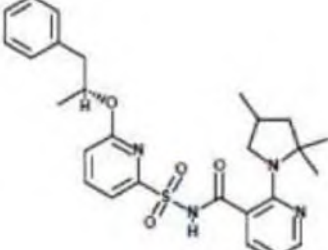
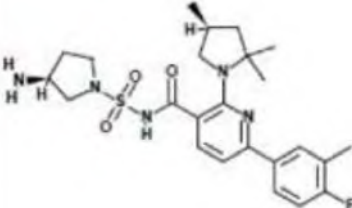
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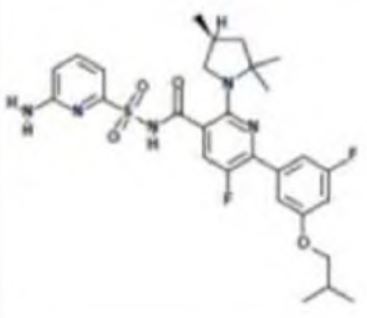
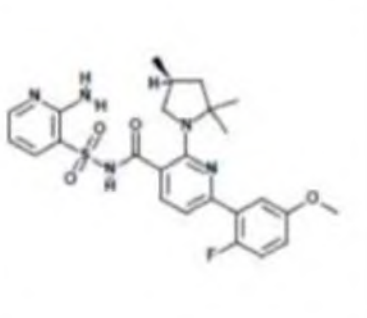
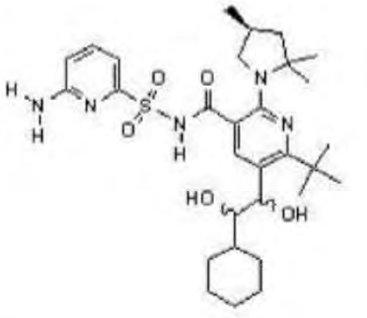
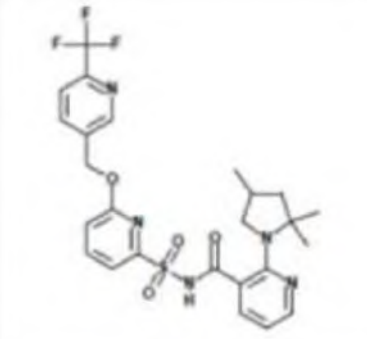
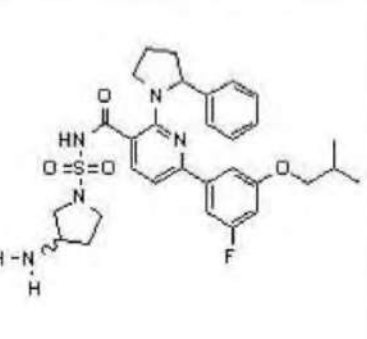
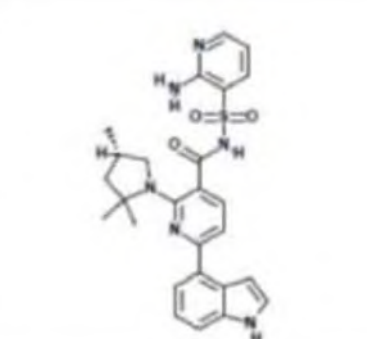
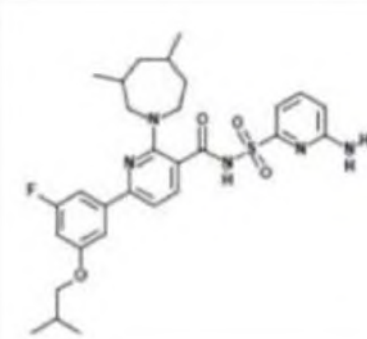
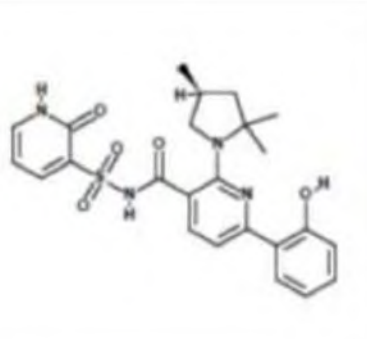
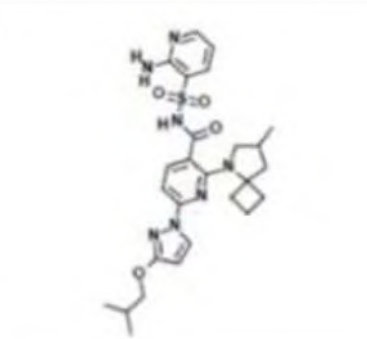
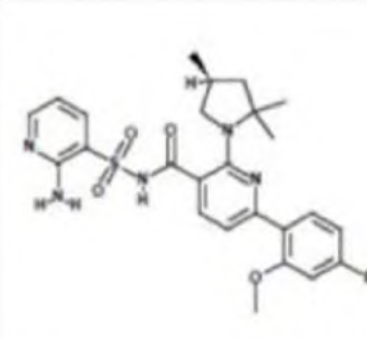
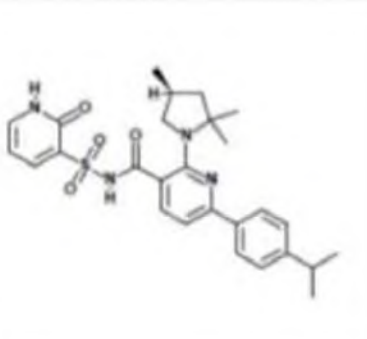
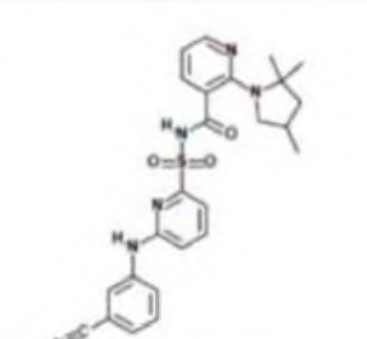
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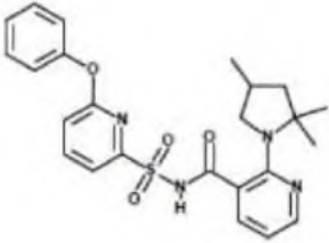
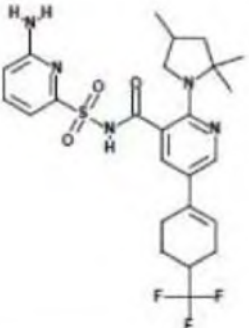
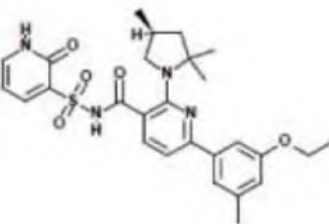
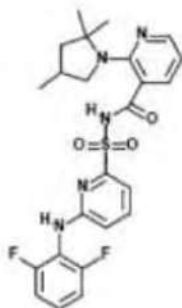
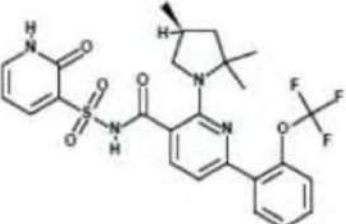
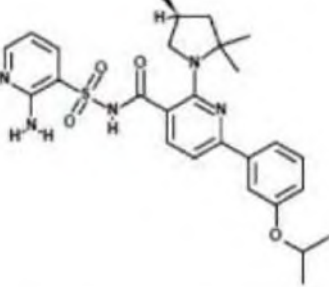
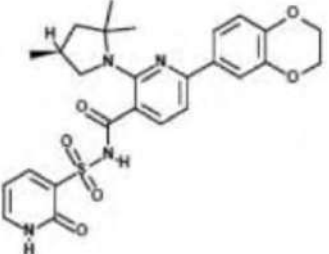
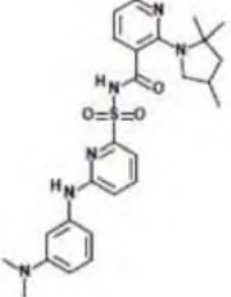
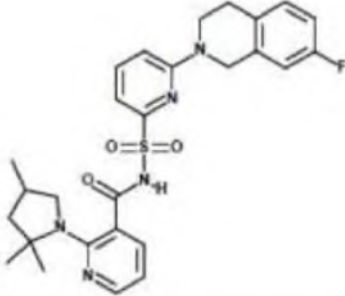
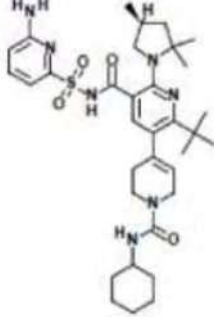
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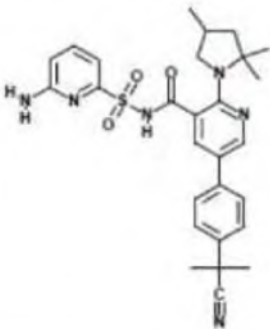
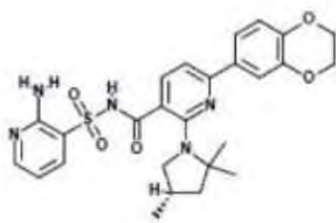
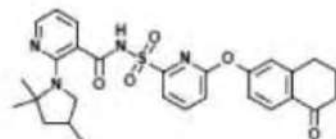
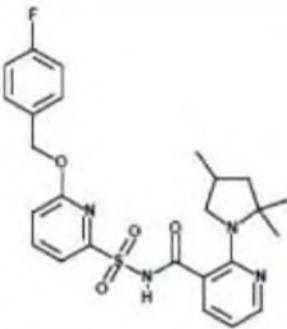
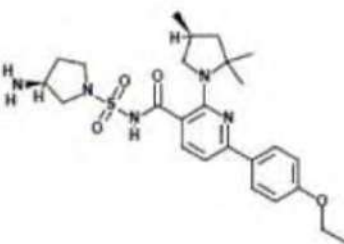
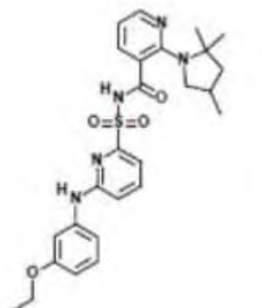
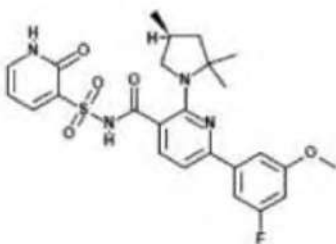
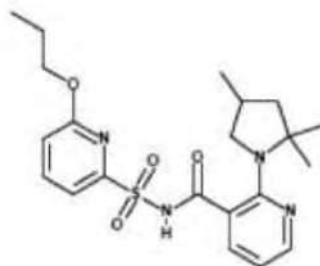
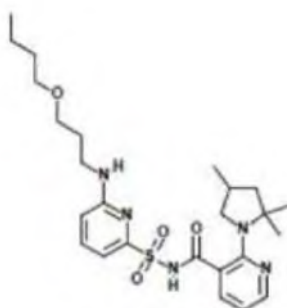
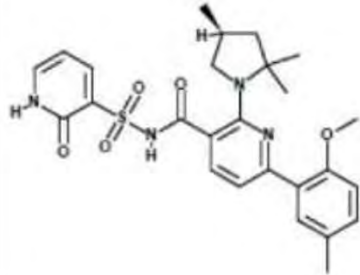
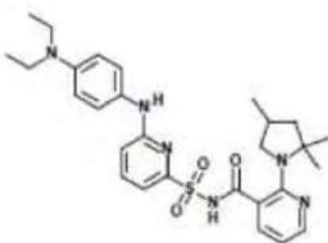
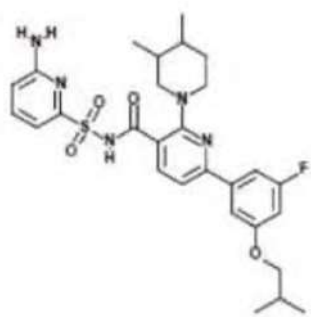
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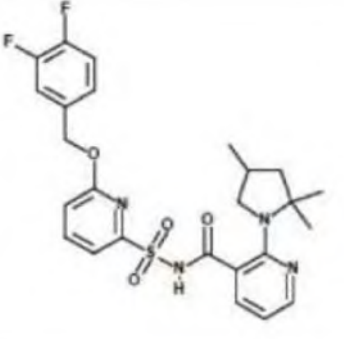
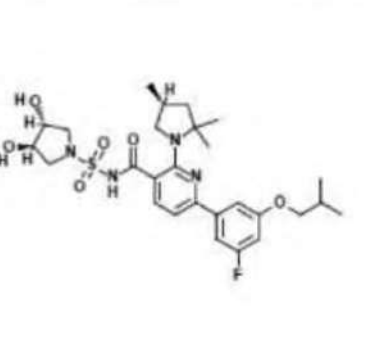
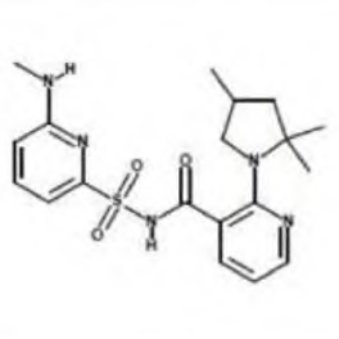
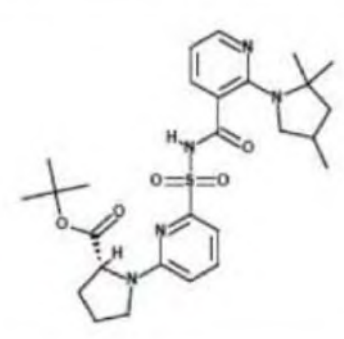
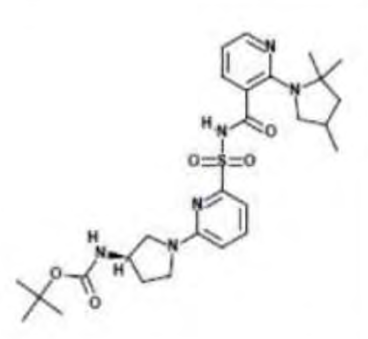
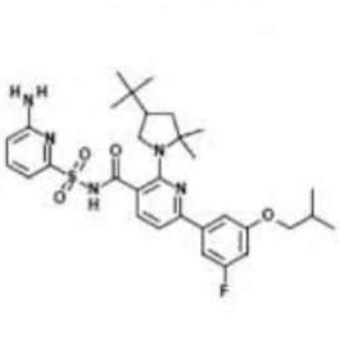
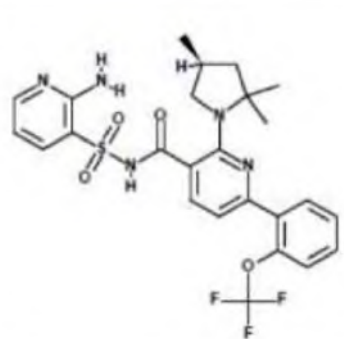
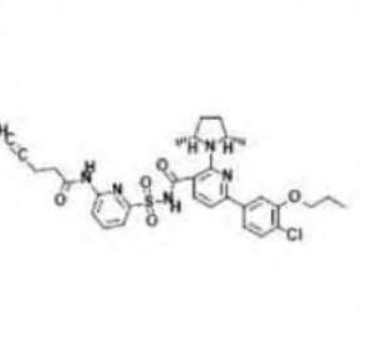
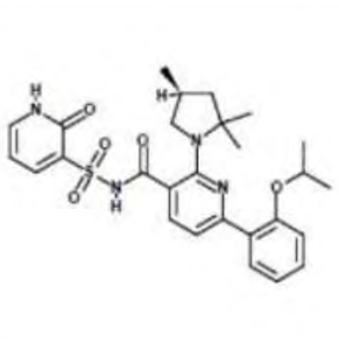
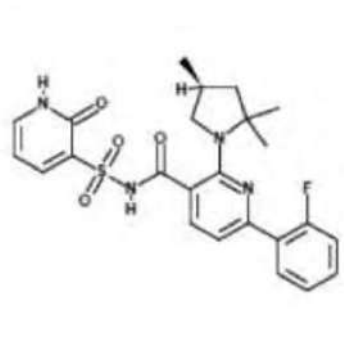
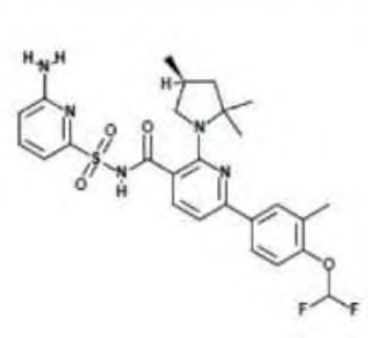
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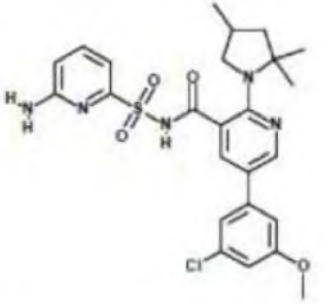
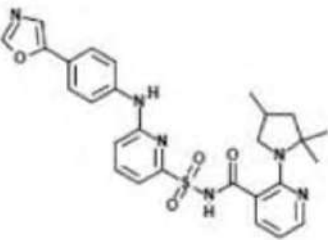
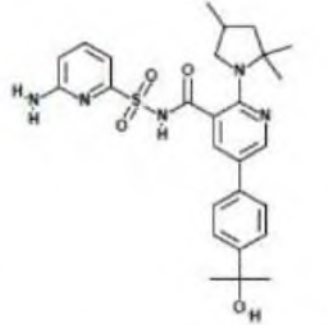
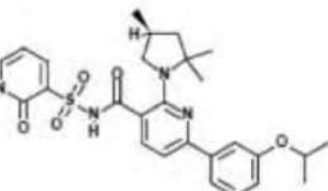
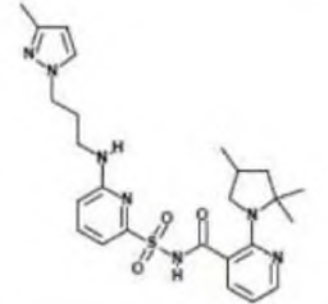
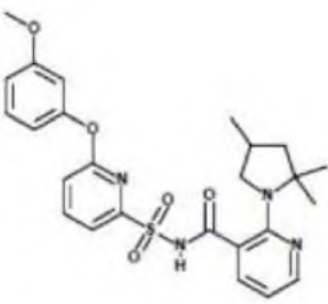
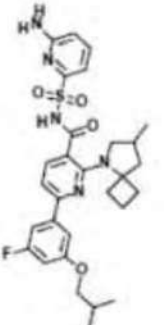
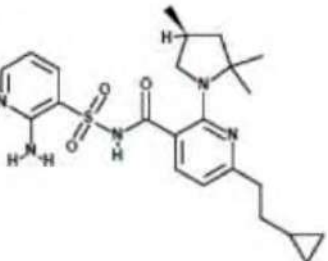
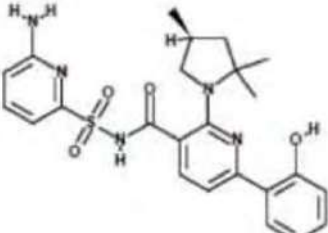
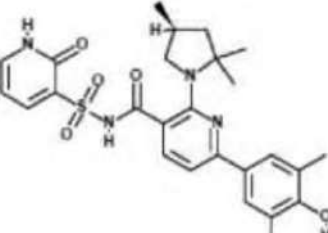
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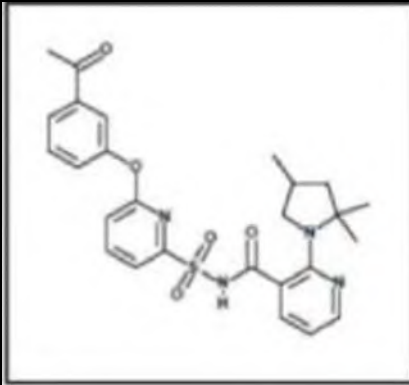
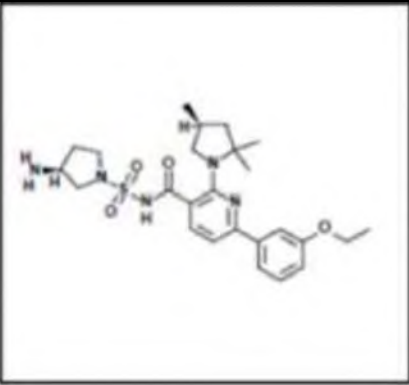
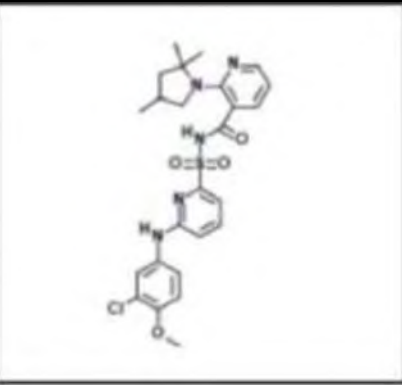
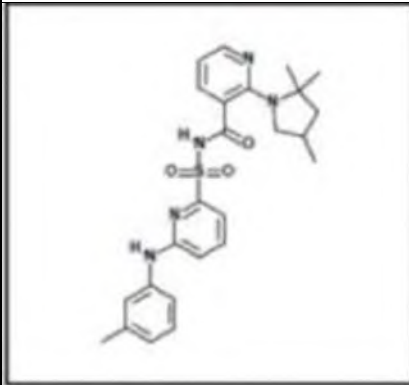
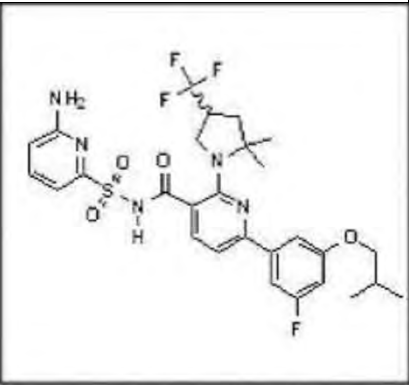
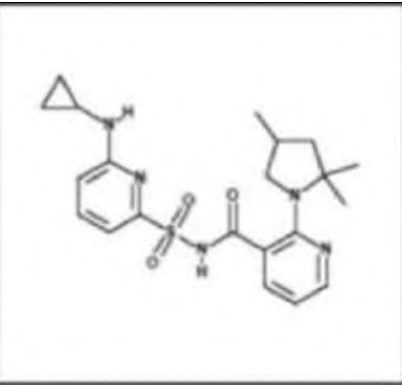
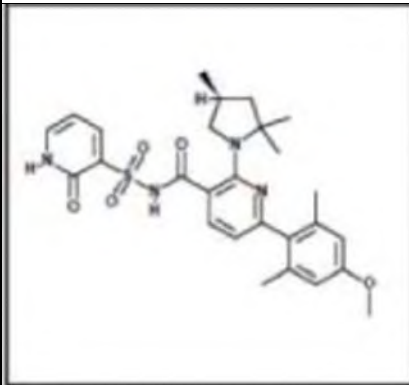
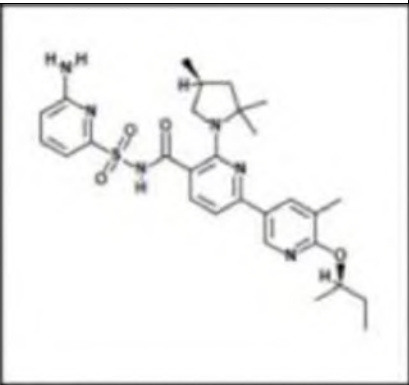
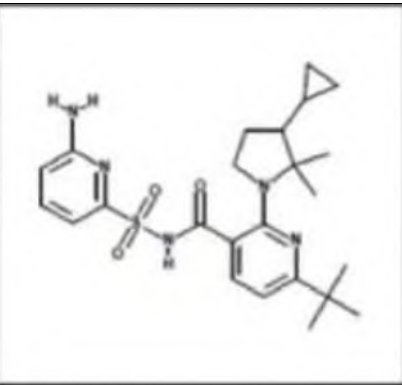
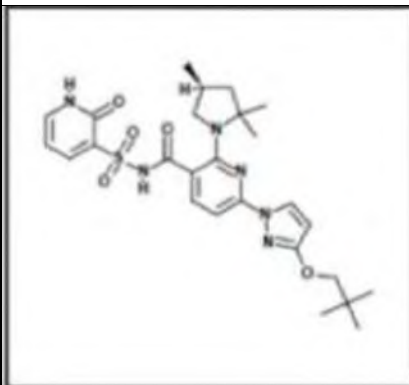
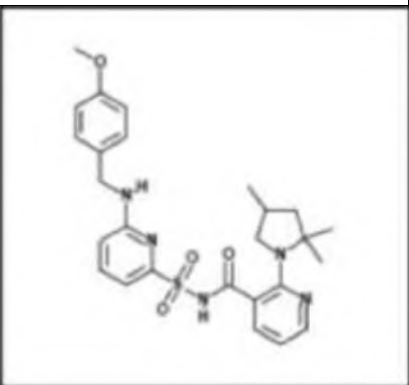
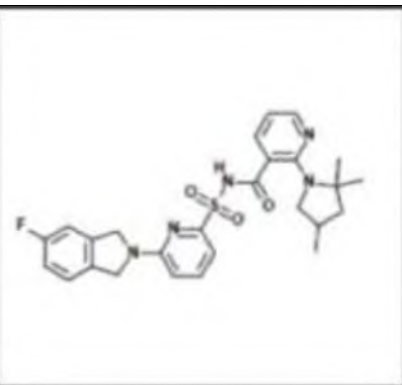
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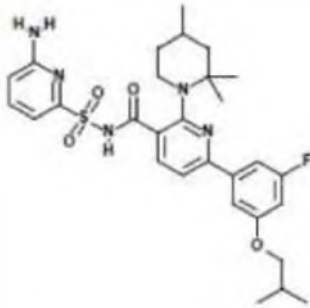
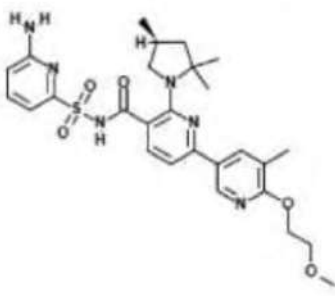
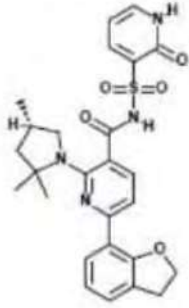
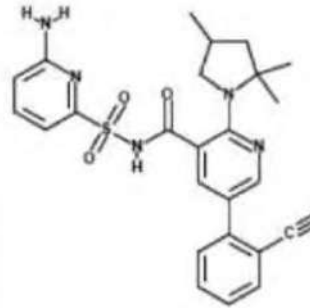
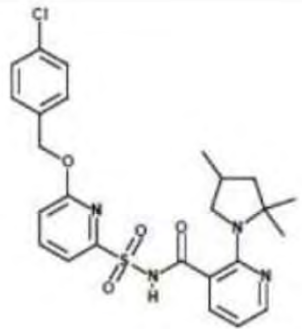
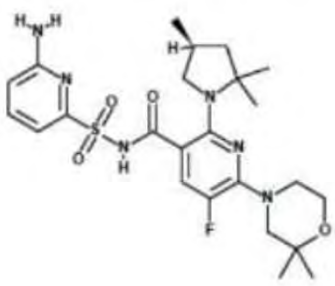
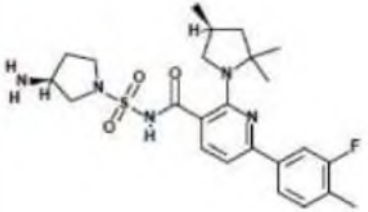
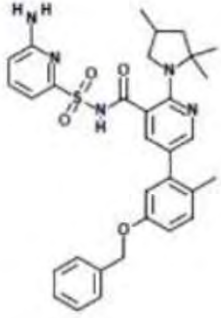
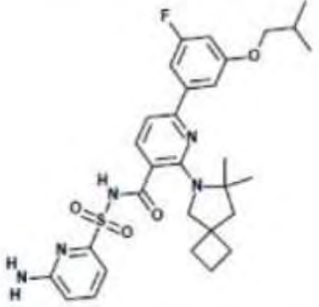
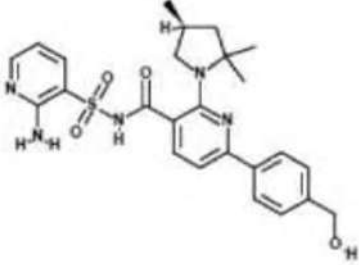
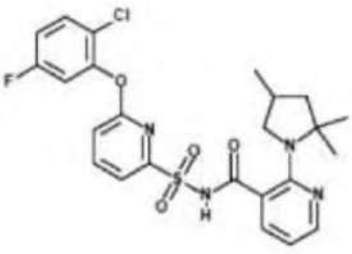
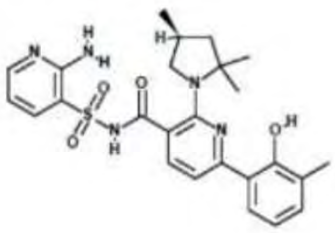
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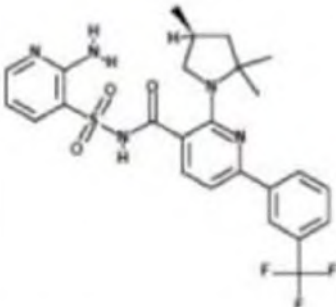
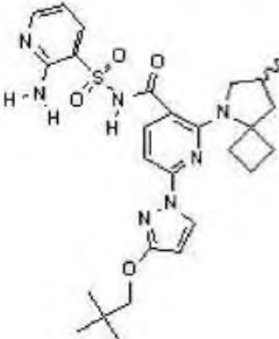
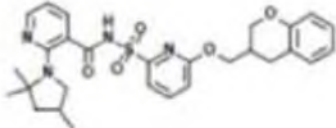
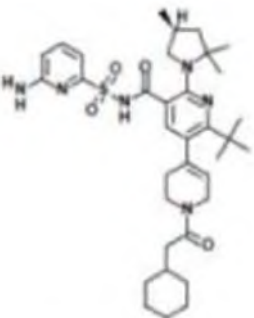
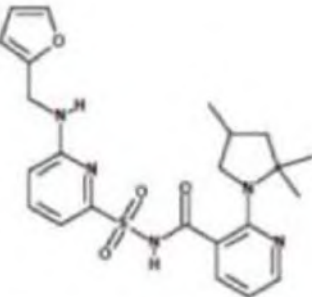
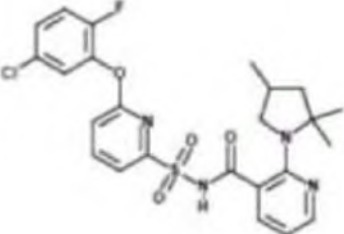
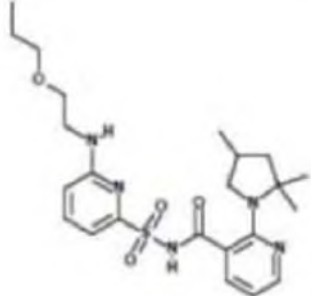
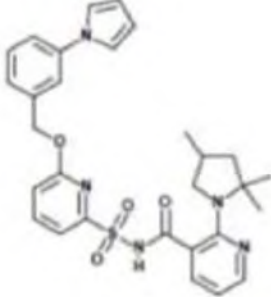
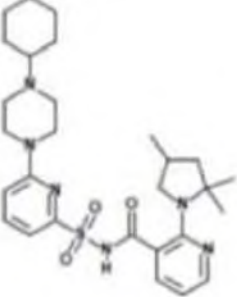
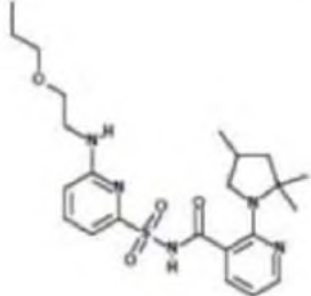
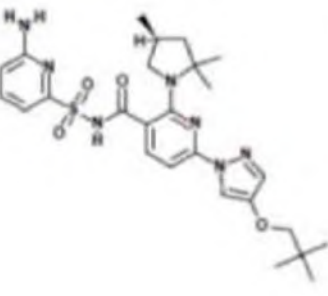
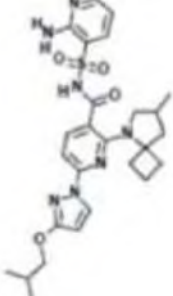
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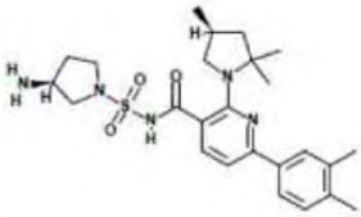
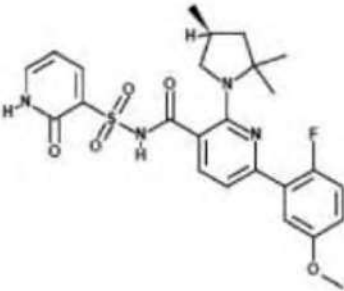
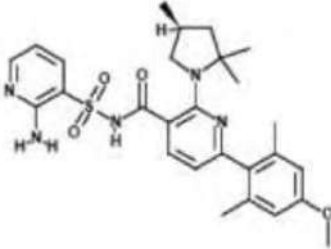
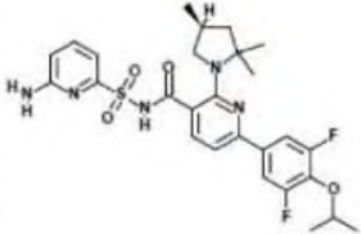
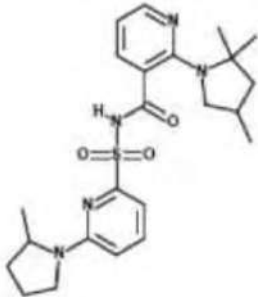
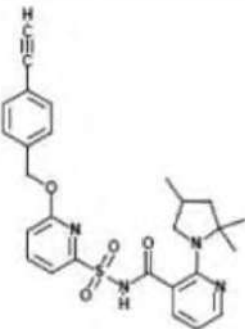
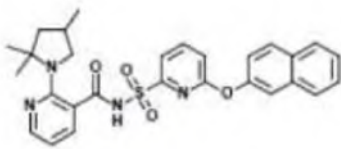
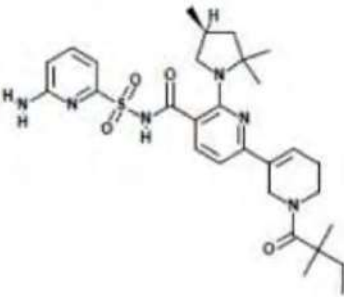
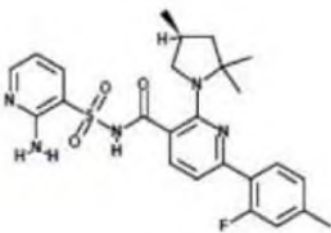
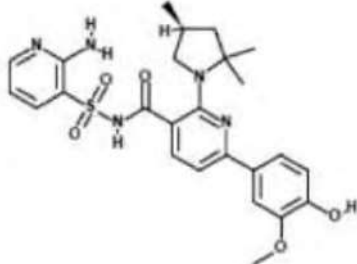
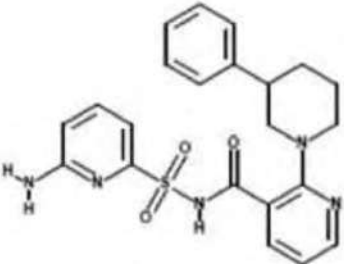
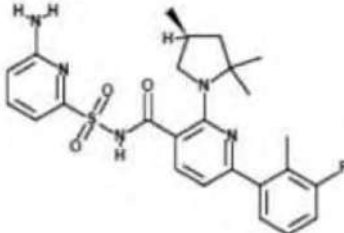
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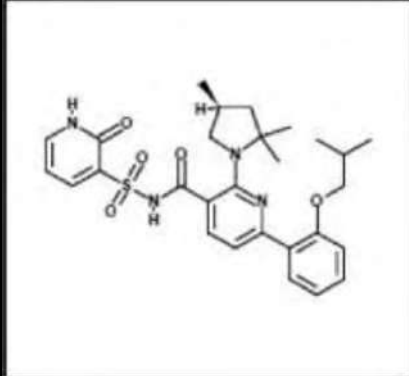
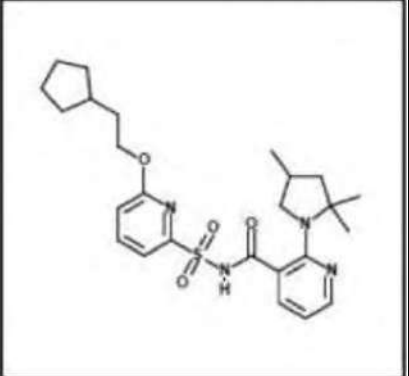
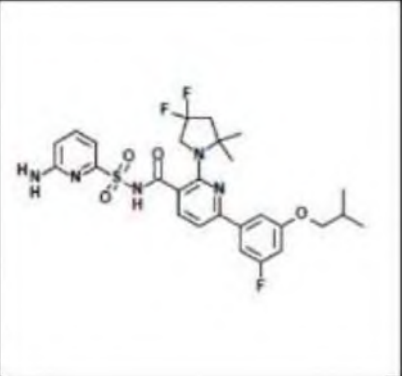
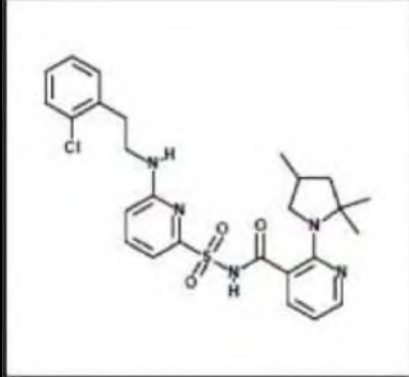
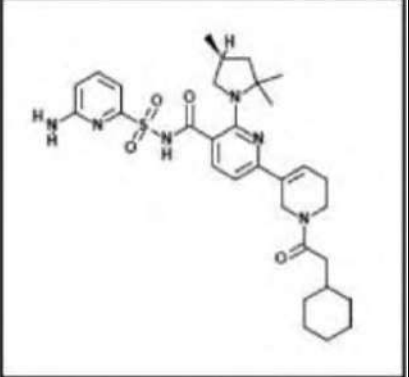
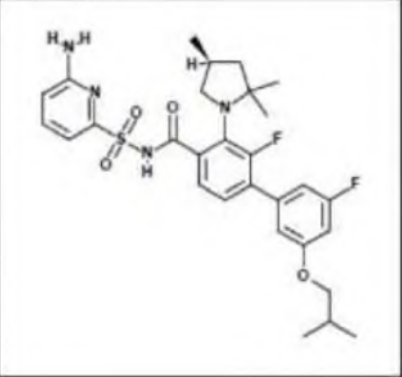
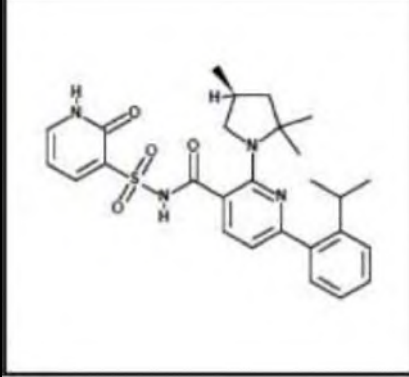
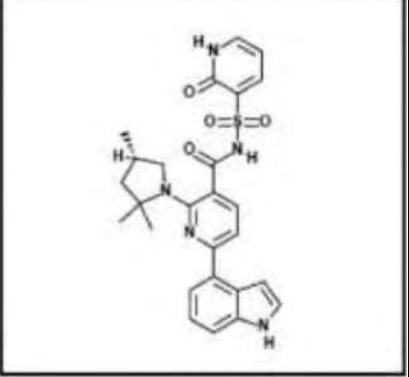
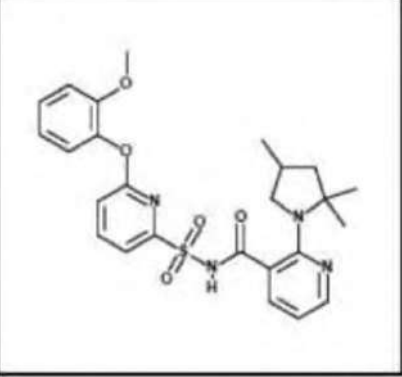
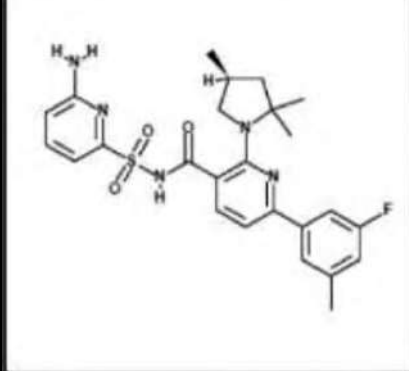
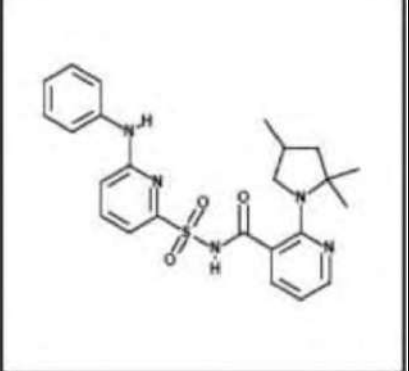
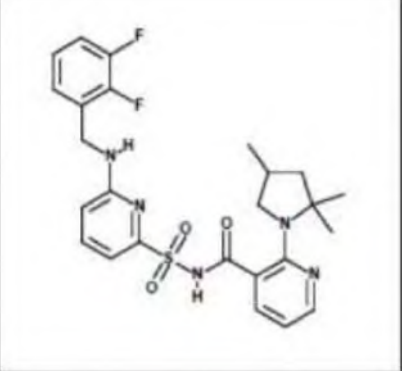
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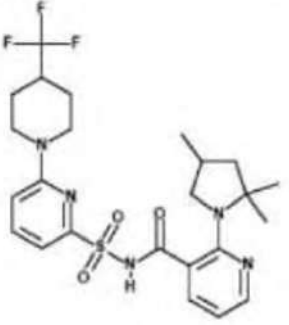
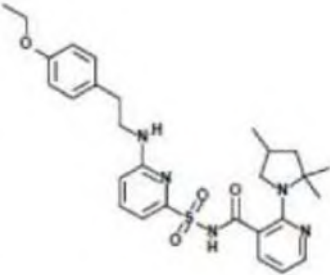
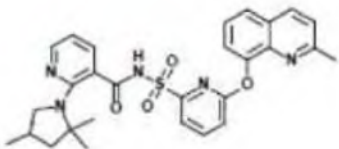
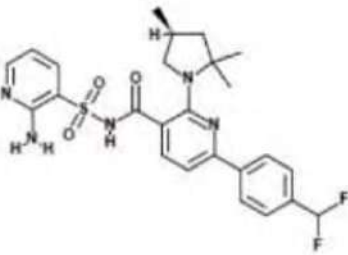
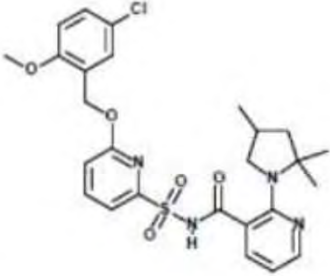
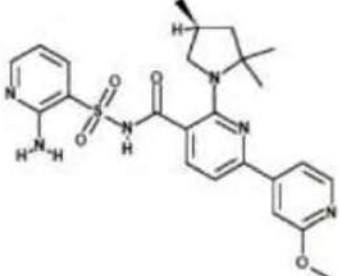
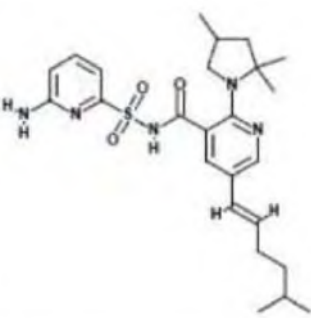
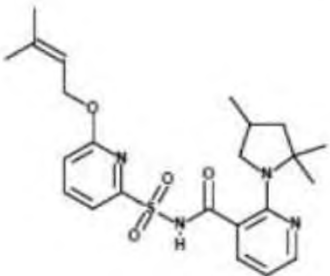
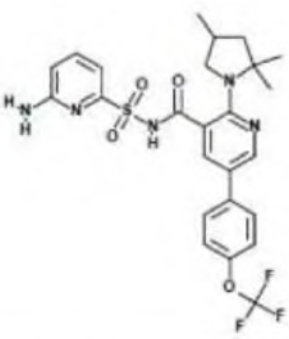
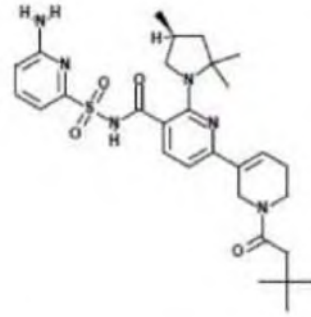
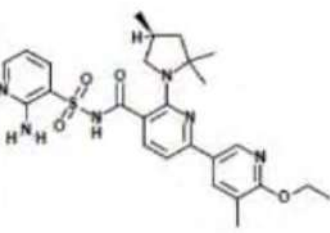
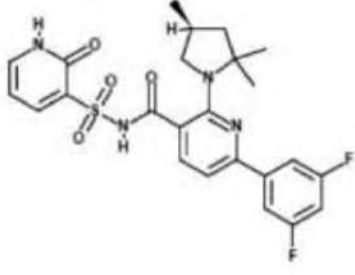
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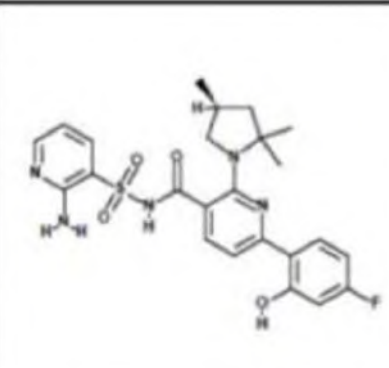
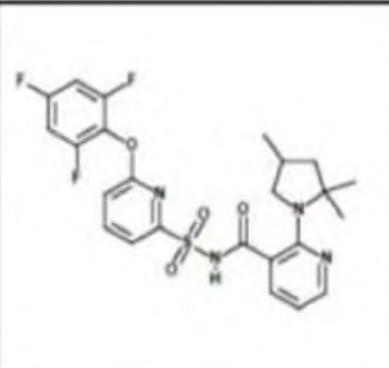
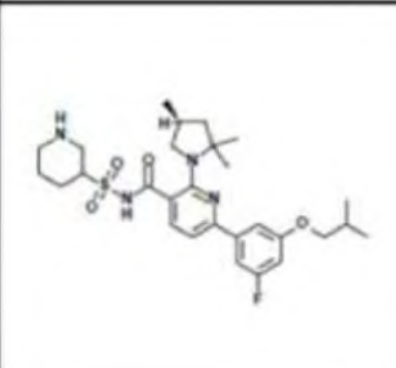
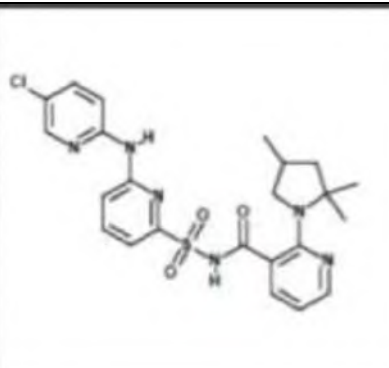
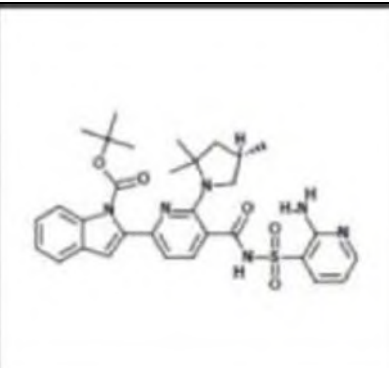
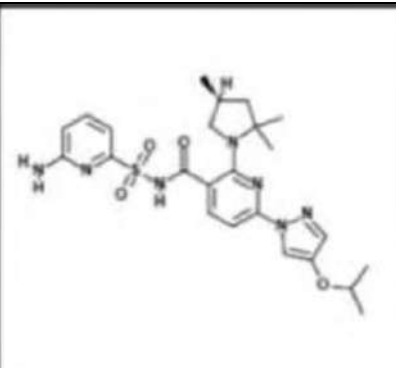
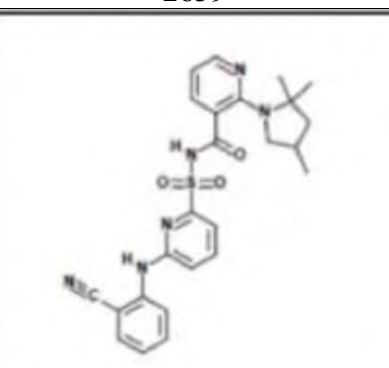
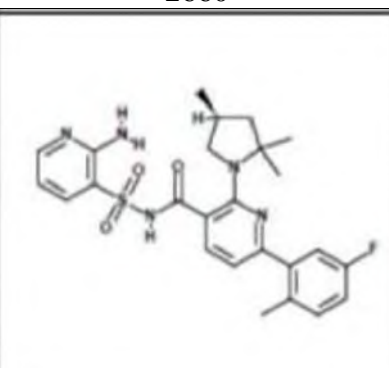
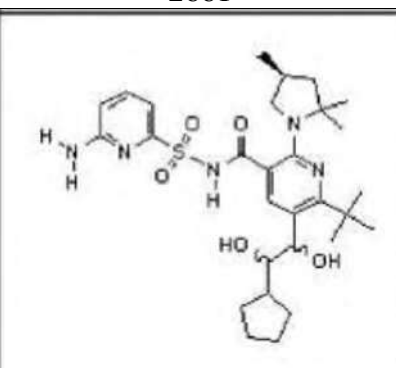
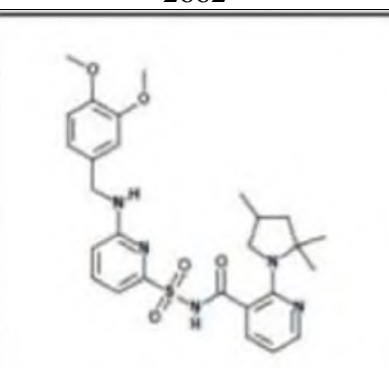
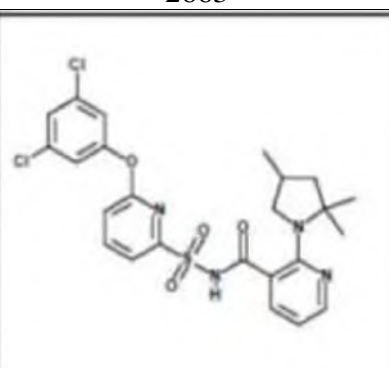
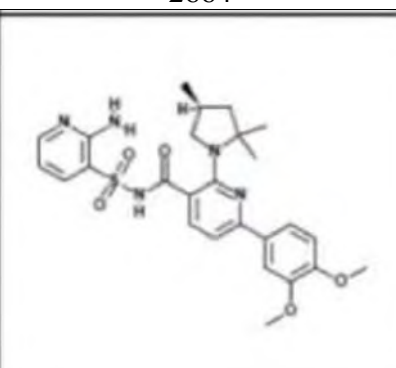
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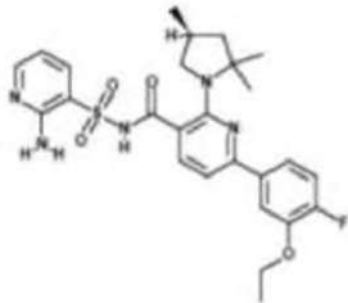
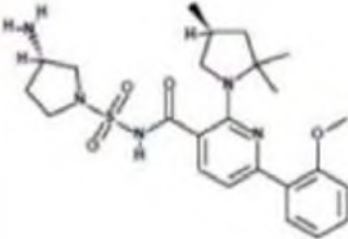
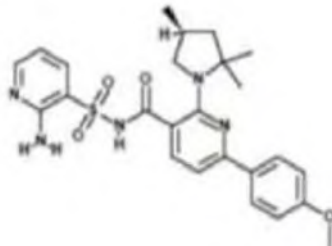
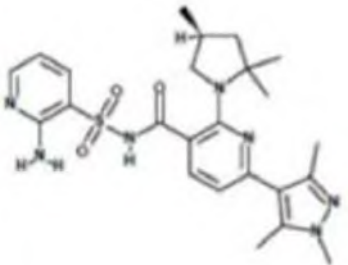
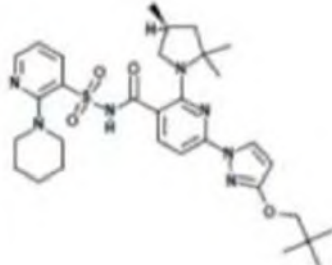
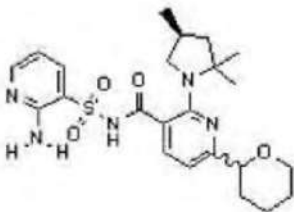
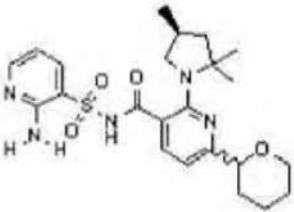
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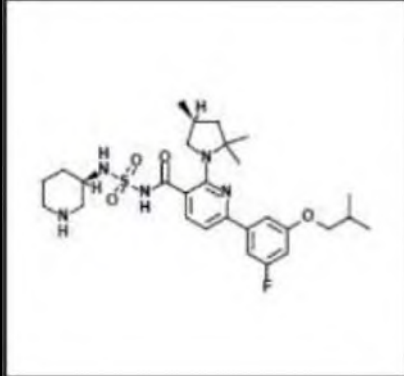
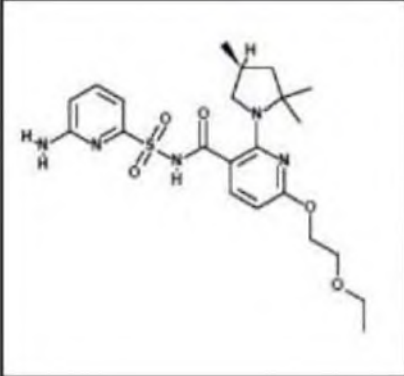
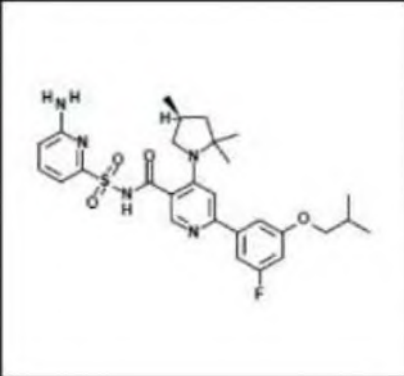
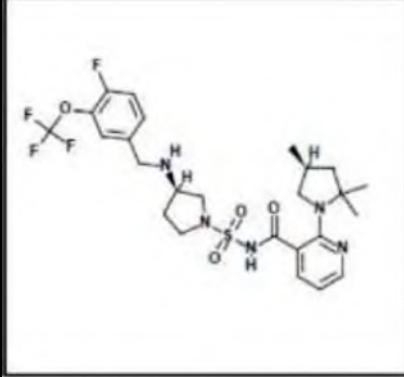
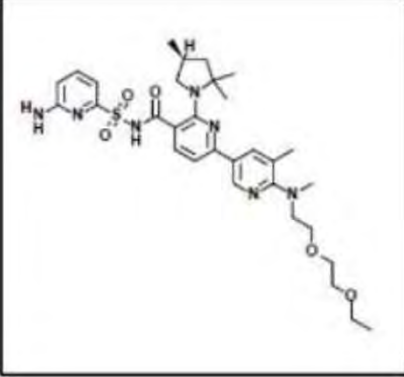
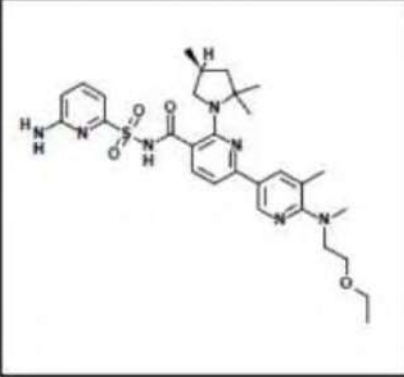
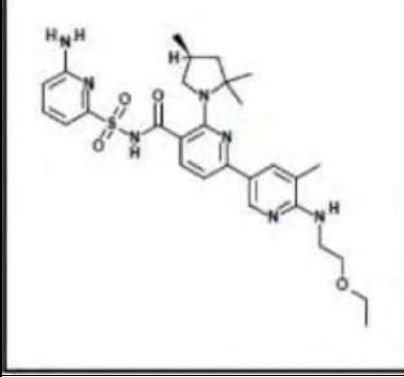
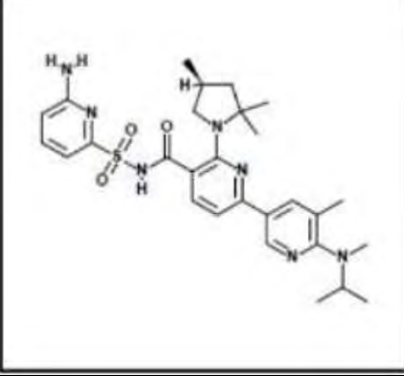
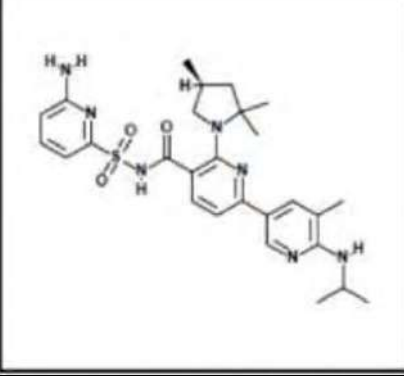
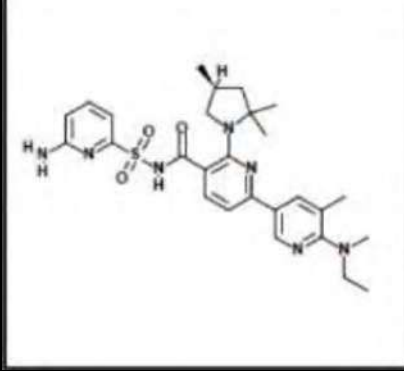
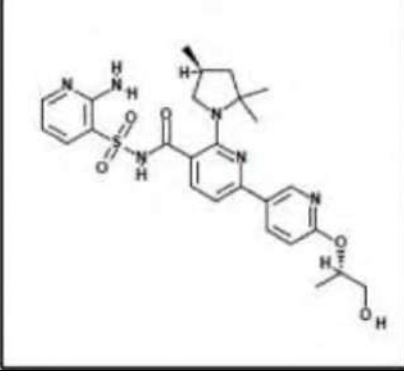
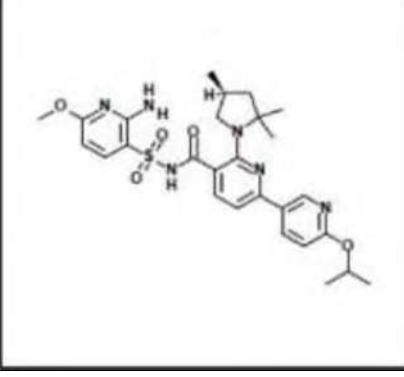
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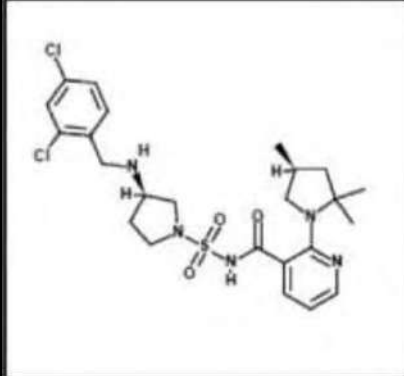
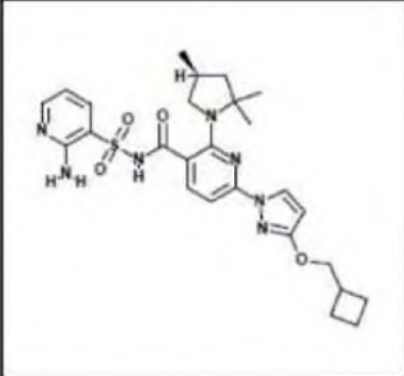
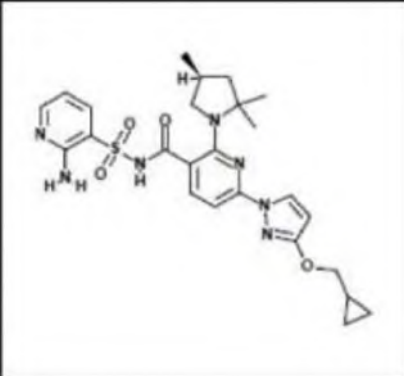
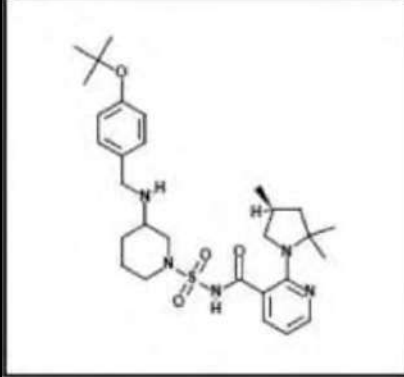
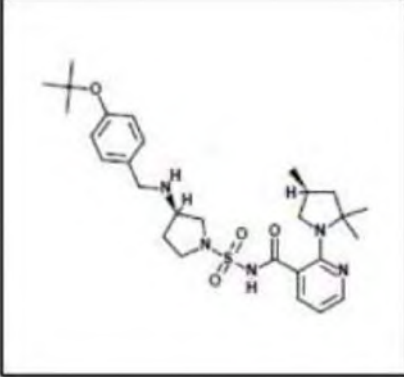
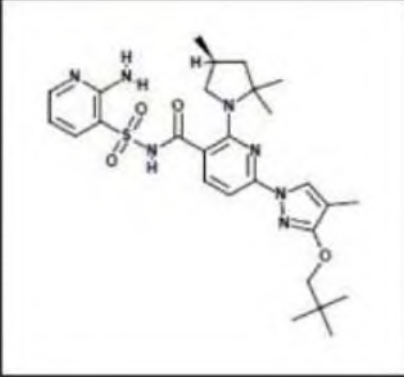
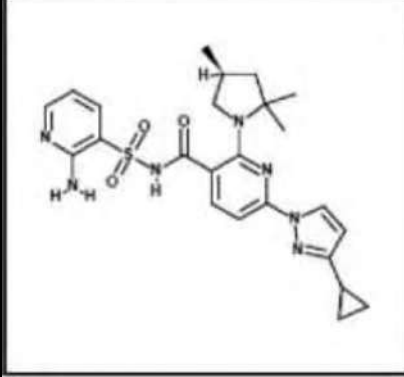
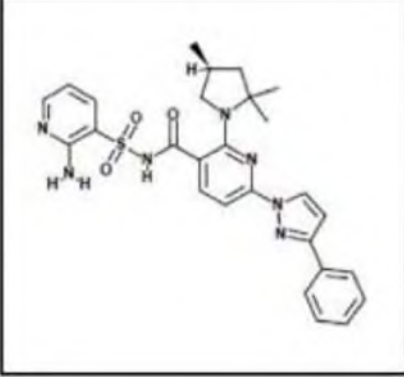
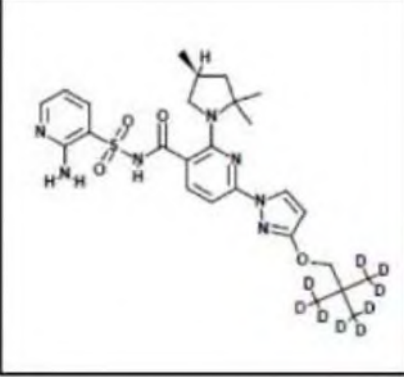
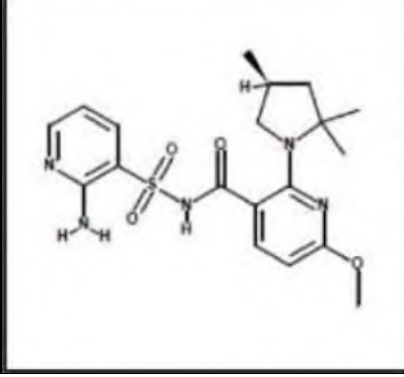
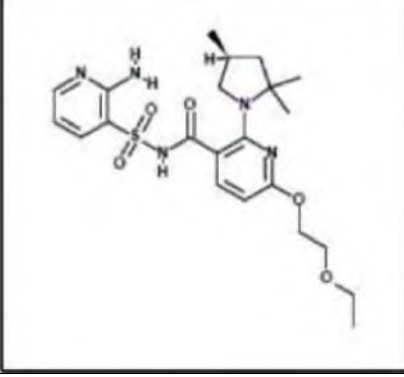
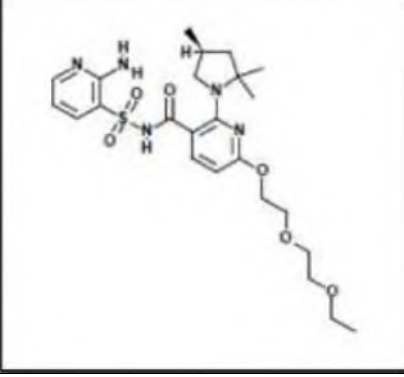
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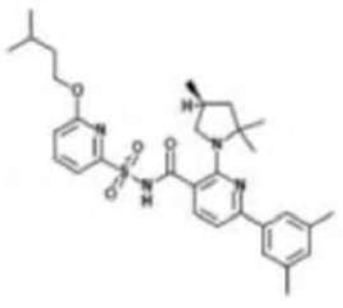
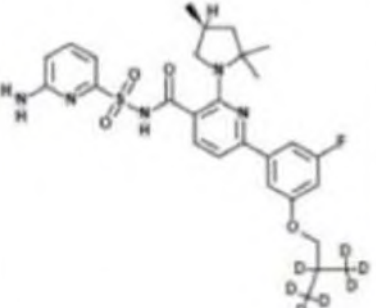
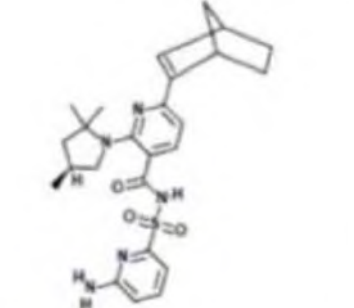
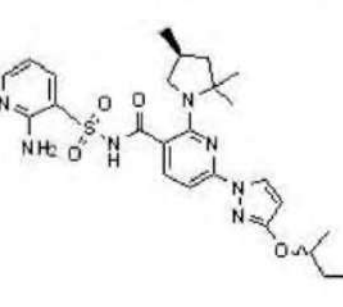
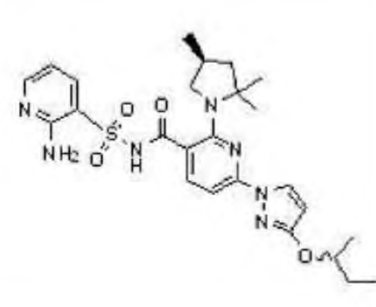
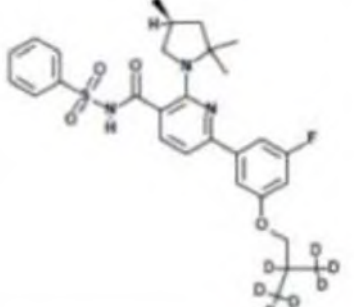
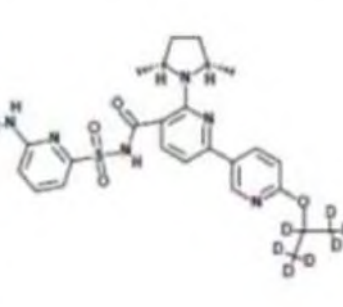
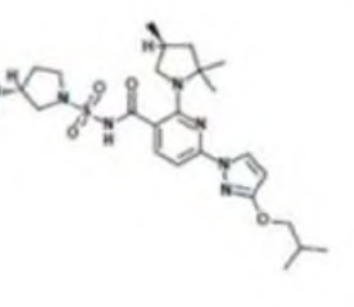
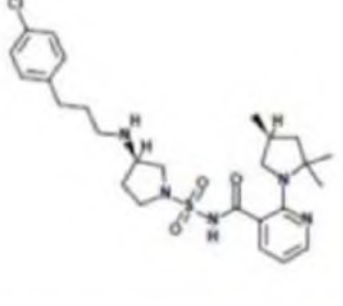
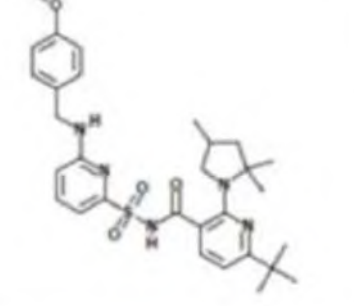
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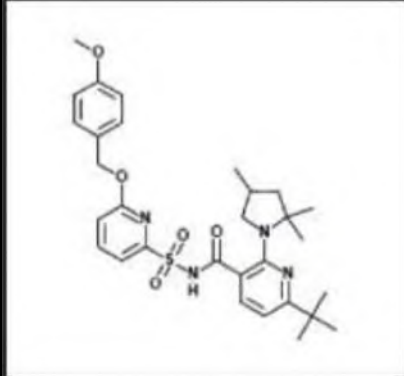
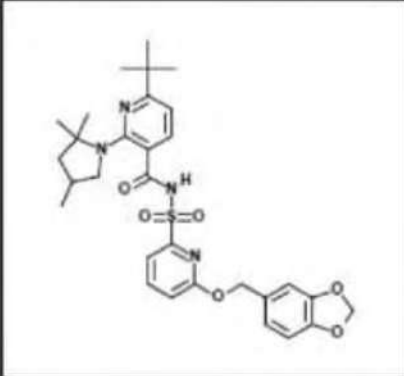
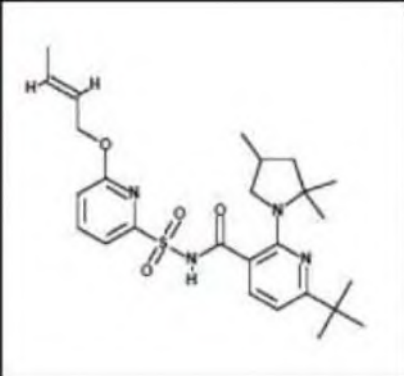
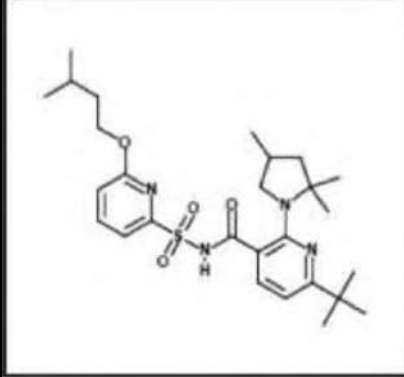
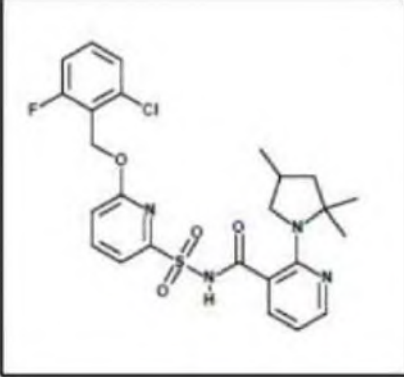
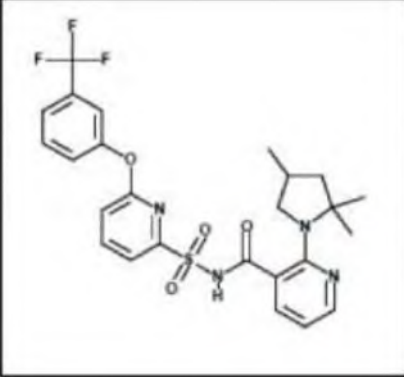
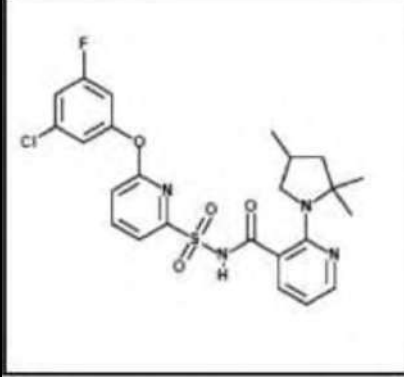
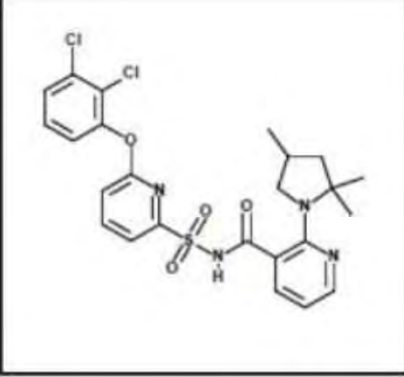
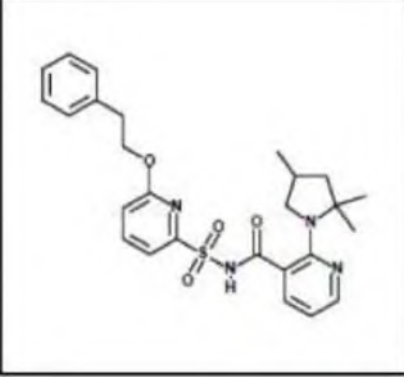
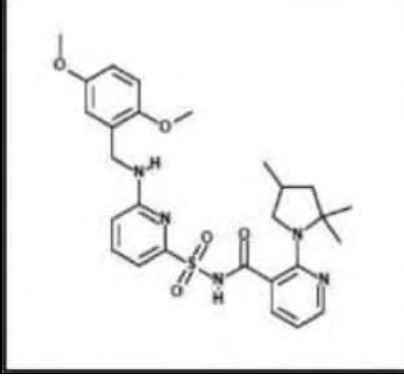
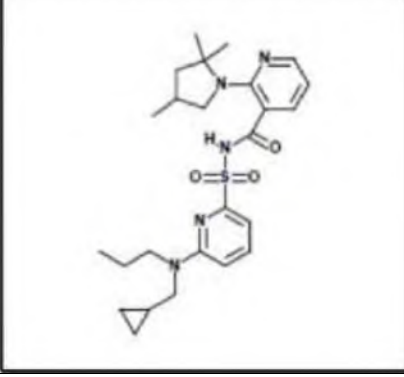
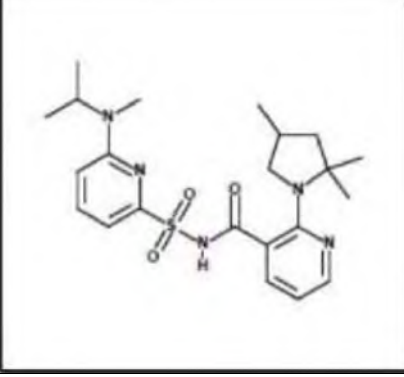
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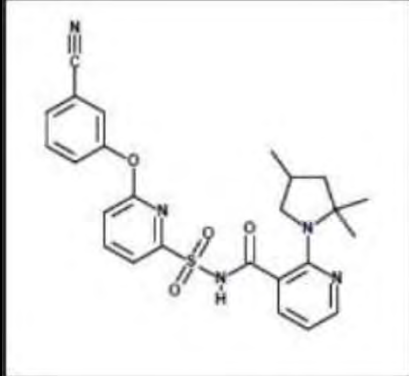
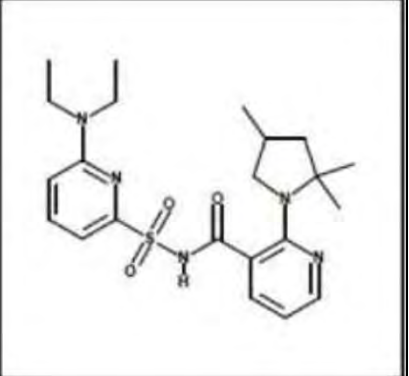
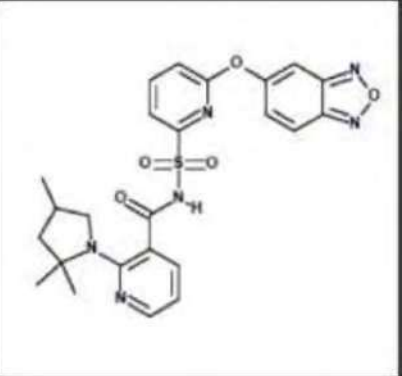
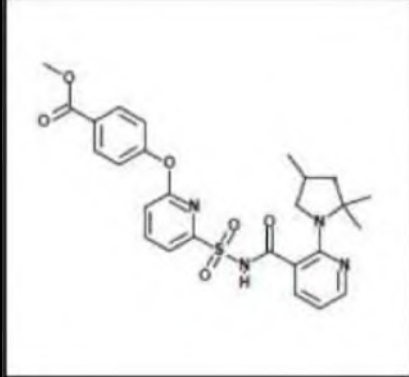
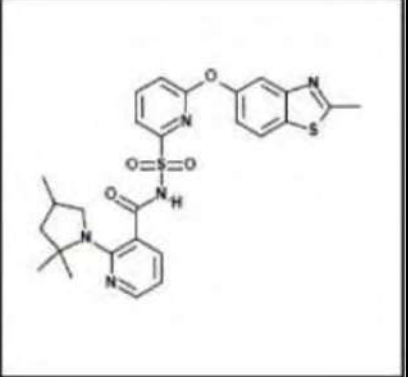
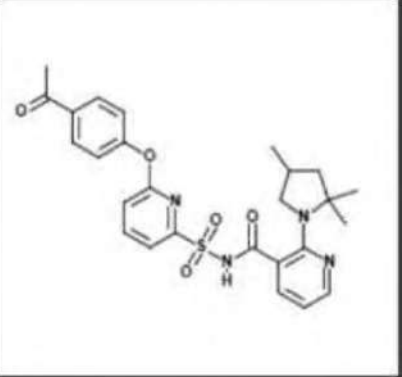
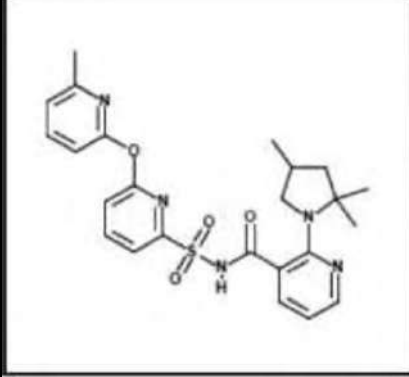
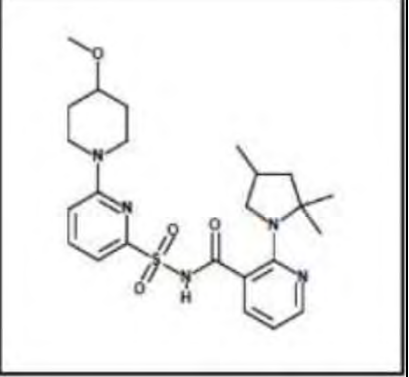
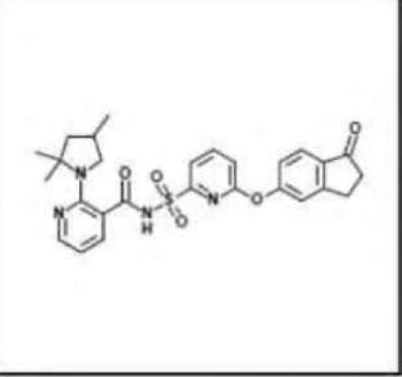
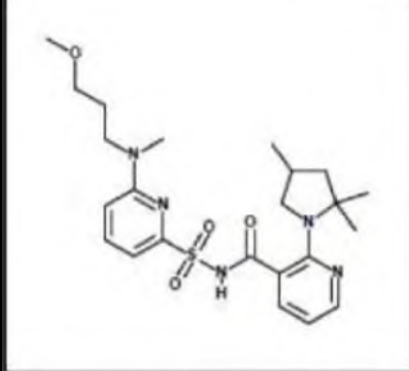
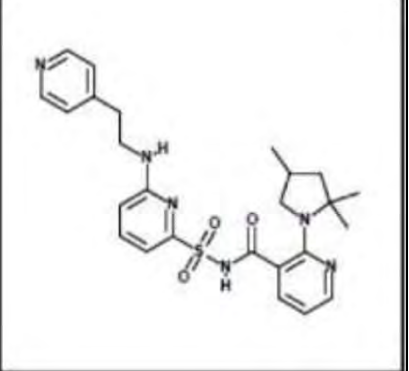
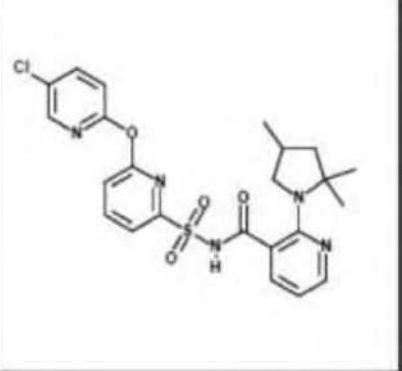
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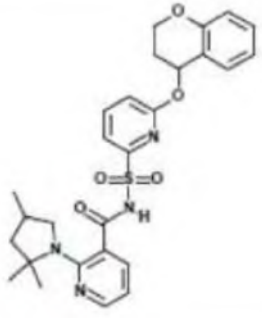
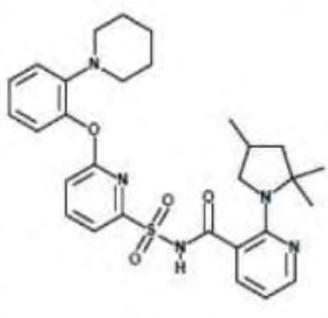
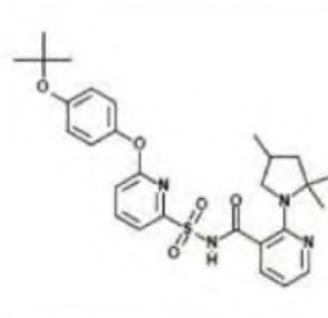
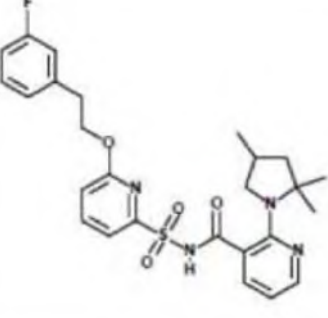
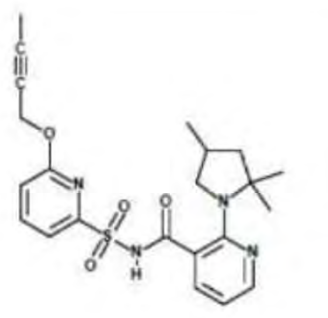
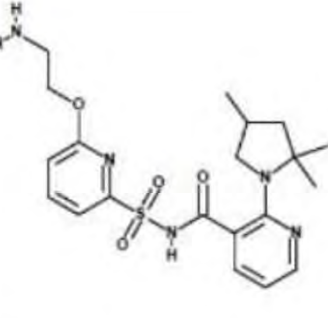
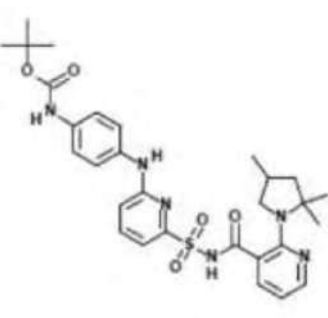
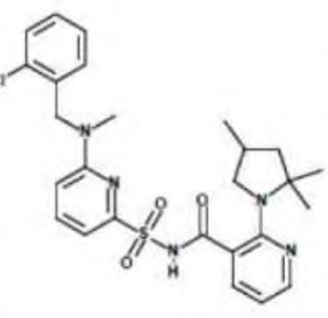
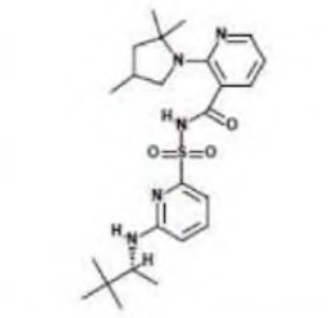
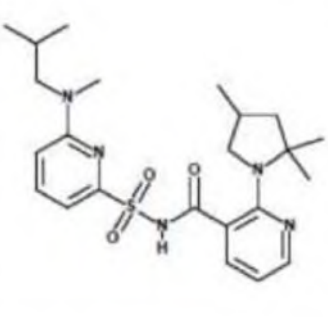
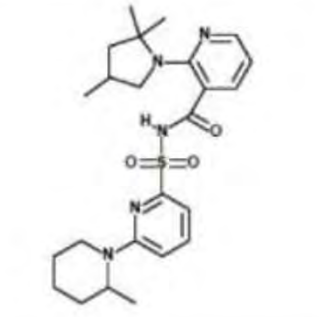
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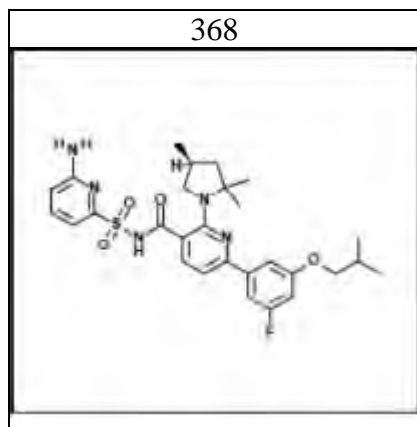
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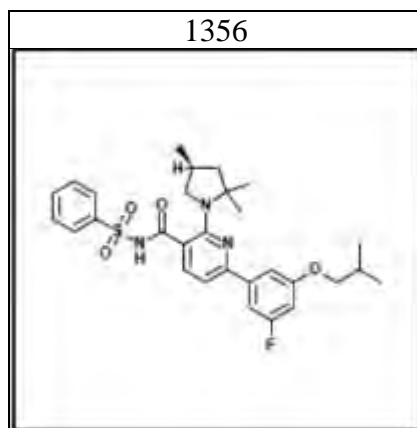
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18. The compound as claimed in claim 17, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

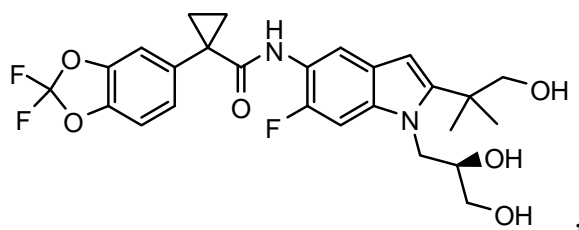


19. The compound as claimed in claim 17, or a pharmaceutically acceptable salt thereof, wherein the compound is:



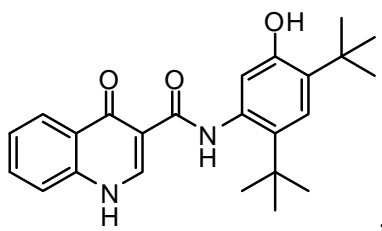
20. A pharmaceutical composition comprising the compound or salt as claimed in any one of claims 1 to 19 and a pharmaceutically acceptable carrier.
21. The pharmaceutical composition as claimed in claim 20, further comprising one or more additional therapeutic agent(s).
22. The pharmaceutical composition as claimed in claim 21, wherein the one or more additional therapeutic agent(s) comprises a CFTR modulator.

23. The pharmaceutical composition as claimed in any one of claims 21 or 22, wherein the one or more additional therapeutic agent(s) comprises



or pharmaceutically acceptable salt thereof.

24. The pharmaceutical composition as claimed in any one of claims 21 to 23, wherein the one or more additional therapeutic agent(s) comprises



or pharmaceutically acceptable salt thereof.

Dated this 5th day of May 2017

(Archana Shanker)

IN/PA-149

**Of Anand and Anand Advocates
Agents for the Applicants**

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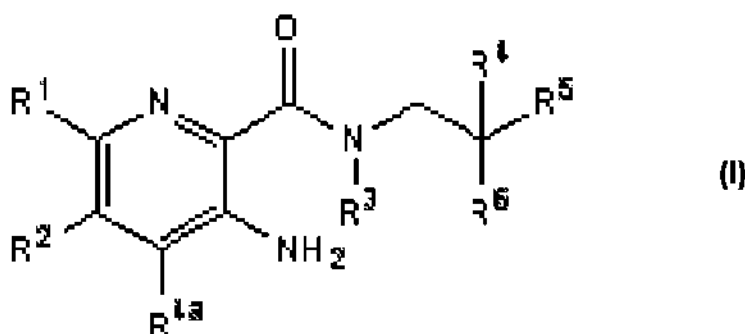
Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

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(54) Title: PYRIDINE AMIDE DERIVATIVES



(57) Abstract: The present invention provides pyridine derivatives which restore or enhance the function of mutant and/or wild type CFTR to treat cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma, respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sicca, or constipation (IBS, IBD, opioid induced). Pharmaceutical compositions comprising such derivatives are also encompassed.

Title

PYRIDINE AMIDE DERIVATIVES USEFUL IN THE TREATMENT OF CYSTIC FIBROSIS

Field of the invention

- 5 This invention relates to pyridine amide derivatives, their preparation and use as pharmaceuticals.

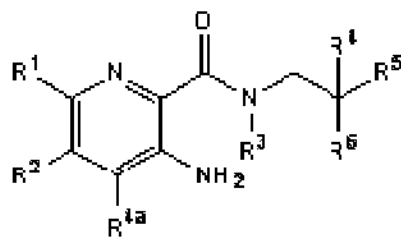
Background

- Cystic fibrosis (CF) is a fatal genetic disease caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR), a protein kinase A (PKA)-
 10 activated epithelial anion channel involved in salt and fluid transport in multiple organs, including the lung. Most CF mutations either reduce the number of CFTR channels at the cell surface (e.g., synthesis or processing mutations) or impair channel function (e.g., gating or conductance mutations) or both. There are currently no approved therapies
 15 that target CFTR directly. The present invention discloses compounds which restore or enhance the function of mutant and/or wild type CFTR to treat cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma, respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sicca, or constipation (IBS, IBD, opioid induced).

20

Description of the invention

In a first aspect, the invention provides compounds according to Formula I:



I

wherein:

25

R^1 is H; C_1 - C_8 alkyl optionally substituted by one or more halogen atoms; C_2 - C_8 alkenyl; C_2 - C_8 alkynyl; C_3 - C_{10} cycloalkyl; C_5 - C_{10} cycloalkenyl; $-C_1$ - C_4 alkyl- C_3 - C_8 cycloalkyl; C_1 - C_8

alkoxy optionally substituted by one or more halogen atoms; halogen; $\text{SO}_2\text{NR}^8\text{R}^9$; SO_2R^{10} ; $\text{S-C}_1\text{-C}_8$ alkyl optionally substituted by one or more halogen atoms; $\text{S-C}_6\text{-C}_{14}$ aryl; $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl; $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-3 to 14}$ membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; CN;
 5 $\text{NR}^{11}\text{R}^{12}$; $\text{CONR}^{13}\text{R}^{14}$; $\text{NR}^{13}\text{SO}_2\text{R}^{15}$; $\text{NR}^{13}\text{C}(\text{O})\text{R}^{15}$ and CO_2R^{15} , wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^2 is $\text{C}_1\text{-C}_4$ haloalkyl;

10

R^3 and R^4 are each independently H or $\text{C}_1\text{-C}_8$ alkyl optionally substituted by one or more halogen atoms;

R^{4a} is selected from halogen; $\text{C}_2\text{-C}_8$ alkenyl; $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl; $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-3 to 14}$ membered heterocyclyl; and $\text{C}_1\text{-C}_8$ hydroxyalkyl; wherein the $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl and $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-3 to 14}$ membered heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^5 and R^6 are each independently H; $\text{C}_1\text{-C}_8$ alkyl optionally substituted by one or more halogen atoms; $\text{C}_2\text{-C}_8$ alkenyl; $\text{C}_2\text{-C}_8$ alkynyl; $\text{C}_3\text{-C}_{10}$ cycloalkyl; $\text{C}_5\text{-C}_{10}$ cycloalkenyl; $\text{-C}_1\text{-C}_4$ alkyl- $\text{C}_3\text{-C}_8$ cycloalkyl; $\text{C}_1\text{-C}_8$ alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl; $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-3 to 14}$ membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; or $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-CO}_2\text{R}^{15}$, wherein the cycloalkyl, cycloalkenyl,
 20 $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl and $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-3 to 14}$ membered heterocyclic group groups are each optionally substituted by one or more Z substituents; or

R^5 and R^6 are each independently a group of the formula:

$-(\text{CH}_2)_m\text{-NR}^{17}\text{R}^{18}$; or

30

R^5 and R^6 are each independently a group of the formula:

$-(\text{CH}_2)_m\text{-OR}^4$; or

R⁴ and R⁵ together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

5 R⁵ and R⁶ together with the carbon atoms to which they are bound form a 5 to 8 membered carbocyclic ring system or a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

10 R⁴, R⁵ and R⁶ cannot all be the same;

m is 0, 1, 2 or 3;

R⁸, R¹¹, R¹³ and R¹⁷ are each independently H, C₁-C₈ alkyl optionally substituted by one or more halogen atoms, C₃-C₁₀ cycloalkyl or -(C₁-C₄ alkyl)-C₃-C₈ cycloalkyl;

15 R⁹, R¹⁰, R¹², R¹⁴, R¹⁵, R¹⁶ and R¹⁸ are each independently H; C₁-C₈ alkyl optionally substituted by one or more halogen atoms; C₂-C₈ alkenyl; C₂-C₈ alkynyl; C₃-C₁₀ cycloalkyl; C₅-C₁₀ cycloalkenyl; -(C₁-C₄ alkyl)-C₃-C₈ cycloalkyl; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; or -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group
20 contains at least one heteroatom selected from N, O and S, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

25 R⁸ and R⁹, R¹¹ and R¹², R¹³ and R¹⁴, and R¹⁷ and R¹⁸ together with the nitrogen atom to which they are attached may form a 4 to 14 membered heterocyclic group optionally substituted by one or more Z substituents;

30 Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C₁-C₆ alkyl optionally substituted by one or more OH groups or NH₂ groups, C₁-C₆ alkyl optionally substituted by one or more halogen atoms, C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy, NR¹⁸(SO₂)R²¹, (SO₂)NR¹⁹R²¹, (SO₂)R²¹, NR¹⁸C(O)R²¹, C(O)NR¹⁹R²¹, NR¹⁸C(O)NR¹⁹R²¹, NR¹⁸C(O)OR¹⁹, NR¹⁹R²¹, C(O)OR¹⁹, C(O)R¹⁹, SR¹⁹, OR¹⁹, oxo, CN,

NO₂, halogen or a 3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S;

R¹⁹ and R²¹ are each independently H; C₁-C₈ alkyl; C₃-C₈ cycloalkyl; C₁-C₄ alkoxy-C₁-C₄ alkyl; (C₀-C₄ alkyl)-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; (C₀-C₄ alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C₁-C₆ alkyl and C(O)C₁-C₆ alkyl; (C₀-C₄ alkyl)-O-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; and (C₀-C₄ alkyl)- O-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C₁-C₆ alkyl or C(O)C₁-C₆ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C₁-C₄ alkoxy, C(O)NH₂, C(O)NHC₁-C₆ alkyl or C(O)N(C₁-C₆ alkyl)₂; or

R¹⁹ and R²¹ together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(O)₂-aryl; S(O)₂-C₁-C₆ alkyl; C₁-C₆ alkyl optionally substituted by one or more halogen atoms; C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy; and C(O)OC₁-C₆ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by C₁-C₆ alkyl, C₁-C₆ haloalkyl or C₁-C₆ alkoxy; or a pharmaceutically acceptable salt thereof.

Various embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

In an embodiment of the invention as described anywhere herein, R¹ is selected from H; C₁-C₈ alkoxy optionally substituted by one or more halogen atoms; or halogen.

In an embodiment of the invention as described anywhere herein, R^1 is C_1 - C_4 alkyl optional substituted by one or more halogen atoms. For example, $-CH_3$ or CF_3 .

- 5 In an embodiment of the invention as described anywhere herein, R^1 is C_1 - C_4 alkoxy optional substituted by one or more halogen atoms. For example, $-OCH_3$ or $-OCF_3$.

- 10 In an embodiment of the invention as described anywhere herein, R^1 is aryl, wherein aryl is phenyl optionally substituted by one or more Z substituents, specific example are 4-fluorophenyl, 4-chloro-2-methylphenyl, or 2,4-dichlorophenyl.

- 15 In an embodiment of the invention as described anywhere herein, R^1 is 6 membered heterocyclyl group, wherein 6 membered heterocyclyl group is pyridyl optionally substituted by one or more Z substituents, specific example is 1-methyl-4-pyridyl.

In an embodiment of the invention as described anywhere herein, R^1 is Br, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, 4-fluorophenyl, 4-chloro-2-methylphenyl, or 2,4-dichlorophenyl.

- 20 In an embodiment of the invention as described anywhere herein, R^2 is CF_3CF_2 -, $(CF_3)_2CH$ -, CH_3CF_2 -, CF_3CF_2 -, CF_3 , CF_2H -, CH_3CCl_2 -, $CF_3CFCClH$ -, CBR_3 , CBr_2H -, $CF_3CF_2CHCF_3$ or $CF_3CF_2CF_2CF_2$ -.

In an embodiment of the invention as described anywhere herein, R^2 is CF_3 .

- 25 In an embodiment of the invention as described anywhere herein, R^3 is H or methyl.

An embodiment of the invention, as defined above provides a compound, where R^5 provides a heteroatom two carbons from the amide nitrogen, wherein the heteroatom is oxygen or nitrogen.

30

An embodiment of the invention as defined above provides a compound according to Formula I, wherein

R^4 is H, C_1 - C_4 alkyl optionally substituted by one or more halogen atoms or not present;

R^5 is C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms; $-(CH_2)_m-$
 $NR^{17}R^{18}$; $-(CH_2)_m-OR'$; or OH;

m is 0, or 1;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; C_1 - C_4 alkoxy
 5 optionally substituted by one or more halogen atoms; OH; CN; halogen; $-(C_0$ - C_4 alkyl)-
 C_6 - C_{14} aryl; or $-(C_0$ - C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the
 heterocyclic group contains at least one heteroatom selected from N, O and S, wherein
 the aryl and heterocyclyl groups are each optionally substituted by one or more Z
 substituents; or

10 R^4 and R^5 together form an oxo group ($C=O$); or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 8
 membered heterocyclic ring system containing one or more heteroatoms selected from
 N, O and S, wherein the ring system is optionally substituted by one or more Z
 substituents;

15 R^{17} and R^{18} are each independently H; or C_1 - C_4 alkyl optionally substituted by one or
 more halogen atoms.

An embodiment of the invention as defined above provides compounds according to
 Formula I, wherein

20 R^1 is halogen, C_1 - C_4 alkyl optionally substituted by one or more halogen atoms, or C_1 - C_4
 alkoxy optionally substituted by one or more halogen atoms;

R^2 is C_1 - C_4 haloalkyl;

R^3 is H;

R^4 is H or Me;

25 R^5 is $-(CH_2)_m-NR^{17}R^{18}$; $-(CH_2)_m-OR'$; or OH;

m is 0, or 1;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6
 membered heterocyclic ring system containing one or more heteroatoms selected from
 30 N, O and S, wherein the ring system is optionally substituted by one or more Z
 substituents; and

R^{17} and R^{18} are each independently H; or C_1 - C_4 alkyl optionally substituted by one or
 more halogen atoms.

An embodiment of the invention as defined above provides compounds according to Formula I, wherein

R¹ is halogen, C₁-C₄ alkyl optionally substituted by one or more halogen atoms, or C₁-C₄ alkoxy optionally substituted by one or more halogen atoms;

R² is C₁-C₄ haloalkyl;

R³ is H;

R⁴ and R⁵ together form an oxo group (C=O); and

R⁶ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms; C₁-C₄ alkoxy optionally substituted by one or more halogen atoms; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; or -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents..

An embodiment of the invention as defined above provides compounds according to Formula I, wherein

R¹ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms;

R² is C₁-C₄ haloalkyl;

R³ is H;

R⁴ is H or Me;

R⁵ is -(CH₂)_m-NR¹⁷R¹⁸; -(CH₂)_m-OR¹; or OH;

m is 0, or 1;

R⁶ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms; or

R⁵ and R⁶ together with the carbon atoms to which they are bound form a 5 to 6

membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; and

R¹⁷ and R¹⁸ are each independently H; or C₁-C₄ alkyl optionally substituted by one or more halogen atoms.

An embodiment of the invention as defined above provides compounds according to Formula I, wherein

R¹ is C₁-C₄ alkoxy optionally substituted by one or more halogen atoms;

R^2 is C_1 - C_4 haloalkyl;

R^3 is H;

R^4 is H or Me;

R^5 is $-(CH_2)_m-NR^{17}R^{18}$; $-(CH_2)_m-OR$; or OH;

5 m is 0, or 1;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z

10 substituents; and

R^{17} and R^{18} are each independently H; or C_1 - C_4 alkyl optionally substituted by one or more halogen atoms.

An embodiment of the invention as defined above provides compounds according to

15 Formula I, wherein

R^1 is C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms;;

R^2 is C_1 - C_4 haloalkyl;

R^3 is H;

R^4 is H or Me;

20 R^5 is $-NR^{17}R^{18}$; or OH;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z

25 substituents; and

R^{17} and R^{18} are each independently H; or C_1 - C_4 alkyl optionally substituted by one or more halogen atoms.

An embodiment of the invention as defined above provides compounds according to

30 Formula I, wherein

R^1 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms;

R^2 is C_1 - C_4 haloalkyl;

R^3 is H;

R⁴ is H or Me;

R⁵ is -NR¹⁷R¹⁸; or OH;

R⁶ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms; and

5 R¹⁷ and R¹⁸ are each independently H; or C₁-C₄ alkyl optionally substituted by one or more halogen atoms.

An embodiment of the invention as defined above provides compounds according to Formula I, wherein

R¹ is C₁-C₄ alkoxy optionally substituted by one or more halogen atoms;

10 R² is C₁-C₄ haloalkyl;

R³ is H;

R⁴ is H or Me;

R⁵ is -NR¹⁷R¹⁸; or OH;

R⁶ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms; and

15 R¹⁷ and R¹⁸ are each independently H; or C₁-C₄ alkyl optionally substituted by one or more halogen atoms.

In an embodiment of the invention as described anywhere herein, wherein

Z is independently OH, C₁-C₄ alkyl optionally substituted by one or more OH groups or

20 NH₂ groups, C₁-C₄ alkyl optionally substituted by one or more halogen atoms, C₁-C₄ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy, NR¹⁹R²¹, C(O)OR¹⁹, C(O)R¹⁹, SR¹⁹, OR¹⁹, CN, NO₂, or halogen;

R¹⁹ and R²¹ are each independently H; C₁-C₄ alkyl; C₃-C₆ cycloalkyl; or C₁-C₄ alkoxy-C₁-C₄ alkyl, wherein all alkyls are optionally substituted with halogens.

25

In an embodiment of the invention as described anywhere herein, wherein

Z is independently OH, C₁-C₄ alkyl optionally substituted by one or more OH groups or

NH₂ groups, C₁-C₄ alkyl optionally substituted by one or more halogen atoms, C₁-C₄ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy, C(O)OR¹⁹,

30 C(O)R¹⁹, OR¹⁹, CN, or halogen;

R¹⁹ is H; C₁-C₄ alkyl; C₃-C₆ cycloalkyl; or C₁-C₄ alkoxy-C₁-C₄ alkyl, wherein all alkyl are optionally substituted with halogens.

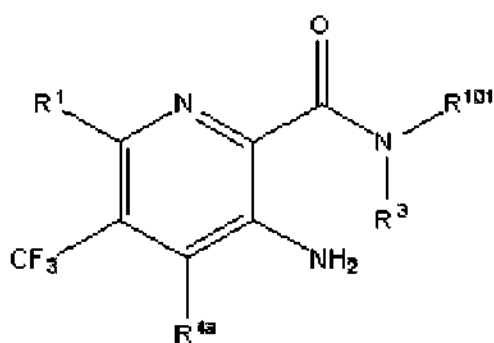
In an embodiment of the invention as described anywhere herein, wherein Z is independently, C₁-C₄ alkyl optionally substituted by one or more halogen atoms, C₁-C₄ alkoxy or halogen.

- 5 Another embodiment of the invention as defined above provides compounds with substantially pure enantiomers with the R configuration.

Another embodiment of the invention as defined above provides compounds with substantially pure enantiomers with the S configuration.

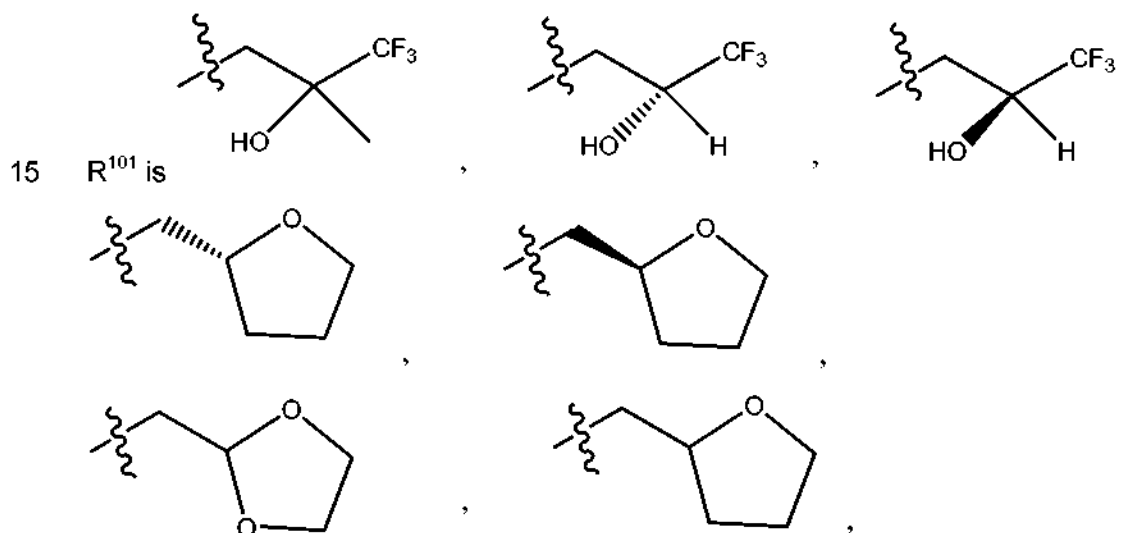
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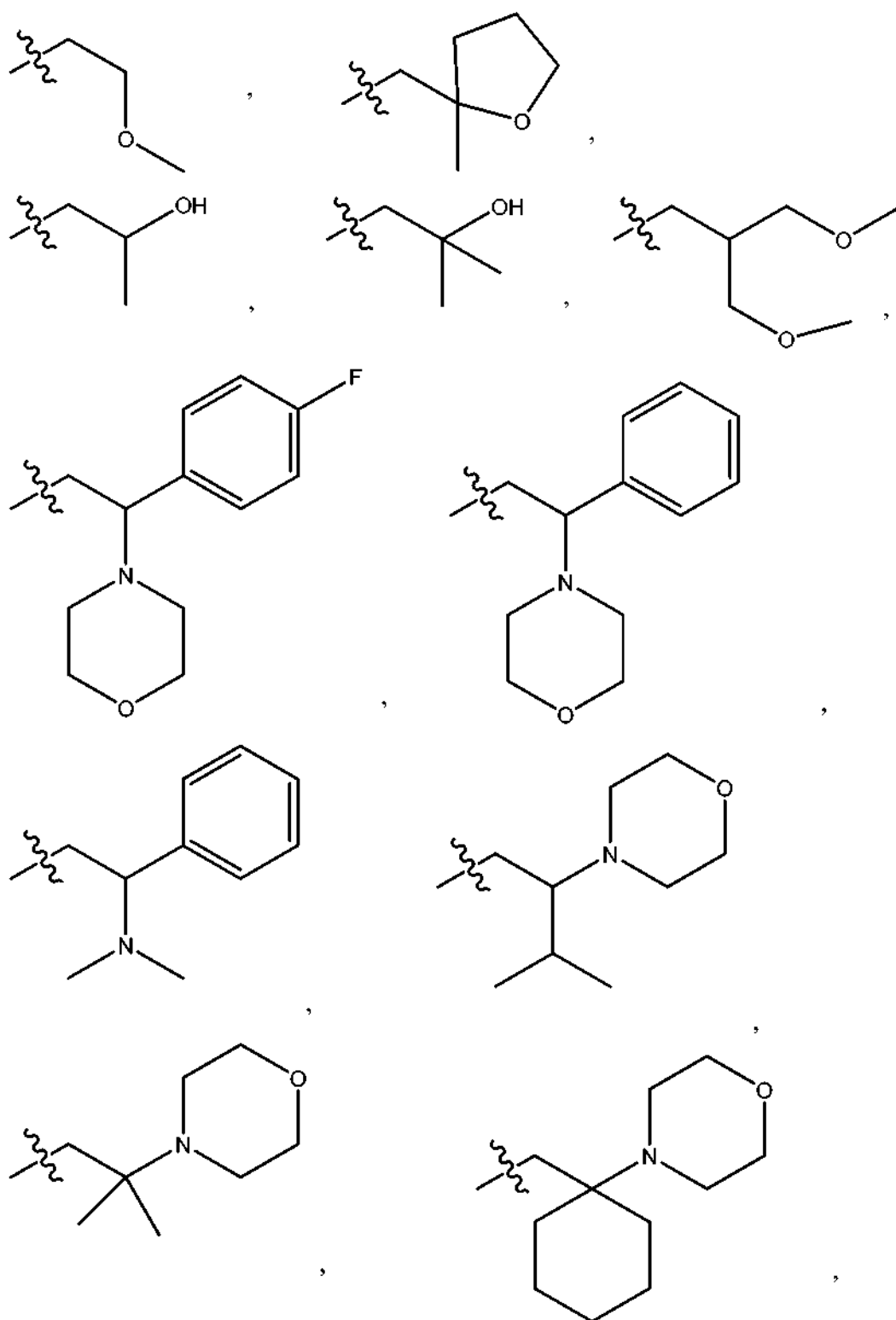
Certain compounds of Formula I include compounds of Formula II:

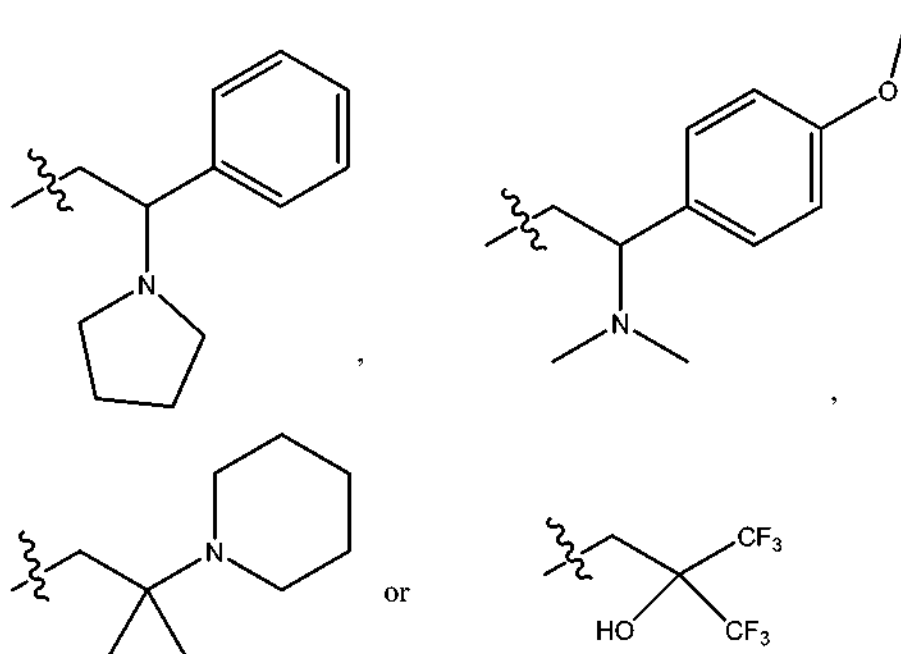


II

or a pharmaceutically acceptable salt thereof, wherein A, R¹, R² and R³ have the definitions of Formula I and







In a further embodiment of Formula II of the invention herein, R^1 is selected from H; C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms; halogen; C_6 - C_{14} aryl; $-(C_0$ - C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; and $NR^{11}R^{12}$, wherein the aryl and heterocyclic groups are each optionally substituted by one or more Z substituents.

In a further embodiment of Formula II of the invention wherein, R^1 is C_1 - C_4 alkyl optional substituted by one or more halogen atoms, C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms; halogen; C_6 aryl; or 6 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl and heterocyclic groups are each optionally substituted by one or more Z substituents.

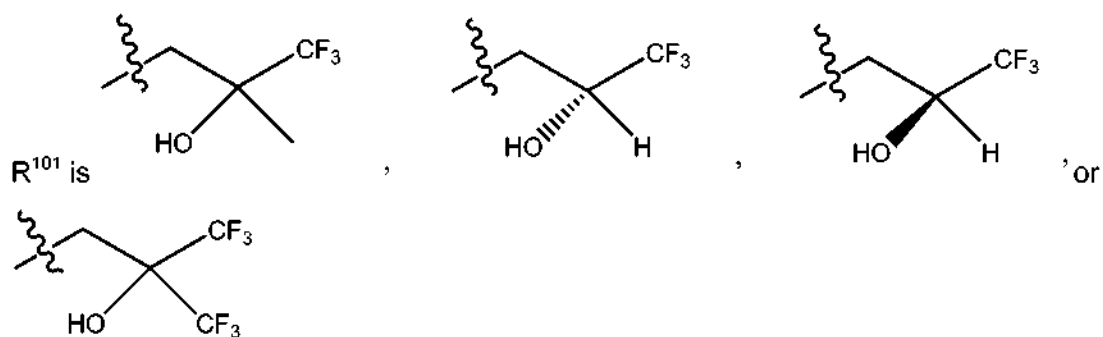
In a further embodiment of Formula II of the invention wherein, R^1 is C_1 - C_4 alkyl optional substituted by one or more halogen atoms, C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms; or halogen.

In a further embodiment of Formula II of the invention herein, R^3 is H or methyl.

An embodiment of the invention as defined above provides compounds according to Formula II, wherein

5 R^1 is halogen;

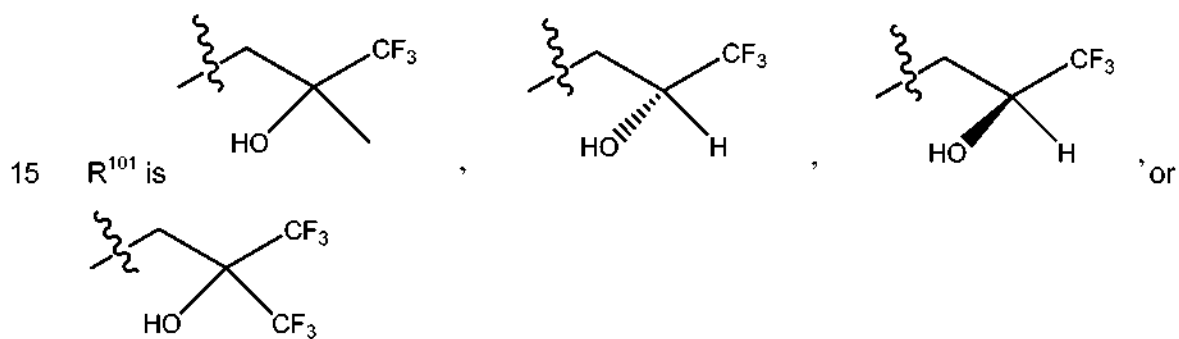
R^3 is H;



10 An embodiment of the invention as defined above provides compounds according to Formula II, wherein

R^1 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms;

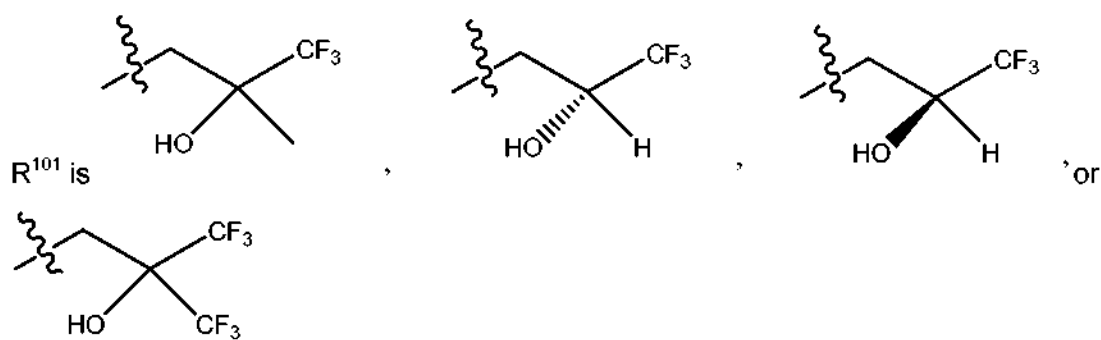
R^3 is H;



An embodiment of the invention as defined above provides compounds according to Formula II, wherein

20 R^1 is C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms;

R^3 is H;

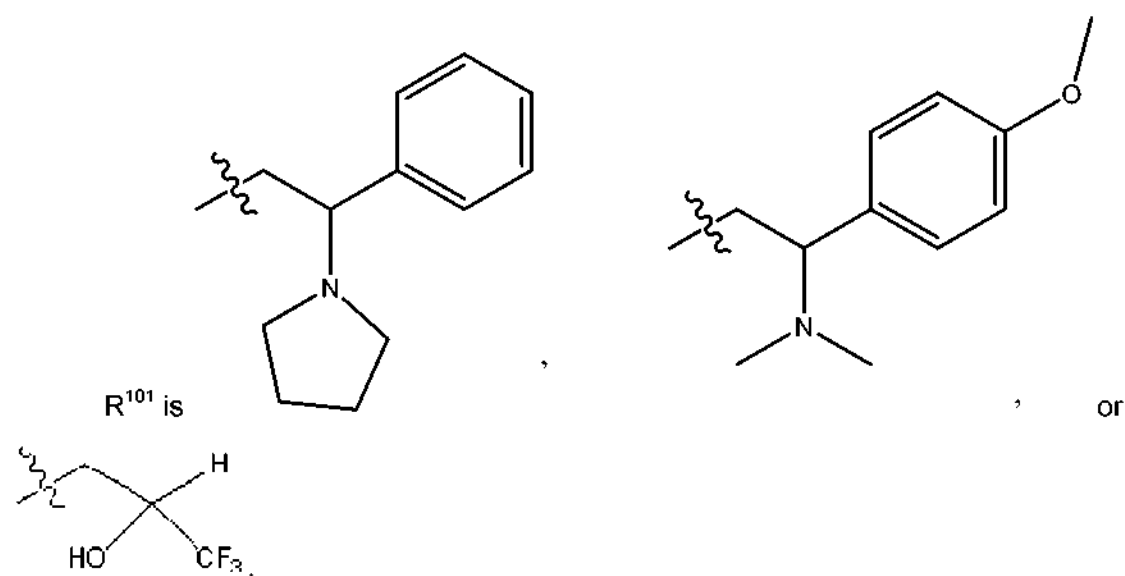


An embodiment of the invention as defined above provides compounds according to

5 Formula II, wherein

R¹ is halogen, C₁-C₄ alkyl optionally substituted by one or more halogen atoms, or C₁-C₄ alkoxy optionally substituted by one or more halogen atoms;

R³ is H;

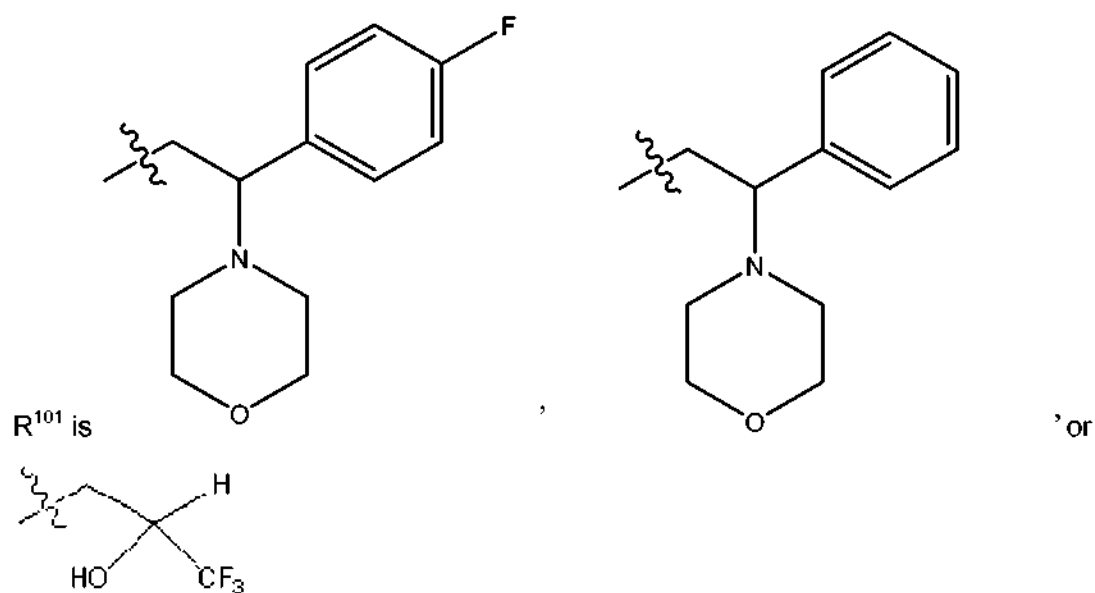


An embodiment of the invention as defined above provides compounds according to

Formula II, wherein

R¹ is halogen, C₁-C₄ alkyl optionally substituted by one or more halogen atoms, or C₁-C₄ alkoxy optionally substituted by one or more halogen atoms;

15 R³ is H;

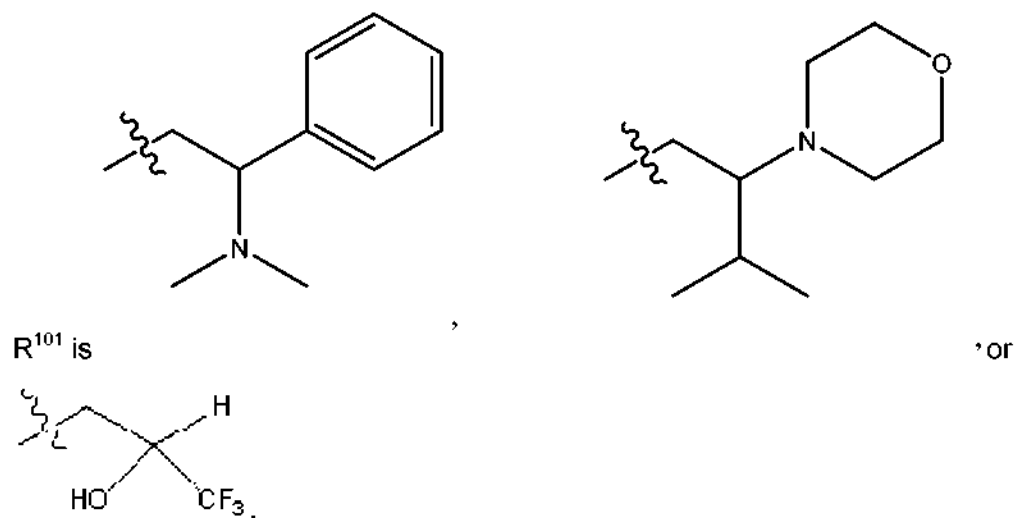


An embodiment of the invention as defined above provides compounds according to

5 Formula II, wherein

R¹ is halogen, C₁-C₄ alkyl optionally substituted by one or more halogen atoms, or C₁-C₄ alkoxy optionally substituted by one or more halogen atoms;

R³ is H;



10

Another embodiment of the invention as defined above provides compounds according to Formula I and Formula II, represented by

(S)-3-Amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide;
 (S)-3-Amino-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoro methyl)-4-vinylpicolinamide; and

- 5 3-Amino-6-methoxy-4-phenyl-5-trifluoromethyl-pyridine-2-carboxylic acid ((S)-3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide;
 or a pharmaceutically acceptable salt thereof.

10 It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments. It is understood by those skilled in the art that combinations of substituents where not possible are not an aspect of the present invention.

15

Especially preferred specific compounds of formula (I) or formula II are those described hereinafter in the Examples.

Definitions

- 20 Terms used in the specification have the following meanings:

"Optionally substituted" means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

- 25 "Optionally substituted by one or more Z groups" denotes that the relevant group may include one or more substituents, each independently selected from the groups included within the definition of Z. Thus, where there are two or more Z group substituents, these may be the same or different.

"Halo" or "halogen", as used herein, may be fluorine, chlorine, bromine or iodine.

30

"C₁-C₈-Alkyl", as used herein, denotes straight chain or branched alkyl having 1-8 carbon atoms. If a different number of carbon atoms is specified, such as C₆ or C₃, then

the definition is to be amended accordingly, such as "C₁-C₄-Alkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

"C₁-C₈-Alkoxy", as used herein, denotes straight chain or branched alkoxy having
 5 1-8 carbon atoms. If a different number of carbon atoms is specified, such as C₆ or C₃, then the definition is to be amended accordingly, such as "C₁-C₄-Alkoxy" will represent methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy.

"C₁-C₄-Haloalkyl", as used herein, denotes straight chain or branched alkyl having 1-4
 10 carbon atoms with at least one hydrogen substituted with a halogen. If a different number of carbon atoms is specified, such as C₆ or C₃, then the definition is to be amended accordingly, such as "C₁-C₄-Haloalkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl that have at least one hydrogen substituted with halogen, such as where the halogen is fluorine: CF₃CF₂-, (CF₃)₂CH-,
 15 CH₃-CF₂-, CF₃CF₂-, CF₃, CF₂H-, CF₃CF₂CHCF₃ or CF₃CF₂CF₂CF₂-.

"C₁-C₈-hydroxyalkyl", as used herein, denotes straight chain or branched alkyl having 1-
 8 carbon atoms with at least one hydrogen substituted with a hydroxy group. If a
 different number of carbon atoms is specified, such as C₆ or C₃, then the definition is to
 20 be amended accordingly, such as "C₁-C₄-hydroxyalkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl that have at least one hydrogen substituted with a hydroxy group.

The term 'C₂₋₈ alkenyl' as used herein refers to a linear or branched saturated
 25 hydrocarbon group containing from 2 to 8 carbon atoms that contains at least one carbon to carbon double bond. Examples of such groups include ethenyl, propenyl, butenyl and pentenyl. Unless a particular structure is specified, the terms butenyl and pentenyl etc. include all possible *E* and *Z* isomers.

30 The term "C₂₋₈ alkynyl" as used herein refers to a linear or branched saturated hydrocarbon group containing from 2 to 8 carbon atoms that contains at least one carbon to carbon triple bond. Examples of such groups include ethynyl, propynyl, butynyl and pentynyl.

The term 'C₃₋₈ cycloalkyl' as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 6 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

5

The term "alkylene" denotes a straight chain or branched saturated hydrocarbon chain containing between 1 and 8 carbon atoms. If a different number of carbon atoms is specified, such as C₆ or C₃, then the definition is to be amended accordingly.

"Amino-C₁-C₈-alkyl" and "amino-C₁-C₈-alkoxy" denote amino attached by a nitrogen atom to C₁-C₈-alkyl, e.g., NH₂-(C₁-C₈)-, or to C₁-C₈-alkoxy, e.g., NH₂-(C₁-C₈)-O-. If a different number of carbon atoms is specified, such as C₆ or C₃, then the definition is to be amended accordingly.

"C₁-C₈-Alkylamino" and "di(C₁-C₈-alkyl)amino" denote C₁-C₈-alkyl, as hereinbefore defined, attached by a carbon atom to an amino group. The C₁-C₈-alkyl groups in di(C₁-C₈-alkyl)amino may be the same or different. If a different number of carbon atoms is specified, such as C₆ or C₃, then the definition is to be amended accordingly.

"Amino-(hydroxy)-C₁-C₈-alkyl" denotes amino attached by a nitrogen atom to C₁-C₈-alkyl and hydroxy attached by an oxygen atom to the same C₁-C₈-alkyl. If a different number of carbon atoms is specified, such as C₆ or C₃, then the definition is to be amended accordingly.

"C₁-C₈-Alkylcarbonyl" and "C₁-C₈-alkoxycarbonyl", as used herein, denote C₁-C₈-alkyl or C₁-C₈-alkoxy, respectively, as hereinbefore defined, attached by a carbon atom to a carbonyl group. If a different number of carbon atoms is specified, such as C₆ or C₃, then the definition is to be amended accordingly.

"C₃-C₈-Cycloalkylcarbonyl", as used herein, denotes C₃-C₈-cycloalkyl, as hereinbefore defined, attached by a carbon atom to a carbonyl group. If a different number of carbon atoms is specified, such as C₆ or C₃, then the definition is to be amended accordingly.

"C₇-C₁₄-Aralkyl", as used herein, denotes alkyl, e.g., C₁-C₄-alkyl, as hereinbefore defined, substituted by a C₆-C₁₀-aromatic carbocyclic group, as herein defined. If a

different number of carbon atoms is specified, such as C₆ or C₃, then the definition is to be amended accordingly.

"C₃-C₁₅-Cycloalkyl", as used herein, denotes a cycloalkyl having 3- to 15-ring carbon atoms that is saturated or partially saturated, such as a C₃-C₈-cycloalkyl. Examples of C₃-C₁₅-cycloalkyls include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl or a bicyclic group, such as bicyclooctyl, bicyclononyl including indanyl and indenyl and bicyclodecyl. If a different number of carbon atoms is specified, such as C₆, then the definition is to be amended accordingly.

"aryl" or "C₆-C₁₅-Aromatic carbocyclic group", as used herein, denotes an aromatic group having 6- to 15-ring carbon atoms. Examples of C₆-C₁₅-aromatic carbocyclic groups include, but are not limited to, phenyl, phenylene, benzenetriyl, naphthyl, naphthylene, naphthalenetriyl or anthrylene. If a different number of carbon atoms is specified, such as C₁₀, then the definition is to be amended accordingly.

"4- to 8-Membered heterocyclyl", "5- to 6- membered heterocyclyl", "3- to 10-membered heterocyclyl", "3- to 14-membered heterocyclyl", "4- to 14-membered heterocyclyl" and "5- to 14-membered heterocyclyl", refers, respectively, to 4- to 8-membered, 5- to 6-membered, 3- to 10-membered, 3- to 14-membered, 4- to 14-membered and 5- to 14-membered heterocyclic rings containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, which may be saturated, partially saturated or unsaturated (aromatic). The heterocyclyl includes single ring groups, fused ring groups and bridged groups. Examples of such heterocyclyls include, but are not limited to, furan, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, isotriazole, tetrazole, thiadiazole, isothiazole, oxadiazole, pyridine, piperidine, pyrazine, oxazole, isoxazole, pyrazine, pyridazine, pyrimidine, piperazine, pyrrolidine, pyrrolidinone, morpholine, triazine, oxazine, tetrahydrofuran, tetrahydrothiophene, tetrahydrothiopyran, tetrahydropyran, 1,4-dioxane, 1,4-oxathiane, indazole, quinoline, indazole, indole, 8-azabicyclo[3.2.1]octane or thiazole.

A second aspect of the invention provides a compound of Formula I or II as defined anywhere herein for use as a pharmaceutical.

A further aspect of the invention provides a compound of Formula I or II for use in the treatment of an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease or mucosal hydration. Such conditions include, for example, cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma, respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sicca, or constipation (IBS, IBD, opioid induced).

A still further aspect of the present invention provides for the use of a compound of formula (I) or (II), as defined in any of the aforementioned embodiments, in free or pharmaceutically acceptable salt form, for the manufacture of a medicament for the treatment of an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease or mucosal hydration.

An embodiment of the present invention provides for the use of a compound of formula (I) or (II), as defined in any of the aforementioned embodiments, in free or pharmaceutically acceptable salt form, for the manufacture of a medicament for the treatment of an inflammatory or allergic condition selected from cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma, respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sicca, or constipation (IBS, IBD, opioid induced).

An embodiment of the present invention provides for the use of a compound of formula (I) or (II), as defined in any of the aforementioned embodiments, in free or pharmaceutically acceptable salt form, for the manufacture of a medicament for the treatment of an inflammatory or allergic condition which is cystic fibrosis.

An embodiment of the present invention provides method for the prevention or treatment of a CFTR mediated condition or disease comprising administering an effective amount of at least one compound as described herein to a subject in need of such treatment. Such CFTR mediated condition or disease are selected from cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma,

respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sicca, or constipation (IBS, IBD, opioid induced).

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", should be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlorotheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, and sulfosalicylic acid.

Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

5 Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

10

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, 15 piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods.

Generally, such salts can be prepared by reacting free acid forms of these compounds 20 with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two.

Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or 25 acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

30 Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

Compounds of the invention, i.e. compounds of formula (I) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures
5 include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I).

10 As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present
15 invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic
20 mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is
25 unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present
30 invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z

configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a *cis*- or *trans*-configuration. All tautomeric forms are also intended to be included.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Since the compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight

basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1 %, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention.

- 5 Compounds of the present invention are either obtained in the free form, or as a salt thereof.

When both a basic group and an acid group are present in the same molecule, the compounds of the present invention may also form internal salts, e.g., zwitterionic molecules.

- 10 Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of
- 15 hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^3H , ^{13}C , and ^{14}C , are present. Such isotopically labeled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for
- 20 example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention can generally be prepared by
- 25 carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

- Further, substitution with heavier isotopes, particularly deuterium (i.e., ^2H or D) may
- 30 afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a

substituent of a compound of the formula (I) or (II). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a

5 compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least

10 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Isotopically-labeled compounds of formula (I) or (II) can generally be prepared by

15 conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those

20 wherein the solvent of crystallization may be isotopically substituted, e.g. D₂O, d₆-acetone, d₆-DMSO.

Compounds of the invention, i.e. compounds of formula (I) or formula (II) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be

25 capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) or formula (II) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) or formula (II) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-

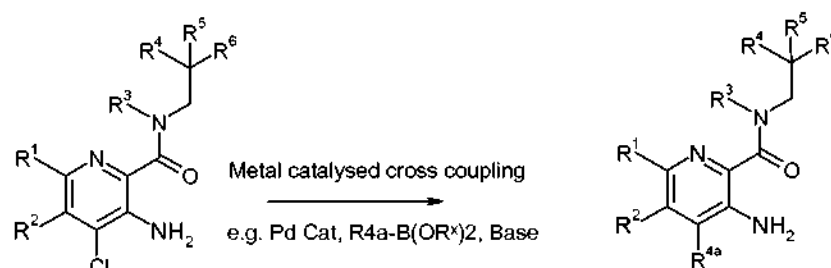
30 crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I) or formula (II).

Synthesis

Generally, compounds according to Formula I or (II) can be synthesized by the routes described in Scheme 1, 2 and 3 and the Examples.

When R^{4a} is alkenyl, aryl or heteroaryl, compounds may be synthesized according to
 5 general scheme 1

Scheme 1

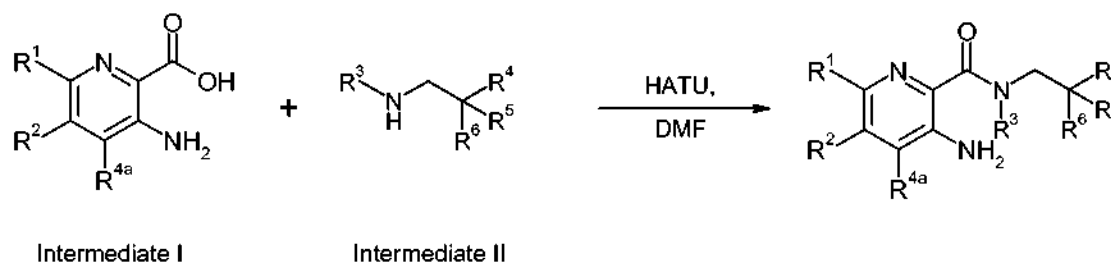


- 10 wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as previously defined for compounds of formula I and II, and $B(OR^x)_2$ refers to a boronic acid or boronate ester coupling agent.

A suitable palladium catalyst to use is [1,1'-bis(di-tertbutylphosphino)ferrocene] dichloropalladium(II). A skilled person would understand that other palladium catalysts
 15 may also be suitable.

The right hand side of the moiety is typically added via an amide formation reaction as shown below in general scheme 2.

Scheme 2

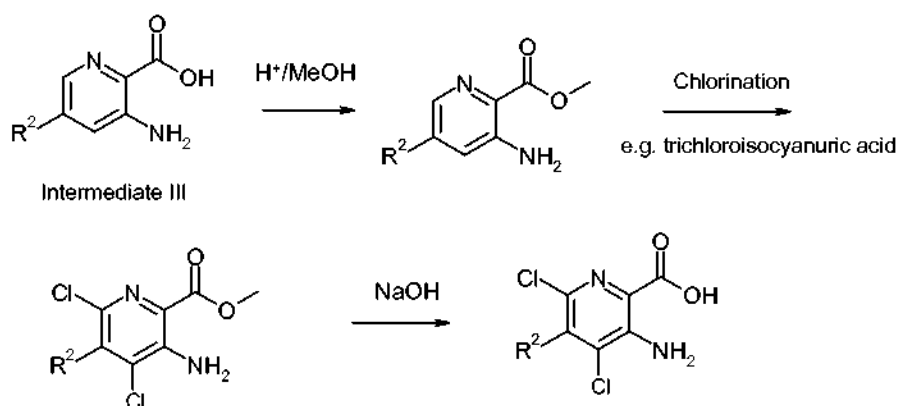


HATU (2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium) is a peptide coupling agent. A skilled person would understand that other coupling agents could possibly work.

- 5 The amine intermediate II, is either available commercially, or has a published synthesis.

When R^1 is halogen and R^{4a} is halogen, intermediate I may be synthesized according to scheme 3.

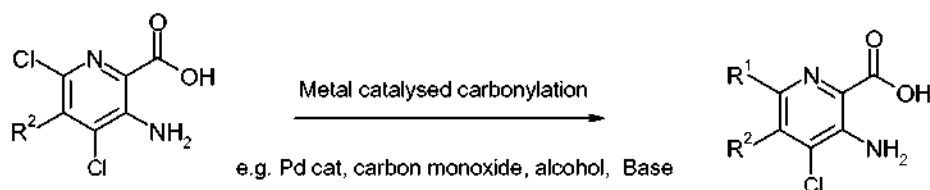
10 Scheme 3



When R^1 is carboxylate, and R^{4a} is halogen, intermediate I may be synthesized according to the method in scheme 4

15

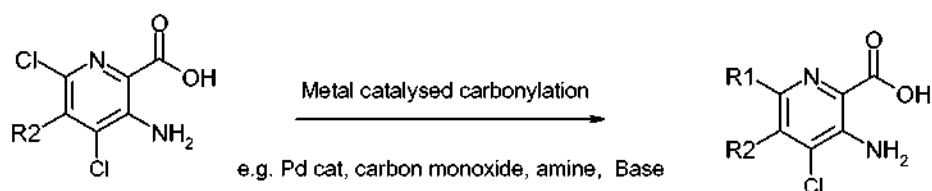
Scheme 4



When R^1 is carboxamide, and R^{4a} is halogen, intermediate I may be synthesized according to the method in scheme 5

20

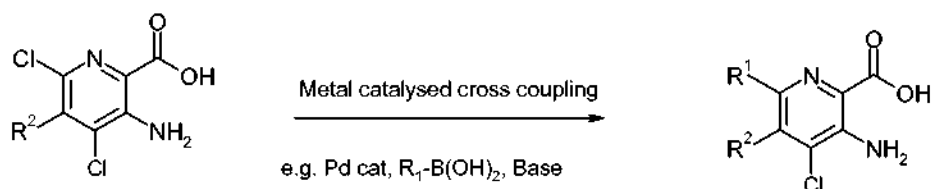
Scheme 5



When R¹ is alkyl, aryl, or heteroaryl, and R^{4a} is halogen intermediate I may be synthesized according to scheme 6.

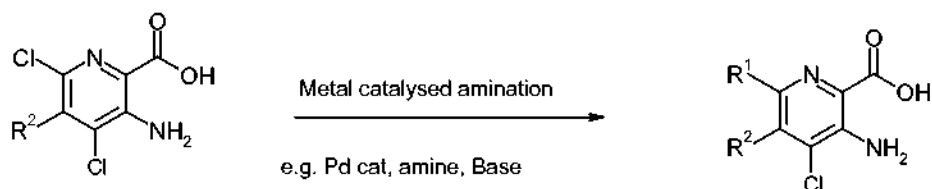
5

Scheme 6



- 10 When R¹ is alkyl amino and R⁴ is halogen, intermediate I may be synthesized according to the general scheme 7

Scheme 7

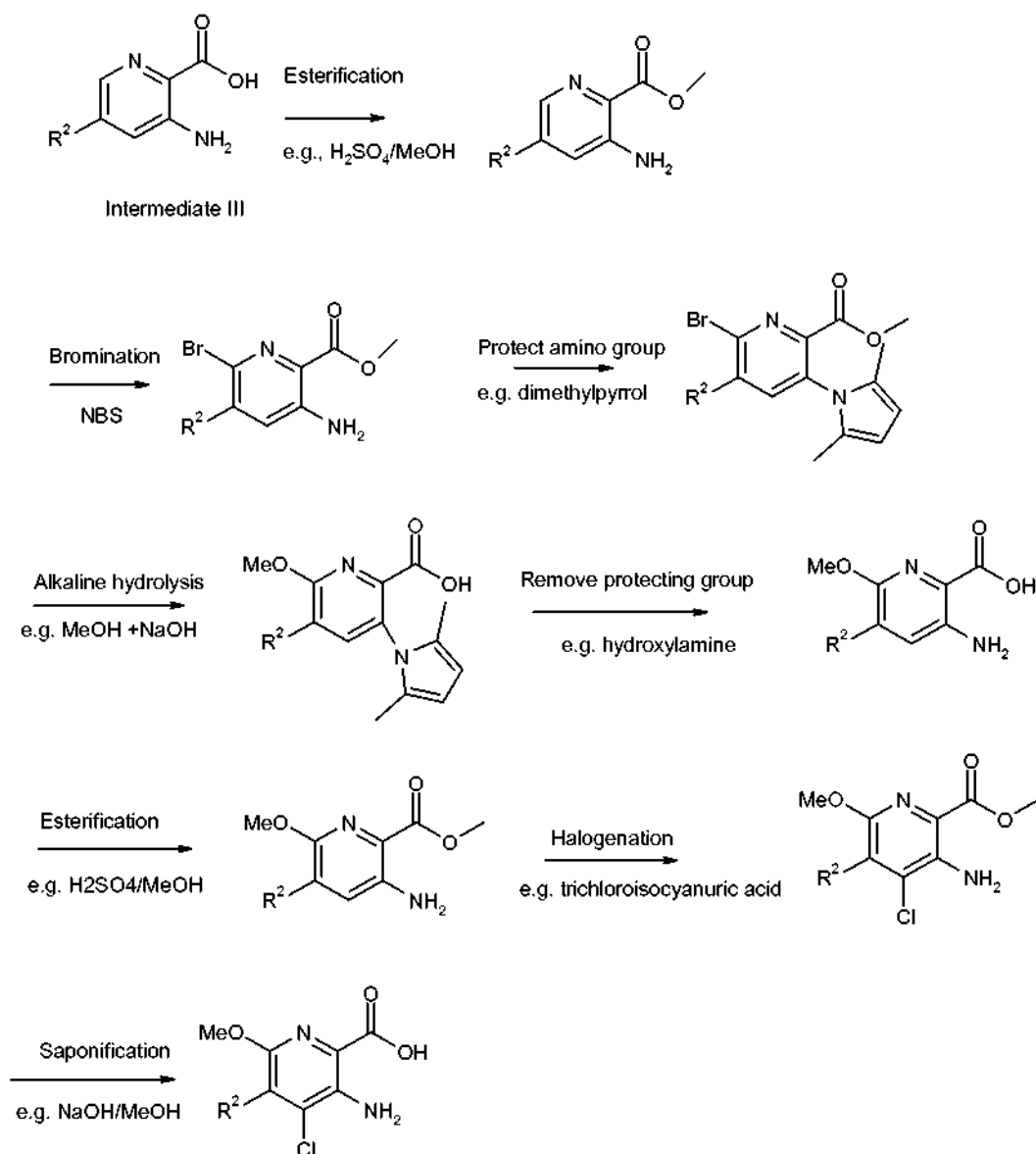


15

For schemes 4 to 7, a suitable palladium catalyst to use is [1,1'-bis(di-tertbutylphosphino)ferrocene] dichloropalladium(II). A skilled person would understand that other palladium catalysts may also be suitable.

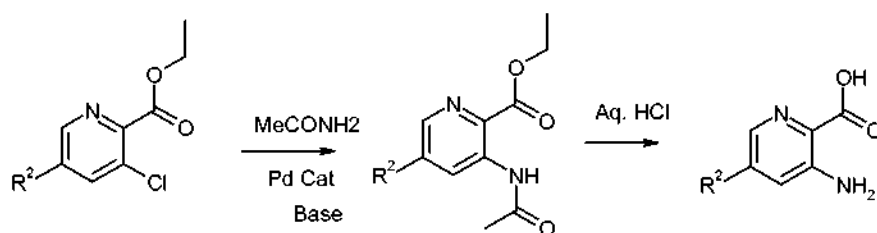
20

When R¹ is methoxy, R^{4a} is halogen, Intermediate I may be synthesized according to the general scheme 8

Scheme 8

- 5 Intermediate III may be synthesized according to the general scheme 9 or scheme 10

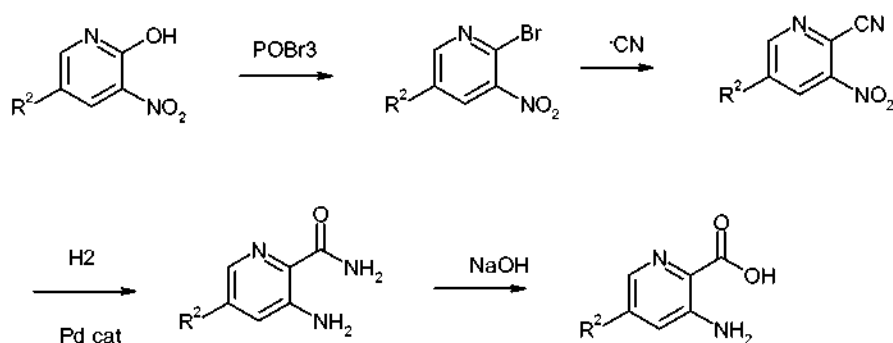
Scheme 9.



Or alternatively

Scheme 10

5



The skilled person will appreciate that the general synthetic routes detailed above show common reactions to transform the starting materials as required. The specific reaction conditions are not provided, but these are well known to those skilled in the art and appropriate conditions considered to be within the skilled person's common general knowledge.

The starting materials are either commercially available compounds or are known compounds and can be prepared from procedures described in the organic chemistry art.

Compounds of formula (I) or (II), in free form, may be converted into salt form, and vice versa, in a conventional manner understood by those skilled in the art. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula (I) or (II) can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as stereoisomers, may be obtained in a conventional manner, e.g., by fractional

crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g., optically active, starting materials.

The compounds of formula (I) or (II) can be prepared, e.g., using the reactions and techniques described below and in the Examples. The reactions may be performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

The various substituents on the synthetic intermediates and final products shown in the following reaction schemes can be present in their fully elaborated forms, with suitable protecting groups where required as understood by one skilled in the art, or in precursor forms which can later be elaborated into their final forms by methods familiar to one skilled in the art. The substituents can also be added at various stages throughout the synthetic sequence or after completion of the synthetic sequence. In many cases, commonly used functional group manipulations can be used to transform one intermediate into another intermediate, or one compound of formula (I) or (II) into another compound of formula (I) or (II). Examples of such manipulations are conversion of an ester or a ketone to an alcohol; conversion of an ester to a ketone; interconversions of esters, acids and amides; alkylation, acylation and sulfonylation of alcohols and amines; and many others. Substituents can also be added using common reactions, such as alkylation, acylation, halogenation or oxidation. Such manipulations are well-known in the art, and many reference works summarize procedures and methods for such manipulations. Some reference works which gives examples and references to the primary literature of organic synthesis for many functional group manipulations, as well as other transformations commonly used in the art of organic synthesis are *March's Organic Chemistry*, 5th Edition, Wiley and Chichester, Eds. (2001); *Comprehensive Organic Transformations*, Larock, Ed., VCH (1989); *Comprehensive Organic Functional Group Transformations*, Katritzky et al. (series editors), Pergamon (1995); and *Comprehensive Organic Synthesis*, Trost and Fleming (series editors),

Pergamon (1991). It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. Multiple protecting groups within the same molecule can be chosen
5 such that each of these protecting groups can either be removed without removal of other protecting groups in the same molecule, or several protecting groups can be removed using the same reaction step, depending upon the outcome desired. An authoritative account describing many alternatives to the trained practitioner is Greene and Wuts, *Protective Groups in Organic Synthesis*, Wiley and Sons (1999).

Pharmacological activity

Having regard to their modulation of CFTR activity, compounds of formula (I), in free or pharmaceutically acceptable salt form, hereinafter alternately referred to as "agents of the invention", are useful in the treatment of conditions which respond to the modulation
15 of CFTR activity, particularly conditions benefiting from mucosal hydration such as cystic fibrosis.

Diseases mediated by modulation of CFTR activity, include diseases associated with the regulation of fluid volumes across epithelial membranes. For example, the volume of
20 airway surface liquid is a key regulator of mucociliary clearance and the maintenance of lung health. The modulation of CFTR activity will promote fluid accumulation on the mucosal side of the airway epithelium thereby promoting mucus clearance and preventing the accumulation of mucus and sputum in respiratory tissues (including lung airways). Such diseases include respiratory diseases, such as cystic fibrosis, primary
25 ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, respiratory tract infections (acute and chronic; viral and bacterial) and lung carcinoma. Diseases mediated by modulation of CFTR activity also include diseases other than respiratory diseases that are associated with abnormal fluid regulation across an epithelium, perhaps involving abnormal physiology of the protective surface liquids on
30 their surface, e.g., Sjögren's Syndrome, xerostomia (dry mouth) or keratoconjunctivitis sicca (dry eye). Furthermore, modulation of CFTR activity in the kidney could be used to promote diuresis and thereby induce a hypotensive effect.

Treatment in accordance with the invention may be symptomatic or prophylactic.

Asthma includes intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of
5 asthma is also to be understood as embracing treatment of subjects, e.g., of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular
10 asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g., of acute asthmatic or bronchoconstrictor attack, improvements in lung function or improved airways hyperreactivity. It may further be
15 evidenced by reduced requirement for other, symptomatic therapy, i.e., therapy for or intended to restrict or abort symptomatic attack when it occurs, e.g., anti-inflammatory (e.g., cortico-steroid) or bronchodilatory. Prophylactic benefit in asthma may, in particular, be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome, common to a substantial percentage of asthmatics and
20 characterized by asthma attack, e.g., between the hours of about 4-6 am, i.e., at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Chronic obstructive pulmonary disease includes chronic bronchitis or dyspnea
25 associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular, other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis.

30 Dry eye disease is characterized by a decrease in tear aqueous production and abnormal tear film lipid, protein and mucin profiles. There are many causes of dry eye, some of which include age, laser eye surgery, arthritis, medications, chemical/thermal burns, allergies and diseases, such as cystic fibrosis and Sjögren's Syndrome.

Increasing anion secretion via CFTR would enhance fluid transport from the corneal endothelial cells and secretory glands surrounding the eye to increase corneal hydration. This would help to alleviate the symptoms associated with dry eye disease.

- 5 Sjögren's Syndrome is an autoimmune disease in which the immune system attacks moisture-producing glands throughout the body, including eye, mouth, skin, respiratory tissue, liver, vagina and gut. Symptoms include dry eye, dry mouth and dry vagina, as well as lung disease. The disease is also associated rheumatoid arthritis, systemic lupus, systemic sclerosis and polymyositis/dermatomyositis. Defective protein
- 10 trafficking is believed to cause the disease, for which treatment options are limited. Modulators of CFTR activity may hydrate the various organs affected by the disease and help to alleviate the associated symptoms.

The suitability of CFTR activity modulators as a treatment of a disease benefiting from

15 mucosal hydration may be tested by determining the movement of chloride ions in a suitable cell-based assay. For example single cells or confluent epithelia, endogenously expressing or engineered to overexpress CFTR can be used to assess channel function using electrophysiological techniques or ion flux studies. See methods described in: Hirsh et al., *J Pharm Exp Ther* (2004); Moody et al., *Am J Physiol Cell Physiol* (2005).

20 CFTR activity modulators, including the compounds of formula (I), are also useful as co-therapeutic agents for use in combination with other drug substances, such as anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substances, particularly in the treatment of cystic fibrosis or obstructive or inflammatory airways diseases such

25 as those mentioned hereinbefore, e.g., as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs.

The compounds of Formula (I) or (II) may be mixed with the other drug substance in a

30 fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance.

Accordingly, the invention includes as a further aspect a combination of a CFTR activity modulator with osmotic agents (hypertonic saline, dextran, mannitol, Xylitol), ENaC blockers, an anti-inflammatory, bronchodilatory, antihistamine, anti-tussive, antibiotic and/or DNase drug substance, wherein the CFTR activity modulator and the further drug
 5 substance may be in the same or different pharmaceutical composition.

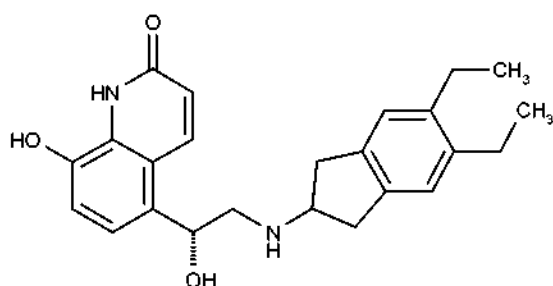
Suitable antibiotics include macrolide antibiotics, e.g., tobramycin (TOBI™).

Suitable DNase drug substances include dornase alfa (Pulmozyme™), a highly-purified
 10 solution of recombinant human deoxyribonuclease I (rhDNase), which selectively cleaves DNA. Dornase alfa is used to treat cystic fibrosis.

Other useful combinations of CFTR activity modulators with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g., CCR-1, CCR-2, CCR-3, CCR-4,
 15 CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists, such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D; Takeda antagonists, such as *N*-[[4-[[[6,7-dihydro-2-(4-methyl-phenyl)-5*H*-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-*N,N*-dimethyl-2*H*-pyran-4-amin-ium chloride (TAK-770); and CCR-5 antagonists
 20 described in USP 6,166,037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), WO 00/66559 (particularly claim 9), WO 04/018425 and WO 04/026873.

Suitable anti-inflammatory drugs include steroids, in particular, glucocorticosteroids, such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide
 25 or mometasone furoate, or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/35668, WO 03/48181, WO 03/62259, WO 03/64445, WO 03/72592, WO 04/39827 and WO 04/66920; non-steroidal glucocorticoid receptor agonists, such as those described in DE 10261874, WO
 30 00/00531, WO 02/10143, WO 03/82280, WO 03/82787, WO 03/86294, WO 03/104195, WO 03/101932, WO 04/05229, WO 04/18429, WO 04/19935 and WO 04/26248; LTD4 antagonists, such as montelukast and zafirlukast; PDE4 inhibitors, such as cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004

(Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659/PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), and those disclosed in WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607 and WO 04/037805; adenosine A2B receptor antagonists such as those described in WO 02/42298; and beta-2 adrenoceptor agonists, such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol, carmoterol or pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula (I) of WO 0075114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula:

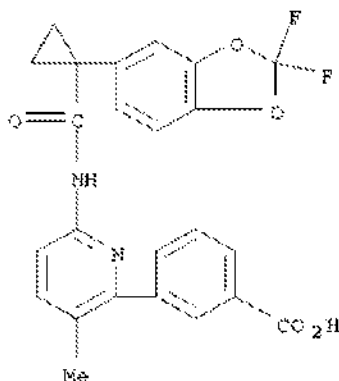


USP 5,171,744, WO 01/04118, WO 02/00652, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/33495, WO 03/53966, WO 03/87094, WO 04/018422 and WO 04/05285.

- 5 Suitable dual anti-inflammatory and bronchodilatory drugs include dual beta-2 adrenoceptor agonist/muscarinic antagonists such as those disclosed in USP 2004/0167167, WO 04/74246 and WO 04/74812.

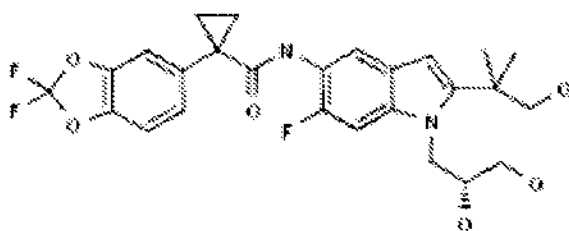
- 10 Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine, as well as those disclosed in JP 2004107299, WO 03/099807 and WO 04/026841.

- 15 The invention includes as a further aspect a combination of a CFTR activity modulator with a CFTR corrector, wherein the CFTR activity modulator and the CFTR corrector may be in the same or different pharmaceutical composition. Suitable CFTR correctors include VX-809



;

- 20 and
VX-661



In accordance with the foregoing, the invention also provides as a further aspect a
 5 method for the treatment of a condition responsive to modulation of CFTR activity, e.g.,
 diseases associated with the regulation of fluid volumes across epithelial membranes,
 particularly an obstructive airways disease, which comprises administering to a subject,
 particularly a human subject, in need thereof a compound of formula (I) or (II), in free
 form or in the form of a pharmaceutically acceptable salt.

10 In another aspect the invention provides a compound of formula (I) or (II), in free form or
 in the form of a pharmaceutically acceptable salt, for use in the manufacture of a
 medicament for the treatment of a condition responsive to modulation of CFTR activity,
 particularly an obstructive airways disease, e.g., cystic fibrosis and COPD.

15 The agents of the invention may be administered by any appropriate route, e.g. orally,
 e.g., in the form of a tablet or capsule; parenterally, e.g., intravenously; by inhalation,
 e.g., in the treatment of an obstructive airways disease; intranasally, e.g., in the
 treatment of allergic rhinitis; topically to the skin; or rectally. In a further aspect, the
 20 invention also provides a pharmaceutical composition comprising a compound of formula
 (I), in free form or in the form of a pharmaceutically acceptable salt, optionally together
 with a pharmaceutically acceptable diluent or carrier therefor. The composition may
 contain a co-therapeutic agent, such as an anti-inflammatory, broncho-dilatory,
 antihistamine or anti-tussive drug as hereinbefore described. Such compositions may be
 25 prepared using conventional diluents or excipients and techniques known in the galenic
 art. Thus oral dosage forms may include tablets and capsules. Formulations for topical
 administration may take the form of creams, ointments, gels or transdermal delivery

systems, e.g., patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, e.g., a
5 hydro-fluoro-alkane (HFA) propellant, such as HFA134a or HFA227 or a mixture of
these, and may contain one or more co-solvents known in the art, such as ethanol (up to
20% by weight), and/or one or more surfactants, such as oleic acid or sorbitan trioleate,
and/or one or more bulking agents, such as lactose. When the composition comprises a
dry powder formulation, it preferably contains, e.g., the compound of formula (I) or (II)
10 having a particle diameter up to 10 microns, optionally together with a diluent or carrier,
such as lactose, of the desired particle size distribution and a compound that helps to
protect against product performance deterioration due to moisture, e.g., magnesium
stearate. When the composition comprises a nebulised formulation, it preferably
contains, e.g., the compound of formula (I) or (II) either dissolved, or suspended, in a
15 vehicle containing water, a co-solvent, such as ethanol or propylene glycol and a
stabilizer, which may be a surfactant.

Further aspects of the invention include:

- 20 (a) a compound of formula (I) or (II) in inhalable form, e.g., in an aerosol or other
atomisable composition or in inhalable particulate, e.g., micronised form;
- (b) an inhalable medicament comprising a compound of formula (I) or (II) in
inhalable form;
- (c) a pharmaceutical product comprising a compound of formula (I) in inhalable
form in association with an inhalation device; and
- 25 (d) an inhalation device containing a compound of formula I or II in inhalable
form.

Dosages of compounds of formula (I) or (II) employed in practicing the present invention
will of course vary depending, e.g., on the particular condition to be treated, the effect
30 desired and the mode of administration. In general, suitable daily dosages for
administration by inhalation are of the order of 0.005-10 mg, while for oral administration
suitable daily doses are of the order of 0.05-100 mg.

Pharmaceutical Use and Assay

Compounds of formula (I) or (II) and their pharmaceutically acceptable salts, hereinafter referred to alternatively as "agents of the invention", are useful as pharmaceuticals. In particular, the compounds are suitable CFTR activity modulators and may be tested in the following assays.

Membrane potential assay

CFTR activity can be quantified by measuring the transmembrane potential. The means for measuring the transmembrane potential in a biological system can employ a number of methods including electrophysiological and optical fluorescence-based membrane potential assays.

The optical membrane potential assay utilises a negatively charged potentiometric dye, such as the FLIPR membrane potential dye (FMP) (see Baxter DF, Kirk M, Garcia AF, Raimondi A, Holmqvist MH, Flint KK, Bojanic D, Distefano PS, Curtis R, Xie Y. 'A novel membrane potential-sensitive fluorescent dye improves cell-based assays for ion channels.' J Biomol Screen. 2002 Feb;7(1):79-85) which when extracellular is bound to a quenching agent. Upon cellular depolarisation the negatively charged dye redistributes to the intracellular compartment, unbinding from the membrane impermeant quench agent, yielding an increase in fluorescence. This change in fluorescence is proportional to the change in transmembrane potential which can result from the activity of CFTR. The changes in fluorescence can be monitored in real time by an appropriately equipped fluorescence detector such as the FLIPR (fluorometric imaging plate reader) in 96 or 384-well microtitre plates.

Cell culture:

Chinese hamster ovary (CHO) cells stably expressing the F508-CFTR channel were used for membrane potential experiments. Cells were maintained at 37 °C in 5% v/v CO₂ at 100% humidity in Modified Eagles medium (MEM) supplemented with 8% v/v foetal calf serum, 100µg/ml methotrexate and 100U/ml penicillin/streptomycin. Cells were grown in 225 cm² tissue culture flasks. For membrane potential assays cells were seeded into 96 well plates at 40,000 cells per well, allowed to adhere and then maintained at 26 °C for 48h to facilitate channel insertion.

Potentiator assay:

The membrane potential screening assay utilised a low chloride ion containing extracellular solution (~5mM) combined with a double addition protocol. The first addition
 5 was of buffer with or without test compound followed 5 minutes later by an addition of forskolin (1-20 μ M) - this protocol favours maximum chloride efflux in response to F508-CFTR activation. The F508-CFTR mediated chloride ion efflux leads to a membrane depolarisation which is optically monitored by the FMP dye.

10 Solutions:

Low chloride extracellular (mM): 120 Na-gluconate, 1.2 CaCl_2 , 3.3 KH_2PO_4 , 0.8 K_2HPO_4 , 1.2 MgCl_2 , 10.0 D-glucose, 20.0 HEPES, pH 7.4 with NaOH

FMP dye: made up as per manufacturers' instructions in low chloride extracellular solution detailed above, at 10x final concentration, and stored as 1 mL aliquots at -20°C.

15

IonWorks Quattro assay:

CFTR activity can also be quantified electrophysiologically using the whole-cell configuration of the patch clamp technique (Hamill et al Pflugers Archive 1981). This assay directly measures the currents associated with chloride flow through CFTR
 20 channels whilst either maintaining or adjusting the transmembrane voltage. This assay can use either single glass micropipettes or parallel planar arrays to measure CFTR activity from native or recombinant cell systems. Currents measured using parallel planar arrays can be quantified using an appropriately equipped instrument such as the IonWorks Quattro (Molecular Devices) or the Qpatch (Sophion). The Quattro system can
 25 measure CFTR currents from either a single cell per recording well (HT configuration) or alternatively from a population of 64 cells per well (Population Patch Clamp PPC) (Finkel A, Wittel A, Yang N, Handran S, Hughes J, Costantin J. 'Population patch clamp improves data consistency and success rates in the measurement of ionic currents.' J Biomol Screen. 2006 Aug;11(5):488-96).

30

Cell culture:

Chinese hamster ovary (CHO) cells stably expressing the F508-CFTR channel were used for IonWorks Quattro experiments. Cells were maintained at 37 °C in 5% v/v CO_2

at 100% humidity in D-MEM supplemented with 10 % (v/v) FCS, 100 U/mL Penicillin/Streptomycin, 1 % (v/v) NEAA, 1 mg/ml Zeocin and 500 ug/ml Hygromycin B. For experiments cells were grown in 225 cm² tissue culture flasks until near confluence and then cultured at 26 °C for 48-72h to facilitate channel insertion. Cells were removed
 5 from the flask and resuspended in either extracellular recording solution for immediate experimentation or alternatively in growth medium supplemented with 10% v/v DMSO and frozen to -80°C as 1-2 mL aliquots for use at a later date.

Potentiator assay:

10 Cells, at a density of 1.5-3 million per mL, were placed on the Quattro system, added to the planar patch array and seals allowed to establish for 5-10 mins. After assessing seal resistances (commonly >50 M Ω), whole-cell access was obtained by perforation with 100 μ g/mL amphotericin B. Baseline currents were measured by a pre-compound scan obtained by application of a voltage ramp from -100 to +100 mV. This was followed by
 15 addition of either buffer or test compound diluted in the extracellular solution supplemented with 20 μ M forskolin, to each of the 384 wells of the planar patch array. After incubation step (5-20 minutes) the post-compound currents were measured again by application of a voltage ramp from -100 to +100 mV. The difference in currents between the pre- and post-compound scans defined the efficacy of CFTR potentiation.

20

Solutions:

Extracellular solution (ECS) : 145 mM NaCl, 4 mM CsCl, 5 mM D-glucose, 10 mM TES, 1 mM CaCl₂, 1 mM MgCl₂, pH 7.4 NaOH

25 Intracellular buffer (ICS): 113 mM L-Aspartic acid, 113 mM CsOH, 27 mM CsCl, 1 mM NaCl, 1 mM MgCl₂, 1 mM EGTA, 10 mM TES. pH 7.2 with CsOH. Filter sterilized before use.

Ion transport assay:

Another method to measure CFTR function is Ussings chamber short circuit current
 30 measurement. Engineered or native epithelial cells are grown to confluent monolayer on a semi-permeable filter and sandwiched between two perspex blocks. The flow of chloride ions via CFTR from one side of the epithelia to the other can be quantified by measuring the flow of current whilst maintaining the transepithelial potential at 0mV. This

is achieved using KCl filled agar-based electrodes to both clamp the cellular monolayer and measure the flow of currents.

Cell culture:

- 5 FRT cells stably expressing $\Delta F508$ -CFTR were cultured on plastic in Coon's modified F-12 medium supplemented with 32mM NaHCO_3 , 10% v/v fetal bovine serum, 2 mM L-glutamine, 100 U/mL penicillin, 100 $\mu\text{g/mL}$ streptomycin and 30 $\mu\text{g/mL}$ hygromycin B as the growth medium. For Ussing chamber experiments, the cells were grown as polarized epithelia on Snapwell permeable support inserts (500000 cells/insert in growth medium) and cultured for 7 to 9 days. The inserts were fed with fresh Coon's modified F-12 growth medium every 48 hours, and 24 hours prior to Ussing chamber experiment. To increase the $\Delta F508$ CFTR protein expression at the cell surface, plates were incubated at 27°C for 48h before performing an Ussing chamber experiment.

15 Potentiator assay:

- Fischer Rat Thyroid (FRT) epithelial cells, stably expressing human $\Delta F508$ -CFTR were used as monolayer cultures on permeable supports. Cl^- current was measured using the short circuit current technique, under an imposed basolateral to apical Cl^- gradient in Ussing chambers. To measure stable Cl^- currents, FRT cells were cultured for 48h at 20 27°C to facilitate the insertion of $\Delta F508$ CFTR into the plasma membrane. Ussing chamber studies were likewise conducted at 27°C. Under these conditions, the effects of cumulative additions of test compounds on $\Delta F508$ CFTR currents could be quantitated with both potency and efficacy endpoints. Compounds were added to both the apical and basolateral sides subsequent to addition of 10 μM forskolin. Efficacy of 25 compounds was compared to a known potentiator such as gensitein.

Solutions:

- Basolateral Ringer solution (mM): 126 NaCl, 24 NaHCO_3 , 0.38 KH_2PO_4 , 2.13 K_2HPO_4 , 1 MgSO_4 , 1 CaCl_2 and 10 glucose.
- 30 Apical Ringer solution (mM): 140 Na-gluconate, 1 MgSO_4 , 2 CaCl_2 , 1 HCl, 10 glucose and 24 NaHCO_3 .

Compounds can also be tested for their ability to stimulate insertion of $\Delta F508$ CFTR into the cell membrane using the above assays. For these assays the protocols were

identical other than cells were not cultured at low temperature (26 or 27°C) but instead incubated with test compounds for 12-24 h prior to assay.

- Compounds of the Examples, herein below, generally have EC₅₀ values in the data measurements described above below 10 µM. Table 1 provides a list of representative compounds with their EC₅₀ value.

Table 1.

Example No	EC ₅₀ µM
1.0	0.0035

- The invention is illustrated by the following Examples.

Examples

General Conditions:

- Mass spectra were run on LCMS systems using electrospray ionization. These were either Agilent 1100 HPLC/Micromass Platform Mass Spectrometer combinations or Waters Acquity UPLC with SQD Mass Spectrometer. [M+H]⁺ refers to mono-isotopic molecular weights.

- NMR spectra were run on open access Bruker AVANCE 400 NMR spectrometers using ICON-NMR. Spectra were measured at 298K and were referenced using the solvent peak.

- The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations used are those conventional in the art. If not defined, the terms have their generally accepted meanings.

Abbreviations:

- app apparent
br broad

	d	doublet
	dd	doublet of doublets
	DCM	dichloromethane
	DIPEA	diisopropylethylamine
5	DMF	N,N-dimethylformamide
	DMSO	dimethylsulfoxide
	EtOAc	ethyl acetate
	h	hour(s)
	HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium
10		hexafluorophosphate
	HPLC	high pressure liquid chromatography
	Int.	intermediate
	LC-MS	liquid chromatography and mass spectrometry
	MeOH	methanol
15	MS	mass spectrometry
	m	multiplet
	min	minutes
	ml	milliliter(s)
	m/z	mass to charge ratio
20	NMR	nuclear magnetic resonance
	ppm	parts per million
	PS	polymer supported
	RT	room temperature
	Rt	retention time
25	s	singlet
	SCX-2	strong cation exchange (e.g. Isolute® SCX-2 columns from Biotage)
	t	triplet
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran

30

Referring to the examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

The various starting materials, intermediates, and compounds of the preferred embodiments may be isolated and purified, where appropriate, using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Unless otherwise stated, all starting materials are obtained from commercial suppliers and used without further purification. Salts may be prepared from compounds by known salt-forming procedures.

It should be understood that the organic compounds according to the preferred embodiments may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the preferred embodiments encompasses any tautomeric form of the drawn structure.

If not indicated otherwise, the analytical LC-MS conditions are as follows:

15

Method 2minLowpH:

Column: Waters Acquity CSH 1.7 μ m, 2.1 x 50mm
Temperature: 50 °C
Mobile Phase: A: Water +0.1% Formic Acid B: Acetonitrile +0.1% Formic Acid
Flow rate: 1.0mL/min
Gradient: 0.0min 5%B, 0.2-1.3min 5-98%B, 1.3-1.55min 98%B, 1.55-1.6min 98-5%B

20

25 **Method 10minLowpH:**

Column: Waters Acquity CSH 1.7 μ m, 2.1 x 100mm
Temperature: 50 °C
Mobile Phase: A: Water +0.1% Formic Acid B: Acetonitrile +0.1% Formic Acid
Flow rate: 0.7mL/min
Gradient: 0.0min 2%B, 0.5-8.0min 2-98%B, 8.0-9.0min 98%B, 9.0-9.1min 98-2%B

30

Method 10minLC_v002

	Column	Waters BEH C18 50x2.1 mm, 1.7 μ m
	Column Temperature	50 °C
	Eluents	A: H ₂ O, B: methanol, both containing 0.1% TFA
5	Flow Rate	0.8 mL/min
	Gradient	0.20 min 5% B; 5% to 95% B in 7.80 min, 1.00 min 95% B

Method 10minLC_v003

	Column	Waters BEH C18 50x2.1 mm, 1.7 μ m
10	Column Temperature	50 °C
	Eluents	A: H ₂ O, B: acetonitrile, both containing 0.1% TFA
	Flow Rate	0.8 mL/min
	Gradient	0.20 min 5% B; 5% to 95% B in 7.80 min, 1.00 min 95% B

Method 2minLC_v002

	Column	Waters BEH C18 50x2.1 mm, 1.7 μ m
	Column Temperature	50 °C
	Eluents	A: H ₂ O, B: methanol, both containing 0.1% TFA
	Flow Rate	0.8 mL/min
20	Gradient	0.20 min 5% B; 5% to 95% B in 1.30 min, 0.25 min 95% B

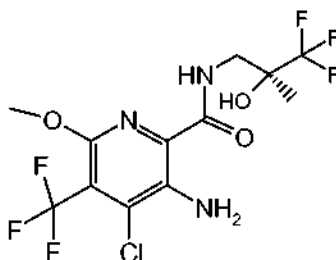
Method 2minLC_v003

	Column	Waters BEH C18 50x2.1 mm, 1.7 μ m
	Column Temperature	50 °C
25	Eluents	A: H ₂ O, B: acetonitrile, both containing 0.1% TFA
	Flow Rate	0.8 mL/min
	Gradient	0.20 min 5% B; 5% to 95% B in 1.30 min, 0.25 min 95% B

Example compounds of the present invention include:

30

Preparation of Final Compounds

Example 1.0**(S)-3-Amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide****5 Step 1: Methyl 3-amino-6-methoxy-5-(trifluoromethyl)picolinate**

3-Amino-6-methoxy-5-trifluoromethyl-pyridine-2-carboxylic acid (Intermediate B)(43 g, 182 mmol) was dissolved in MeOH (650 ml). H₂SO₄ (48.5 ml, 910 mmol) was added dropwise and the solution was heated at reflux overnight. The solvent was removed under reduced pressure and the mixture was diluted with EtOAc, washed with sat.

10 sodium bicarbonate solution and brine. The organic portion was separated, dried (MgSO₄) and concentrated under reduced pressure. Purification by chromatography on silica eluting with 0-20% EtOAc in iso-hexane afforded the title compound;

LC-MS Rt = 1.07 min [M+H]⁺ 251.2 ; Method 2minLC_v003

Step 2: Methyl 3-amino-4-chloro-6-methoxy-5-(trifluoromethyl)picolinate

15 Methyl 3-amino-6-methoxy-5-(trifluoromethyl)picolinate (step 1)(1 g, 4.00 mmol) in acetonitrile (15 ml) was treated with trichloroisocyanuric acid (0.307 g, 1.319 mmol). The resulting mixture was heated using microwave radiation at 130°C for 30 minutes and then partitioned between EtOAc and water. The organic portion was separated and washed with sat.NaHCO₃, brine and dried using a phase separating column. The

20 solvent was removed under reduced pressure and purification of the crude product by chromatography on silica eluting with 0-30% EtOAc in iso-hexane afforded the title compound;

LC-MS Rt = 1.10 mins; [M+H]⁺ 285.3, Method 2minLC_v003.

Step 3: 3-Amino-4-chloro-6-methoxy-5-(trifluoromethyl)picolinic acid

25 To a solution of methyl 3-amino-4-chloro-6-methoxy-5-(trifluoromethyl)picolinate (step 2) (819 mg, 2.88 mmol) in MeOH (20 ml) was added 2M NaOH (8.63 ml, 17.27 mmol) and the mixture was stirred for at RT for 2 hours. The solvent was removed under reduced pressure and the crude was diluted with water. The pH of the mixture was adjusted using

to pH 1 using 2M HCl. The resulting suspension was collected by filtration to afford the title compound;

LC-MS Rt = 1.01 mins; [M+H]⁺ 285.3, Method 2minLC_v003.

Step 4: (S)-3-Amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide

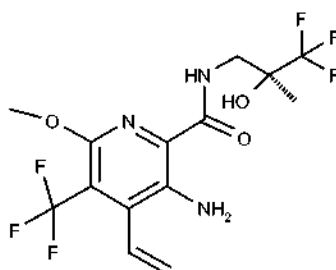
A mixture comprising 3-amino-4-chloro-6-methoxy-5-(trifluoromethyl)picolinic acid (step 3) (1.002 g, 3.70 mmol) and (S)-3-amino-1,1,1-trifluoro-2-methylpropan-2-ol (Intermediate C, free base) (0.530 g, 3.70 mmol) in NMP (15 ml) was treated with HATU (1.690 g, 4.44 mmol) followed by DIPEA (1.617 ml, 9.26 mmol) added dropwise over 5 mins. The mixture was stirred for 2 h at RT and poured into water. The product was extracted with EtOAc and the combined organic extracts were washed with sat NaHCO₃, water, brine dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by chromatography on silica eluting in a 0-50% iso-hexane:EtOAc to afford the title compound;

LC-MS Rt = 1.13 mins; [M+H]⁺ 396.3, Method 2minLowpH

¹H NMR (400 MHz, DMSO-d₆) δ 8.45 (1H, t), 6.93 (2H, s), 6.30 (1H, s), 3.95 (3H, s), 3.66 (1H, mult), 3.49 (1H, mult), 1.27 (3H, s).

Example 2.0

(S)-3-Amino-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)-4-vinylpicolinamide



To a solution of (S)-3-amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide (Ex. 1.0) (500 mg, 1.264 mmol) in 1,4-dioxane (4 ml) was added potassium phosphate (536 mg, 2.53 mmol) followed by [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (41.2 mg, 0.063 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.214 ml, 1.264 mmol) and water (1.0 ml). The mixture was heated using microwave radiation at 100°C for 10 minutes and then

filtered through Celite® (filter material). The filtrate was diluted further with EtOAc and washed with sat. NaHCO₃, water, brine and dried over MgSO₄. Isolute Si-TMT (2,4,6-trimercaptotriazine silica, palladium scavenger) was added and after stirring for 30 mins, the mixture was filtered. The solvent was removed under reduced pressure and

5 purification of the crude product by chromatography on silica eluting with 0-40% EtOAc in iso-hexane afforded the title compound;

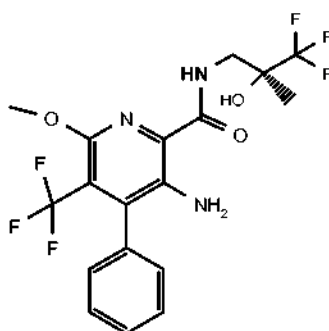
LC-MS Rt = 5.24 min [M+H]⁺ 388.4; Method 10minLowpH.

¹H NMR (400 MHz, DMSO-d₆) δ 8.40 (1H, t), 6.66 (1H, m), 6.46 (2H, s), 6.30 (1H, s), 5.72 (1H, m), 5.41 (1H, m), 3.92 (3H, s), 3.66 (1H, mult), 3.48 (1H, mult), 1.27 (3H, s)

10

Example 2.1

3-Amino-6-methoxy-4-phenyl-5-trifluoromethyl-pyridine-2-carboxylic acid ((S)-3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide



15 The title compound was prepared analogously to Example 2.0 by replacing 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane;

LC-MS Rt = 1.20mins; [M+H]⁺ 438.4, Method 2minLowpH

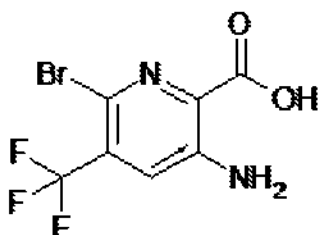
¹H NMR (400 MHz, DMSO-d₆) δ 8.46 (1H, t), 7.52 (3H, m), 7.23 (2H, m), 6.31 (1H, s), 5.84 (2H, s), 3.95 (3H, s), 3.66 (1H, m), 3.52 (1H, m), 1.28 (3H, s).

20

Preparation of Intermediates

Intermediate A

25 3-Amino-6-bromo-5-trifluoromethyl-pyridine-2-carboxylic acid



Step 1: 2-Bromo-3-nitro-5-trifluoromethyl-pyridine

3-Nitro-5-(trifluoromethyl)pyridin-2-ol (31.00 g, 149 mmol) was dissolved in acetonitrile (250 ml) to give a dark brown solution. Phosphorus(V) oxybromide (85 g, 298 mmol) was added and the mixture was heated at reflux for 4 hours and then stirred at RT overnight. The reaction mixture was quenched by pouring into vigorously stirring water (600 ml) containing sodium hydrogencarbonate (110 g). The dark brown mixture was extracted with DCM (3 x 200 ml) and the organic phase was washed with water (200 ml) and brine (100ml), dried (MgSO₄) and concentrated under reduced pressure to afford the title product as a brown oil.

¹H-NMR: [400MHz, CDCl₃, δ 8.87 (1H, d, J = 1.4Hz, ArH), 8.39 (1H, d, J = 1.9Hz, ArH).

Step 2: 3-Nitro-5-trifluoromethyl-pyridine-2-carbonitrile

2-Bromo-3-nitro-5-trifluoromethyl-pyridine (10.00 g, 36.87 mmol) was dissolved in toluene (250 ml) with stirring to give a pale yellow solution. Tetrabutylammonium bromide (11.90 g, 36.9 mmol) was added followed by copper(I) cyanide (9.92 g, 111 mmol) and the mixture was heated at reflux for 9 h. After cooling to RT, the reaction mixture was partitioned between water (750 ml) and EtOAc (750 ml). The organic fractions were combined, washed with water (2 x 250 ml), brine (100 ml), dried (MgSO₄) and concentrated under reduced pressure to afford the title product.

¹H-NMR: [400MHz, DMSO-d₆] δ 9.55 (1H, m, ArH), 9.24 (1H, m, ArH)

Step 3: 3-Amino-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester

3-Nitro-5-trifluoromethyl-pyridine-2-carbonitrile (6.5 g, 29.9 mmol) was dissolved in EtOAc (150 ml) to give a pale yellow solution. 10 % Palladium on activated carbon (3.19 g, 2.99 mmol) was added and the reaction mixture stirred under an atmosphere of hydrogen for 18 hours. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was dissolved in HCl conc. (45 ml) and heated to reflux for 24 hours. The reaction mixture was allowed to cool to RT and concentrated under reduced pressure. The solid was dissolved in MeOH (200 ml) and sulfuric acid (8 ml) was added. The resulting solution was heated at reflux for 84 hours. The reaction

was allowed to cool to RT, then neutralised by addition of 10% $\text{NaHCO}_3(\text{aq})$ (600 ml). The product was extracted into DCM (3 x 200 ml) and the combined organic phases were washed with water (200 ml), brine (50 ml), dried (MgSO_4) and concentrated under reduced pressure. The resulting solid was purified by chromatography on silica : Eluant gradient: iso-hexane (500ml), 10% EtOAc in isohexane (1000 ml), 20% EtOAc in iso-hexane (1500 ml) to afford the titled compound as a pale yellow solid

$^1\text{H-NMR}$: [400MHz, DMSO-d_6] δ 8.13 (1H, d, $J = 1.7\text{Hz}$, ArH), 7.60 (1H, d, $J = 1.3\text{Hz}$, ArH), 7.01 (2H, br, NH_2), 3.85 (3H, s, ArOCH_3), m/z 221.1 $[\text{M}+\text{H}]^+$

Step 4 3-Amino-6-bromo-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester

3-Amino-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester (9.49 g, 43.16 mmol) was dissolved in water (300 ml). Sulfuric acid (4.60 ml, 86 mmol) was added followed by dropwise addition over 30 minutes of a solution of bromine (2.222 ml, 43.1 mmol) in acetic acid (29.6 ml, 517 mmol). The reaction mixture was stirred at RT for 18 hours. A further 100 ml of water was added, followed by a further 0.25 equivalents of the bromine/AcOH mixture (550 μl bromine in 7.4 ml AcOH) and the reaction mixture stirred at RT for an additional 90 minutes. The reaction mixture was diluted with water (500 ml) and neutralised by addition of solid NaHCO_3 (~85 g). The suspension was extracted with DCM (3 x 300 ml) and the combined organic phases washed with sat. $\text{NaHCO}_3(\text{aq})$ (250 ml), water (250 ml) and brine (100 ml), dried (MgSO_4) and concentrated under reduced pressure. The crude material was recrystallised from boiling MeOH (~300 ml) to give the title product as a pale orange solid:

LC-MS m/z 301.0 $[\text{M}+\text{H}]^+$

$^1\text{H-NMR}$ (400MHz, DMSO-d_6) δ 7.77 (1H, s, ArH), 7.17 (2H, s, NH_2), 3.86 (3H, s, ArCO_2CH_3).

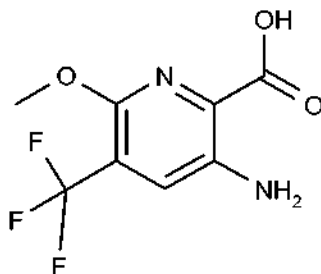
Step 5: 3-Amino-6-bromo-5-trifluoromethyl-pyridine-2-carboxylic acid

3-Amino-6-bromo-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester (1.40 g, 4.68 mmol) was suspended in MeOH (15 ml); Sodium hydroxide (2.0 M aqueous solution) (14.04 ml, 28.1 mmol) was added and the suspension was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in water (100 ml) and then acidified by the addition of 5.0M $\text{HCl}(\text{aq})$. The product was extracted into ethyl acetate (2 x 75 ml) and the combined organic extracts were washed with water (50 ml), brine (25 ml), dried (MgSO_4) and concentrated under reduced pressure to afford the title product as a yellow solid.

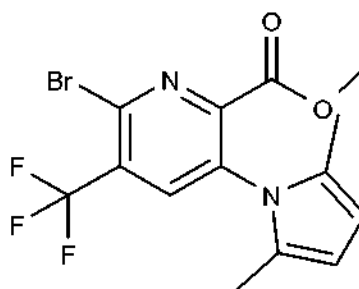
$^1\text{H-NMR}$: 9400MHz, DMSO- d_6) δ 13.24 (1H, br s, CO_2H), 7.74 (1H, s, ArH), 7.17 92H, br s ArNH_2). m/z 285.1, 287.1 $[\text{M}+\text{H}]^+$

Intermediate B

5 3-Amino-6-methoxy-5-trifluoromethyl-pyridine-2-carboxylic acid



Step 1: 6-Bromo-3-(2,5-dimethyl-pyrrol-1-yl)-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester



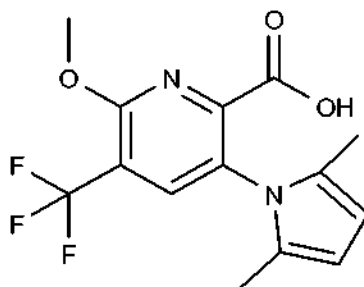
- 10 3-Amino-6-bromo-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester(Intermediate A step 4) (2 g, 6.69 mmol) was suspended in toluene (8 ml), then p-toluenesulfonic acid (TsOH) (0.115 g, 0.669 mmol) and acetonylacetone (0.941 ml, 8.03 mmol) was added. The reaction mixture was heated at reflux for 2 h and allowed to cool to RT overnight. The resulting dark red/ black solution was concentrated under reduced pressure to
- 15 remove toluene and the crude residue was diluted with EtOAc (200 ml), washed with NaHCO_3 (50 ml), dried (MgSO_4) and concentrated under reduced pressure to give a brown solid;

LC-MS R_t = 5.58 min $[\text{M}+\text{H}]^+$ 377/379 (Method 10minLC_v002).

$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 8.50 (1H, s), 7.77 (2H, s), 5.83 (3H, s), 1.90 (6H, s);

- 20 $^{19}\text{F NMR}$ (400 MHz, DMSO- d_6) δ -62.26 (CF_3 , s)

Step 2: 3-(2,5-Dimethyl-pyrrol-1-yl)-6-methoxy-5-trifluoromethyl-pyridine-2-carboxylic acid



6-Bromo-3-(2,5-dimethyl-pyrrol-1-yl)-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester (2 g, 5.30 mmol) was dissolved in MeOH (40 ml) and treated with 2M NaOH (20 ml) to give a suspension which was stirred at RT for 1h to afford a clear solution. The solvent was removed under reduced pressure and the residue was acidified to pH1 with 5M HCl. The mixture was extracted with EtOAc (200 ml) and the organic extract was dried (MgSO₄) and concentrated under reduced pressure to afford the title compound as a dark brown solid which was used in the next step without further purification;

LC-MS Rt=1.50 min [M+H]⁺ 315.2.1/316.2; Method 2minLC_v002

¹H NMR (400 MHz, DMSO-d₆) δ 14.42-12.61 (COOH, b hump), 8.25 (1H, s), 5.84 (2H, s), 4.13 (3H, s), 1.97 (6H, s);

¹⁹F NMR (400 MHz, DMSO-d₆) δ -62.43 (CF₃, s).

Step 3: 3-Amino-6-methoxy-5-trifluoromethyl-pyridine-2-carboxylic acid

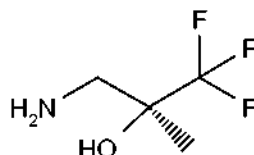
3-(2,5-Dimethyl-pyrrol-1-yl)-6-methoxy-5-trifluoromethyl-pyridine-2-carboxylic acid (833 mg, 2.65 mmol) was dissolved in EtOH (45 ml) and water (23 ml). To this mixture was added TEA (1.102 ml, 7.95 mmol) followed by hydroxylamine hydrochloride (1842 mg, 26.5 mmol). The resulting mixture was heated at reflux overnight. After cooling to RT, the mixture was stirred with 20g Isolute® PE-AX (silica-based sorbent with a chemically bonded quaternary amine functional group used for isolation of acidic compounds) for 30 mins, washed with MeOH (100 ml), 1M HCl: MeCN 2:8 (200 ml). The organic portion was removed and the mixture was filtered. The filtrate was acidified with 2M HCl (50 ml) and the EtOH was removed under reduced pressure. The aqueous portion was extracted with DCM (200 ml) and the organic extract was dried (MgSO₄) and concentrated under reduced pressure to give a brown oil. Purification by chromatography on silica eluting with DCM: MeOH afforded the title product as a yellow solid;

LC-MS Rt = 2.90 min [M+H]⁺ 237 ; Method 10minLC_v002

¹H NMR (400 MHz, DMSO-d₆) δ 9.62-7.79 (NH₂, b hump), 7.70 (1H, s), 3.89 (3H, s);
¹⁹F NMR (400 MHz, DMSO-d₆) δ -62.92 (CF₃, s).

Intermediate C

5 (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol hydrochloride



Route 1:

Step 1: Benzyl 3,3,3-trifluoro-2-hydroxy-2-methylpropylcarbamate

To a stirring suspension of amino-1,1,1-trifluoro-2-methylpropan-2-ol hydrochloride
 10 (Intermediate E) (1.5 g, 8.35 mmol) in DCM (50 ml) was added TEA 93.54 g, 35.0 mmol)
 followed by benzyl 2,5-dioxopyrrolidin-1-yl carbonate (1.983 g, 7.96 mmol). The mixture
 was stirred at RT for 6 hours and then diluted with water. The organic portion was
 separated using a phase separator and concentrated under reduced pressure.
 Purification by chromatography on silica eluting with 0-70% EtOAc in iso-hexane
 15 afforded the title product;

LC-MS: Rt 1.05 min; MS m/z 278.1 [M+H]⁺; Method 2minLC_v003.

¹H NMR (400 MHz, DMSO-d₆) δ 7.34 (6H, m), 5.98 (1H, s), 5.05 (2H, s), 3.31 (1H, m),
 3.18 (1H, m), 1.21 (3H, s)

20 Step 2: Separation of Enantiomers of benzyl 3,3,3-trifluoro-2-hydroxy-2-methyl propylcarbamate

Benzyl 3,3,3-trifluoro-2-hydroxy-2-methylpropylcarbamate (1.7 g) was dissolved in 2-
 propanol (10 ml) and purified using the following chromatographic conditions:

Mobile Phase: 10% 2-propanol / 90% CO₂

25 Column: 2 x Chiralcel OJ-H, 250 x 10 mm id, 5 μm (columns coupled in series)

Detection: UV @ 220nm

Flow rate: 10 ml/min

Sample concentration: 1.7 g in 10 ml 2-propanol

Injection volume: 75 μl

30 First eluted peak: Rt = 6.94 minutes (R)-benzyl 3,3,3-trifluoro-2-hydroxy-2-methyl

propylcarbamate

Second eluted peak: Rt = 8.04 minutes (S)-benzyl 3,3,3-trifluoro-2-hydroxy-2-methyl propylcarbamate

Step 3: (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol hydrochloride

- 5 A mixture comprising (S)-benzyl 3,3,3-trifluoro-2-hydroxy-2-methyl propylcarbamate in EtOH(165 ml) was pumped through a H-Cube (hydrogenation reactor, 1-2 ml/min, 1 bar pressure, RT) for 8 hours using a 10% palladium on carbon catalyst cartridge. 1.25 M HCl in methanol (130 ml) was added to the mixture was stirred for 30mins. The solvent was removed under reduced pressure azeotroping with MeCN to afford the title product
- 10 as a white powder; ¹H NMR (400 MHz, DMSO-d₆) δ 8.3 (3H, broad), 6.8 (1H, s), 3.0 (2H, s), 1.5 (3H, s).

- Alternatively, racemic 3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol can be resolved into separate enantiomers by recrystallisation with either (S)-Mandelic acid or L-tartaric acid
- 15 in isopropanol or ethanol to afford (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol:

Route 2:

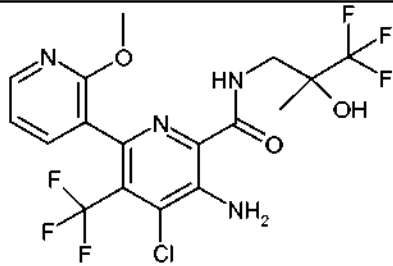
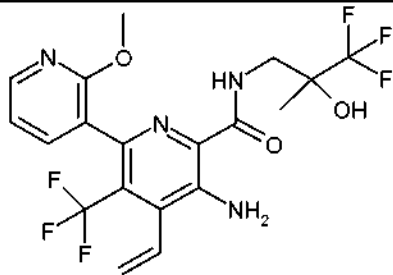
Step 1: (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol L-tartrate salt

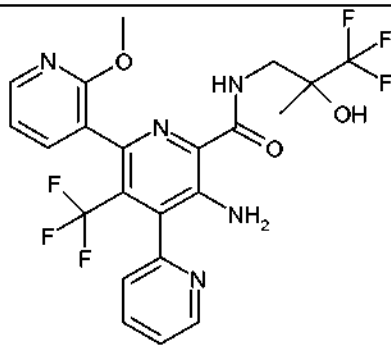
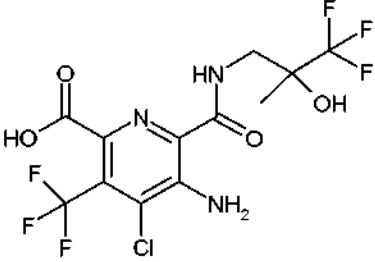
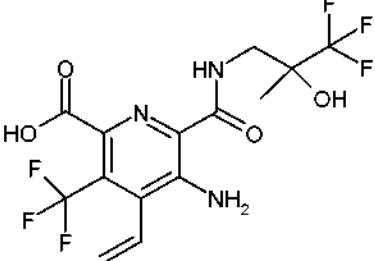
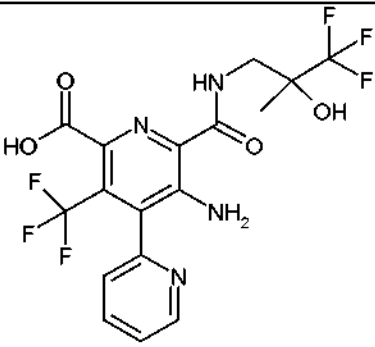
- 3-Amino-1,1,1-trifluoro-2-methyl-propan-2-ol (40 g, 280 mmol) and L-(+)-tartaric acid
- 20 (42.0 g, 280 mmol) were dissolved in EtOH + 4 % H₂O (1398 ml) and warmed to 65 °C in an oil bath at 80 °C over 30 minutes. The resultant solution was left to cool and crystallise overnight at room temperature. The white precipitate was collected by filtration and dried in a vacuum oven at 40 °C for 2 hours to afford the title compound (22.5 g, 27.5 %, enantiomeric excess (e.e) = 76.6 %). A second crystallization was carried out
- 25 as follows to enrich the e.e. (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol L-tartrate salt (22.5 g, 76.7 mmol) was dissolved in EtOH + 4 % H₂O (384 ml, 0.2 M) at 80 °C and left to crystallise overnight. The white precipitate was collected by filtration and allowed to dry at RT overnight (18.4 g, e.e. = 94.4 %). A third crystallisation was carried out; (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol L-tartrate salt (18.4 g, 62.8 mmol) was
- 30 heated in EtOH + 4 % H₂O (314 ml, 0.2 M) at 80 °C for 2 h and allowed to cool and crystallize overnight. The white precipitate was collected by filtration and dried in a vacuum oven at 50 °C for 5 hours to afford the title compound; e.e. = 97.4 %.

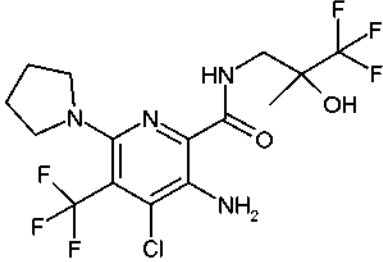
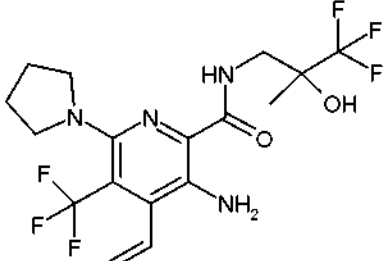
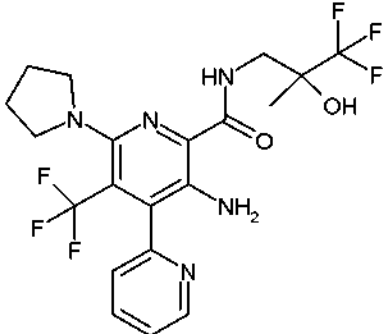
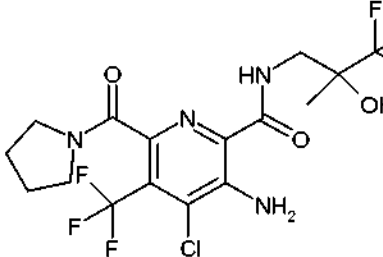
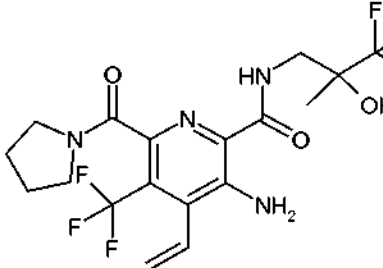
Step 2: (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol

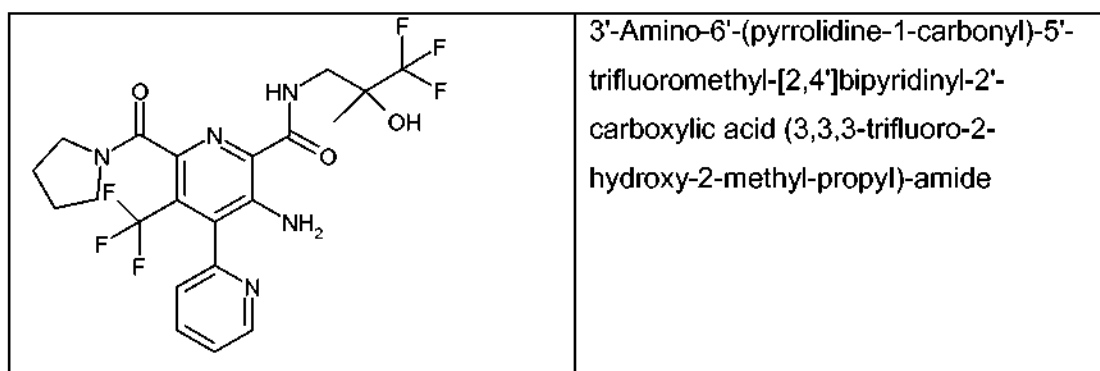
To a suspension of Isolute® SCX-2 (Si-propylsulfonic acid) (537 g, 222 mmol) in DCM (1.5 L) was added (S)-3-amino-1,1,1-trifluoro-2-methylpropan-2-ol L-tartrate salt (step 1)(65 g, 222 mmol) pre-dissolved in warm MeOH (500 ml). The silica suspension was stirred at RT for 30 min and the slurry was poured onto a large silica frit. The frit was washed with 10 % MeOH in DCM (3.5 litres) and the washings were discarded. The plug was eluted with 7M NH₃/MeOH (300 ml) in DCM (2 litres) followed by 2M NH₃/MeOH (300 ml) in DCM (1 litre). The combined washings were concentrated under reduced pressure to afford the title compound.

- 10 The following compounds may be prepared by the processes described in the general schemes above, or by processes analogous to those of Examples 1.0, 2.0 and 3.0, or by processes analogous to those described in international patent application W02011/113894 (PCT/EP2011/054038). .

Structure	Name
	5-Amino-4-chloro-2'-methoxy-3-trifluoromethyl-[2,3']bipyridinyl-6-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide
	5-Amino-4-vinyl-2'-methoxy-3-trifluoromethyl-[2,3']bipyridinyl-6-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide

	<p>5'-Amino-2''-methoxy-3'-trifluoromethyl-[2,4':2',3'']terpyridine-6'-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide</p>
	<p>5-Amino-4-chloro-6-(3,3,3-trifluoro-2-hydroxy-2-methyl-propylcarbamoyl)-3-trifluoromethyl-pyridine-2-carboxylic acid</p>
	<p>5-Amino-4-vinyl-6-(3,3,3-trifluoro-2-hydroxy-2-methyl-propylcarbamoyl)-3-trifluoromethyl-pyridine-2-carboxylic acid</p>
	<p>5'-Amino-6'-(3,3,3-trifluoro-2-hydroxy-2-methyl-propylcarbamoyl)-3'-trifluoromethyl-[2,4']bipyridinyl-2'-carboxylic acid</p>

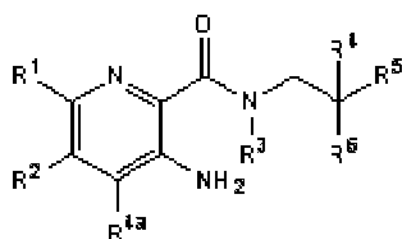
	<p>3-Amino-4-chloro-6-pyrrolidin-1-yl-5-trifluoromethyl-pyridine-2-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide</p>
	<p>3-Amino-4-vinyl-6-pyrrolidin-1-yl-5-trifluoromethyl-pyridine-2-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide</p>
	<p>3'-Amino-6'-pyrrolidin-1-yl-5'-trifluoromethyl-[2,4']bipyridinyl-2'-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide</p>
	<p>3-Amino-4-chloro-6-(pyrrolidine-1-carbonyl)-5-trifluoromethyl-pyridine-2-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide</p>
	<p>3-Amino-4-vinyl-6-(pyrrolidine-1-carbonyl)-5-trifluoromethyl-pyridine-2-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide</p>



From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly,
 5 the invention is not limited except as by the appended claims.

Embodiments:

Embodiment 1. A compound of Formula I



10

I

wherein:

- R^1 is H; C_1 - C_8 alkyl optionally substituted by one or more halogen atoms; C_2 - C_8 alkenyl; C_2 - C_8 alkynyl; C_3 - C_{10} cycloalkyl; C_5 - C_{10} cycloalkenyl; $-C_1$ - C_4 alkyl- C_3 - C_8 cycloalkyl; C_1 - C_8 alkoxy optionally substituted by one or more halogen atoms; halogen; $SO_2NR^8R^9$;
 15 SO_2R^{10} ; S- C_1 - C_8 alkyl optionally substituted by one or more halogen atoms; S- C_6 - C_{14} aryl; $-(C_0$ - C_4 alkyl)- C_6 - C_{14} aryl; $-(C_0$ - C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; CN; $NR^{11}R^{12}$; $CONR^{13}R^{14}$; $NR^{13}SO_2R^{15}$; $NR^{13}C(O)R^{15}$ and CO_2R^{15} , wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more
 20 Z substituents;

R^2 is C_1 - C_4 haloalkyl;

R^3 and R^4 are each independently H or C_1 - C_8 alkyl optionally substituted by one or more
5 halogen atoms;

R^{4a} is selected from halogen; C_2 - C_8 alkenyl; $-(C_0$ - C_4 alkyl)- C_6 - C_{14} aryl; $-(C_0$ - C_4 alkyl)-3 to
14 membered heterocyclyl; and C_1 - C_8 hydroxyalkyl; wherein the $-(C_0$ - C_4 alkyl)- C_6 - C_{14}
10 aryl and $-(C_0$ - C_4 alkyl)-3 to 14 membered heterocyclyl groups are each optionally
substituted by one or more Z substituents;

R^5 and R^6 are each independently H; C_1 - C_8 alkyl optionally substituted by one or more
halogen atoms; C_2 - C_8 alkenyl; C_2 - C_8 alkynyl; C_3 - C_{10} cycloalkyl; C_5 - C_{10} cycloalkenyl; $-(C_1$ -
 C_4 alkyl)- C_3 - C_8 cycloalkyl; C_1 - C_8 alkoxy optionally substituted by one or more halogen
15 atoms; OH; CN; halogen; $-(C_0$ - C_4 alkyl)- C_6 - C_{14} aryl; $-(C_0$ - C_4 alkyl)-3 to 14 membered
heterocyclic group, wherein the heterocyclic group contains at least one heteroatom
selected from N, O and S; or $-(C_0$ - C_4 alkyl)- CO_2R^{15} , wherein the cycloalkyl, cycloalkenyl,
 $-(C_0$ - C_4 alkyl)- C_6 - C_{14} aryl and $-(C_0$ - C_4 alkyl)-3 to 14 membered heterocyclic group groups
are each optionally substituted by one or more Z substituents; or

20

R^5 and R^6 are each independently a group of the formula:

$-(CH_2)_m-NR^{17}R^{18}$; or

R^5 and R^6 are each independently a group of the formula:

25 $-(CH_2)_m-OR^4$; or

R^4 and R^5 together with the carbon atoms to which they are bound form a 3 to 8
membered carbocyclic ring system; or

30 R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 8
membered carbocyclic ring system or a 5 to 8 membered heterocyclic ring system
containing one or more heteroatoms selected from N, O and S, wherein the ring system
is optionally substituted by one or more Z substituents;

R⁴, R⁵ and R⁶ cannot all be the same;

m is 0, 1, 2 or 3;

5

R⁶, R¹¹, R¹³ and R¹⁷ are each independently H, C₁-C₈ alkyl optionally substituted by one or more halogen atoms, C₃-C₁₀ cycloalkyl or -(C₁-C₄ alkyl)-C₃-C₈ cycloalkyl;

10 R⁹, R¹⁰, R¹², R¹⁴, R¹⁵, R¹⁶ and R¹⁸ are each independently H; C₁-C₈ alkyl optionally substituted by one or more halogen atoms; C₂-C₈ alkenyl; C₂-C₈ alkynyl; C₃-C₁₀ cycloalkyl; C₅-C₁₀ cycloalkenyl; -C₁-C₄ alkyl-C₃-C₈ cycloalkyl; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; or -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more
15 Z substituents; or

R⁸ and R⁹, R¹¹ and R¹², R¹³ and R¹⁴, and R¹⁷ and R¹⁸ together with the nitrogen atom to which they are attached may form a 4 to 14 membered heterocyclic group optionally substituted by one or more Z substituents;

20

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C₁-C₆ alkyl optionally substituted by one or more OH groups or NH₂ groups, C₁-C₆ alkyl optionally substituted by one or more halogen atoms, C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy, NR¹⁸(SO₂)R²¹, (SO₂)NR¹⁹R²¹, (SO₂)R²¹, NR¹⁸C(O)R²¹, C(O)NR¹⁹R²¹,
25 NR¹⁸C(O)NR¹⁹R²¹, NR¹⁸C(O)OR¹⁹, NR¹⁹R²¹, C(O)OR¹⁹, C(O)R¹⁹, SR¹⁹, OR¹⁹, oxo, CN, NO₂, halogen or a 3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S;

30 R¹⁹ and R²¹ are each independently H; C₁-C₈ alkyl; C₃-C₈ cycloalkyl; C₁-C₄ alkoxy-C₁-C₄ alkyl; (C₀-C₄ alkyl)-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; (C₀-C₄ alkyl)-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C₁-C₆ alkyl and

C(O)C₁-C₆ alkyl; (C₀-C₄ alkyl)-O-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; and (C₀-C₄ alkyl)-O-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from

5 halogen, C₁-C₆ alkyl or C(O)C₁-C₆ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C₁-C₄ alkoxy, C(O)NH₂, C(O)NHC₁-C₆ alkyl or C(O)N(C₁-C₆ alkyl)₂; or

R¹⁹ and R²¹ together with the nitrogen atom to which they attached form a 5- to 10-

10 membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(O)₂-aryl; S(O)₂-C₁-C₆ alkyl; C₁-C₆ alkyl optionally substituted by one or more

15 halogen atoms; C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy; and C(O)OC₁-C₆ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by C₁-C₆ alkyl, C₁-C₆ haloalkyl or C₁-C₆ alkoxy; or a pharmaceutically acceptable salt thereof.

20 Embodiment 2: The compound according to embodiment 1, wherein R^{4a} is selected from halogen; C₂-C₈ alkenyl; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; -(C₀-C₄ alkyl)-3 to 14 membered heterocyclyl; C₁-C₈ hydroxyalkyl; -(CH₂)_m-NR¹⁷R¹⁸; -(C₀-C₄ alkyl)-CO₂R¹⁵ and -(C₀-C₄ alkyl)-C(O)NR¹⁷R¹⁸.

25 Embodiment 3: The compound according to embodiment 1 or 2, wherein R^{4a} is selected from halogen; C₂-C₈ alkenyl, -(C₀-C₄ alkyl)-C₆-C₁₄ aryl and -(C₀-C₄ alkyl)-3 to 14 membered heterocyclyl.

Embodiment 4: The compound according to any one of embodiments 1 to 3, wherein R^{4a}

30 is selected from chlorine; ethenyl, -(C₀-C₄ alkyl)-phenyl and -(C₀-C₄ alkyl)-pyridyl.

Embodiment 5: The compound according to any one of embodiments 1 to 4, or pharmaceutically acceptable salts thereof, wherein:

- R¹ is H; C₁-C₈ alkyl optionally substituted by one or more halogen atoms; C₂-C₈ alkenyl; C₂-C₈ alkynyl; C₃-C₁₀ cycloalkyl; C₅-C₁₀ cycloalkenyl; -C₁-C₄ alkyl-C₃-C₈ cycloalkyl; C₁-C₈ alkoxy optionally substituted by one or more halogen atoms; halogen; SO₂NR⁸R⁹; SO₂R¹⁰; S-C₁-C₈alkyl optionally substituted by one or more halogen atoms; S-C₆-C₁₄ aryl;
- 5 CN; NR¹¹R¹²; C(O)NR¹³R¹⁴; NR¹³SO₂R¹⁵; NR¹³C(O)R¹⁵; CO₂R¹⁵; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; or -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents;
- 10 R² is C₁-C₄ haloalkyl;
- R³ is H or C₁-C₈ alkyl optionally substituted by one or more halogen atoms;
- R⁴ is H, or C₁-C₈ alkyl optional substituted with one or more halogen;
- R⁵ is -(CH₂)_m-NR¹⁷R¹⁸, -(CH₂)_m-OR¹; C₁-C₈ alkoxy optionally substituted by one or more halogen atoms; -(C₀-C₄ alkyl)-CO₂R¹⁵; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl or -3 to 14 membered
- 15 heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the -(C₀-C₄ alkyl)-C₆-C₁₄ aryl and -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group are each optionally substituted by one or more Z substituents;
- R⁶ is C₁-C₈ alkyl optionally substituted by one or more halogen atoms; C₃-C₁₀ cycloalkyl;
- 20 -C₁-C₄ alkyl-C₃-C₈ cycloalkyl; C₁-C₈ alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; or -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the cycloalkyl, cycloalkenyl, -(C₀-C₄ alkyl)-C₆-C₁₄ aryl and -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group are each optionally substituted
- 25 by one or more Z substituents; or
- R⁶ is H, and R⁵ is -(CH₂)_m-NR¹⁷R¹⁸, -(CH₂)_m-OR¹; C₁-C₈ alkoxy optionally substituted by one or more halogen atoms; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; or -(C₀-C₄ alkyl)-CO₂R¹⁵, wherein -(C₀-C₄ alkyl)-C₆-C₁₄ aryl
- 30 and -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group groups are each optionally substituted by one or more Z substituents; or
- R⁴ and R⁶ together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

R⁴ and R⁵ together form an oxo group (C=O) and R⁶ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms; C₁-C₄ alkoxy optionally substituted by one or more halogen atoms; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; or -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom
 5 selected from N, O and S, wherein the aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

R⁵ and R⁶ together with the carbon atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; or

10 R⁴ and R⁵ and R⁶ together with the carbon atoms to which they are bound form a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

R⁷ is H, or C₁-C₈ alkyl optional substituted with one or more halogen;

15 m is 0, 1, 2 or 3;

R⁸, R¹¹, R¹³ and R¹⁷ are each independently H, C₁-C₈ alkyl optionally substituted by one or more halogen atoms, C₃-C₁₀ cycloalkyl or -(C₁-C₄ alkyl)-C₃-C₈ cycloalkyl;

R⁹, R¹⁰, R¹², R¹⁴, R¹⁵, R¹⁶ and R¹⁸ are each independently H; C₁-C₈ alkyl optionally substituted by one or more halogen atoms; C₂-C₈ alkenyl; C₂-C₈ alkynyl; C₃-C₁₀
 20 cycloalkyl; C₅-C₁₀ cycloalkenyl; -(C₁-C₄ alkyl)-C₃-C₈ cycloalkyl; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; or -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

25 R⁸ and R⁹, R¹¹ and R¹², R¹³ and R¹⁴, and R¹⁷ and R¹⁸ together with the nitrogen atom to which they are attached may form a 4 to 14 membered heterocyclic group optionally substituted by one or more Z substituents;

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C₁-C₆ alkyl optionally substituted by one or more OH groups or NH₂ groups, C₁-C₆ alkyl optionally substituted by one or
 30 more halogen atoms, C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy, NR¹⁸(SO₂)R²¹, (SO₂)NR¹⁹R²¹, (SO₂)R²¹, NR¹⁸C(O)R²¹, C(O)NR¹⁹R²¹, NR¹⁸C(O)NR¹⁹R²¹, NR¹⁸C(O)OR¹⁹, NR¹⁹R²¹, C(O)OR¹⁹, C(O)R¹⁹, SR¹⁹, OR¹⁹, oxo, CN,

NO₂, halogen or a 3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S;

R¹⁹ and R²¹ are each independently H; C₁-C₈ alkyl; C₃-C₈ cycloalkyl; C₁-C₄ alkoxy-C₁-C₄ alkyl; (C₀-C₄ alkyl)-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; (C₀-C₄ alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C₁-C₆ alkyl and C(O)C₁-C₆ alkyl; (C₀-C₄ alkyl)-O-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; and (C₀-C₄ alkyl)- O-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C₁-C₆ alkyl or C(O)C₁-C₆ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C₁-C₄ alkoxy, C(O)NH₂, C(O)NHC₁-C₆ alkyl or C(O)N(C₁-C₆ alkyl)₂; or

R¹⁹ and R²¹ together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(O)₂-aryl; S(O)₂-C₁-C₆ alkyl; C₁-C₆ alkyl optionally substituted by one or more halogen atoms; C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy; and C(O)OC₁-C₆ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by C₁-C₆ alkyl, C₁-C₆ haloalkyl or C₁-C₆ alkoxy.

Embodiment 6: The compound according to any one of embodiments 1 to 5, wherein R¹ is H; C₁-C₄ alkyl optionally substituted by one or more halogen atoms; C₁-C₄ alkoxy optionally substituted by one or more halogen atoms; halogen; C₆-C₁₄ aryl; -(C₀-C₄ alkyl)- 3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; or -NR¹¹R¹², wherein the aryl and heterocyclic groups are each optionally substituted by one or more Z substituents.

Embodiment 7: The compound according to any one of embodiments 1 to 6, wherein R¹ is C₁-C₄ alkyl optional substituted by one or more halogen atoms.

Embodiment 8: The compound according to any one of embodiments 1 to 7, wherein R^1 is $-CH_3$ or CF_3 .

- 5 Embodiment 9: The compound according to any one of embodiments 1 to 6, wherein R^1 is C_1 - C_4 alkoxy optional substituted by one or more halogen atoms.

Embodiment 10: The compound according to any one of embodiments 1 to 6, wherein R^1 is $-OCH_3$, $-OCH_2CH_3$ or $-OCF_3$.

10

Embodiment 11: The compound according to any one of embodiments 1 to 6, wherein R^1 is aryl, wherein aryl is phenyl optionally substituted by one or more Z substituents,

- 15 Embodiment 12: The compound according to any one of embodiments 1 to 6 or 11, wherein R^1 is 4-fluorophenyl, 4-chloro-2-methylphenyl, or 2,4-dichlorophenyl.

Embodiment 13: The compound according to any one of embodiments 1 to 6, wherein R^1 is pyridyl, oxazole, pyrrolidine or pyrazole and is optionally substituted by one or more Z substituents.

20

Embodiment 14: The compound according to any one of embodiment 1 to 6 or 13, wherein R^1 is 1-methyl-4-pyridyl, oxzaoyl-2-yl, 1-methyl-1H-pyrazole-4-yl or pyrrolidin-1yl.

- 25 Embodiment 15: The compound according to any one of embodiments 1 to 14, wherein R^1 is Br, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, 4-fluorophenyl, 4-chloro-2-methylphenyl, 2,4-dichlorophenyl, 1-methyl-4-pyridyl, 1-methyl-1H-pyrazole-4-yl, oxzaoyl-2-yl, or pyrrolidin-1yl.

- 30 Embodiment 16: The compound according to any one of embodiments 1 to 15, wherein R^5 provides a heteroatom two carbons from the amide nitrogen, wherein the heteroatom is oxygen or nitrogen.

Embodiment 17: The compound according to any one of embodiments 1 to 16, wherein

R^4 is H or C_1 - C_4 alkyl optionally substituted by one or more halogen atoms;

R^5 is C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms; $-(CH_2)_m-$

$NR^{17}R^{18}$; $-(CH_2)_m-OR'$; or OH;

5 R' is H, or C_1 - C_4 alkyl optional substituted with one or more halogen;

m is 0, 1 or 2;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; $-(C_0$ - C_4 alkyl)- C_6 aryl; or $-(C_0$ - C_4 alkyl)-5 to 6 membered heterocyclic group, wherein the heterocyclic

10 group contains at least one heteroatom selected from N, O and S, wherein the aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

R^4 and R^6 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

R^5 and R^6 together with the carbon atoms to which they are bound a 5 to 8 membered

15 heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

R^{17} and R^{18} are each independently H; or C_1 - C_4 alkyl optionally substituted by one or more halogen atoms.

20 Embodiment 18: The compound according to any one of embodiments 1 to 17, wherein

R^3 is H;

R^4 is H or Me;

R^5 is $-(CH_2)_m-NR^{17}R^{18}$; $-(CH_2)_m-OR'$; or OH;

m is 0, or 1;

25 R' is H;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z

30 substituents; and

R^{17} and R^{18} are each independently H; or C_1 - C_4 alkyl optionally substituted by one or more halogen atoms.

Embodiment 19: The compound according to any one of embodiments 1 to 18, wherein

R^3 is H;

R^4 is H or Me;

R^5 is $-NR^{17}R^{18}$; or OH;

5 R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; and

10 R^{17} and R^{18} are each independently H; or C_1 - C_4 alkyl optionally substituted by one or more halogen atoms.

Embodiment 20: The compound according to any one of embodiments 1 to 19, wherein

R^3 is H;

15 R^4 is H or Me;

R^5 is $-NR^{17}R^{18}$; or OH;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; and

R^{17} and R^{18} are each independently H; or C_1 - C_4 alkyl optionally substituted by one or more halogen atoms.

20

Embodiment 21: The compound according to one of embodiments 1 to 20, wherein

R^3 is H;

R^4 and R^5 form an oxo group;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; C_1 - C_4 alkoxy

25 optionally substituted by one or more halogen atoms; phenyl; or 5 to 6 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the phenyl and heterocyclyl groups are each optionally substituted by one or more Z substituents.

30 Embodiment 22: The compound according to any one of embodiments 1 to 16 or 21, wherein

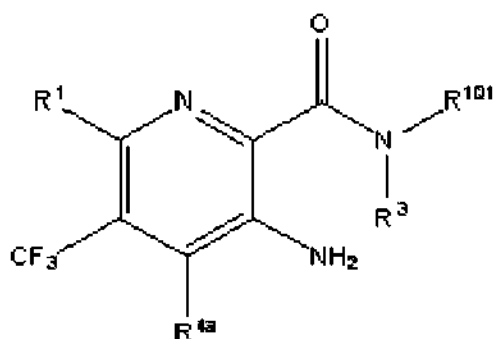
R^3 is H;

R^4 and R^5 form an oxo group;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; or phenyl, wherein the phenyl is optionally substituted by one or more Z substituents;
 Z is independently OH, C_1 - C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1 - C_4 alkyl optionally substituted by one or more halogen atoms, C_1 - C_4 alkoxy optionally substituted by one or more OH groups or C_1 - C_4 alkoxy, $C(O)OR^{19}$, $C(O)R^{19}$, OR^{19} , CN, or halogen;
 R^{19} is H; C_1 - C_4 alkyl; C_3 - C_6 cycloalkyl; or C_1 - C_4 alkoxy- C_1 - C_4 alkyl, wherein all alkyl are optionally substituted with halogens.

- 10 Embodiment 23: The compound according to embodiment 1 to 16 or 21 to 22, wherein R^3 is H;
 R^4 and R^5 form an oxo group;
 R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; or phenyl, wherein the phenyl is optionally substituted by one or more Z substituents;
15 Z is independently, C_1 - C_4 alkyl optionally substituted by one or more halogen atoms, C_1 - C_4 alkoxy or halogen.

Embodiment 24: The compound according to any one of embodiments 1 to 16, wherein the compound is represented by formula II,

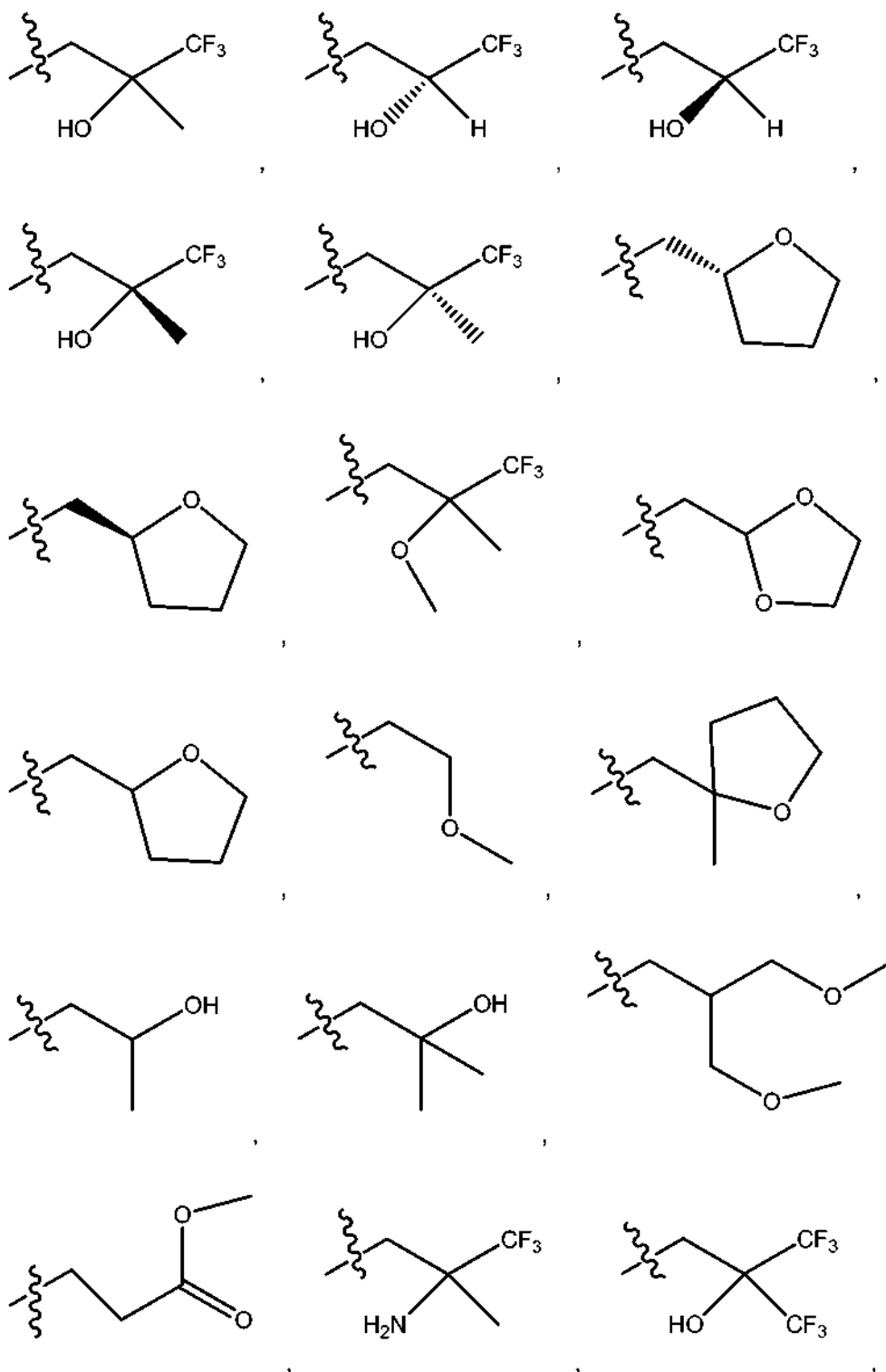


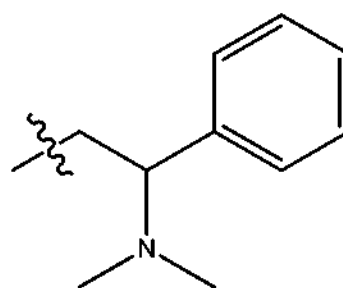
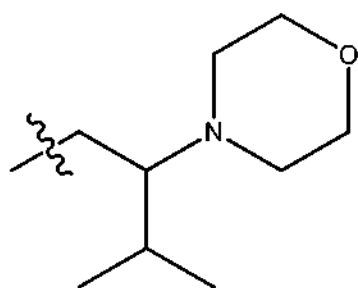
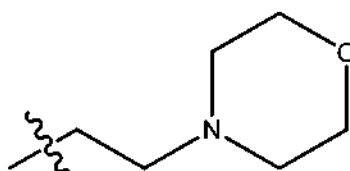
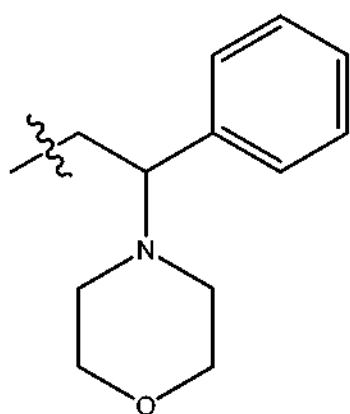
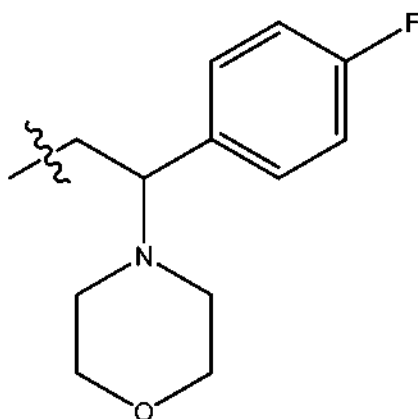
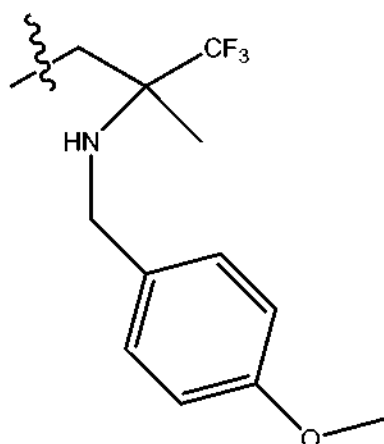
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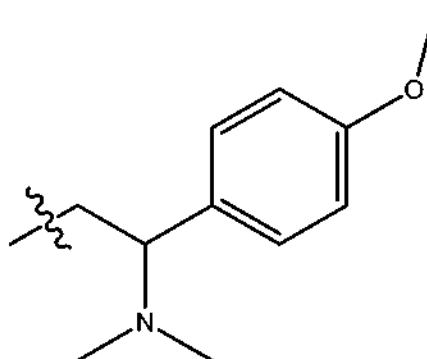
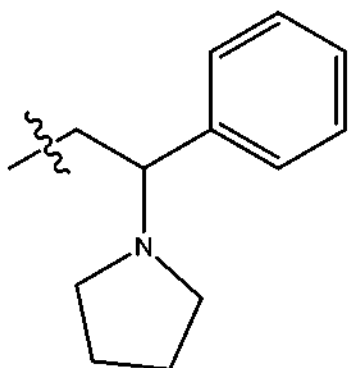
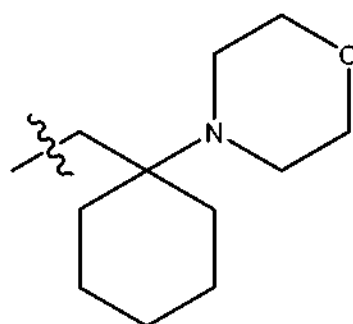
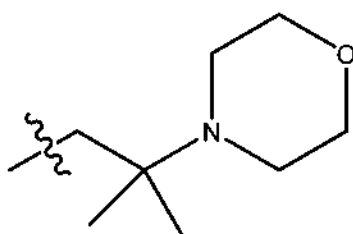
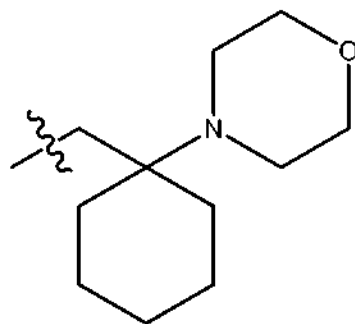
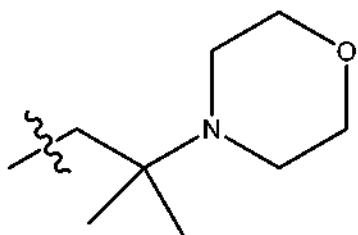
II

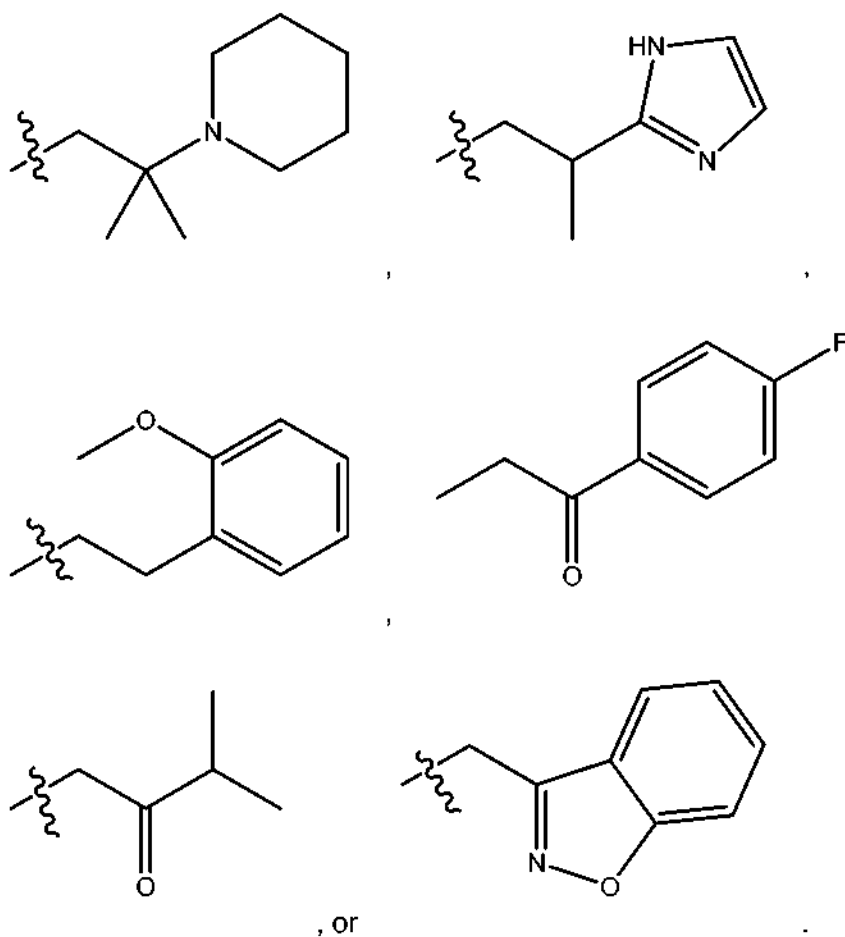
or a pharmaceutically acceptable salt thereof,
 wherein,

R^{101} is selected from the following:

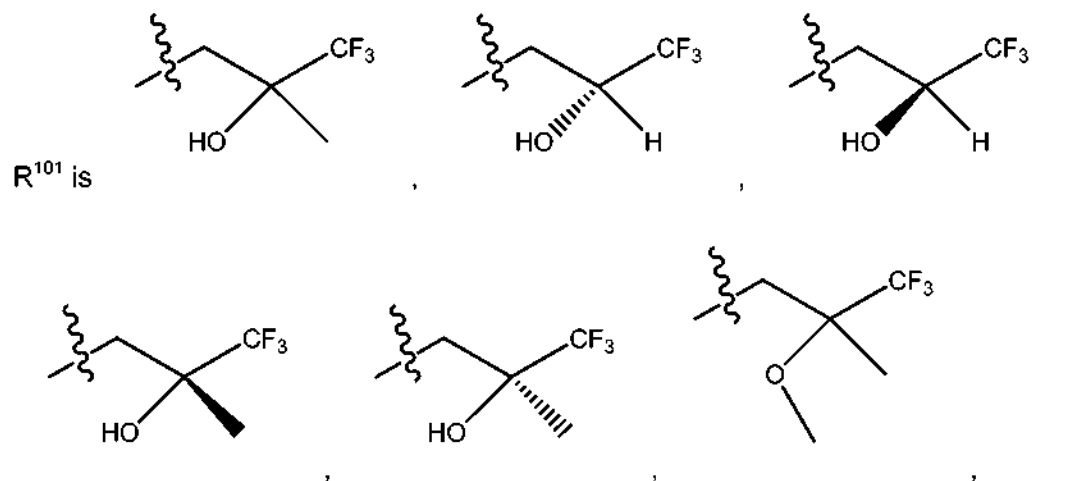


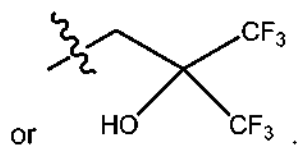






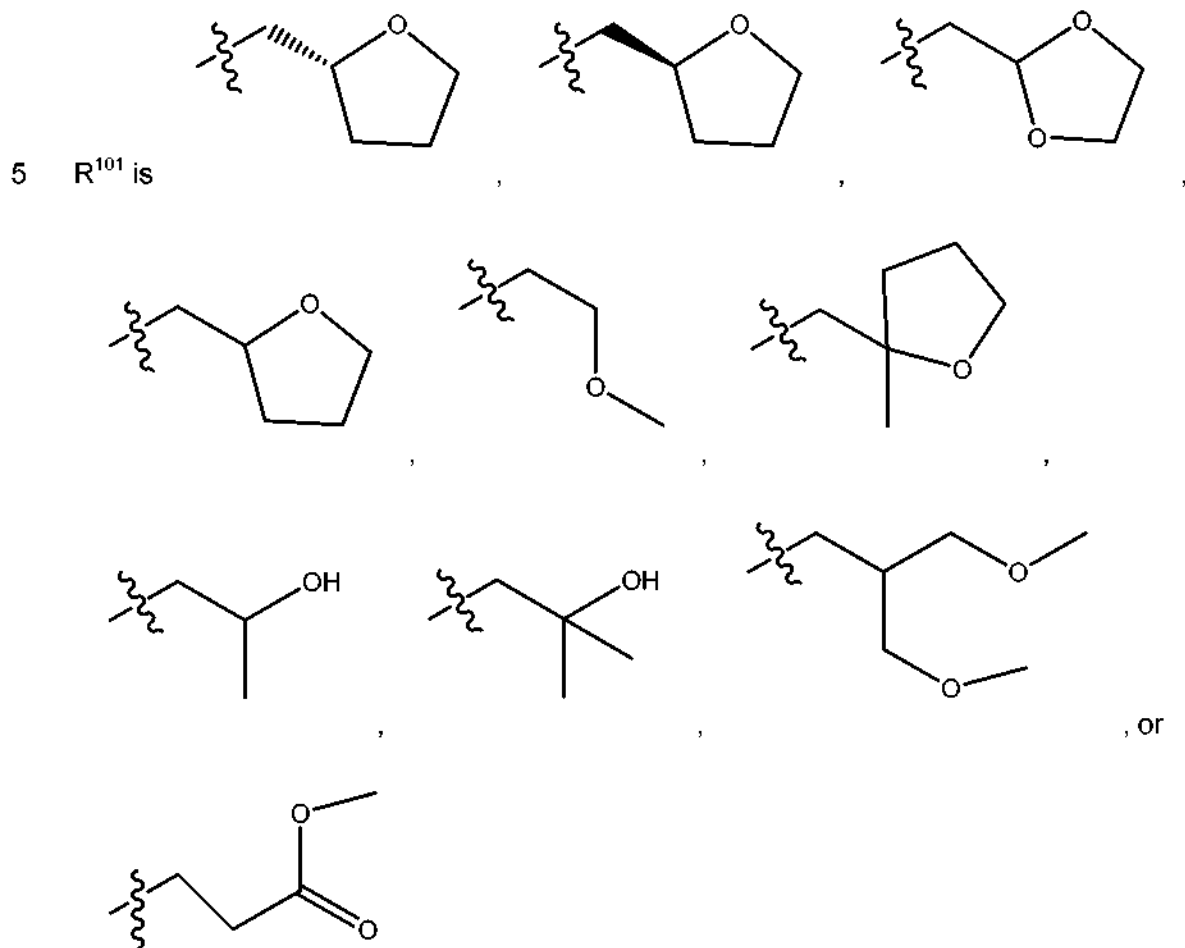
- 5 Embodiment 25: The compound according to embodiment 24, wherein R^3 is H;





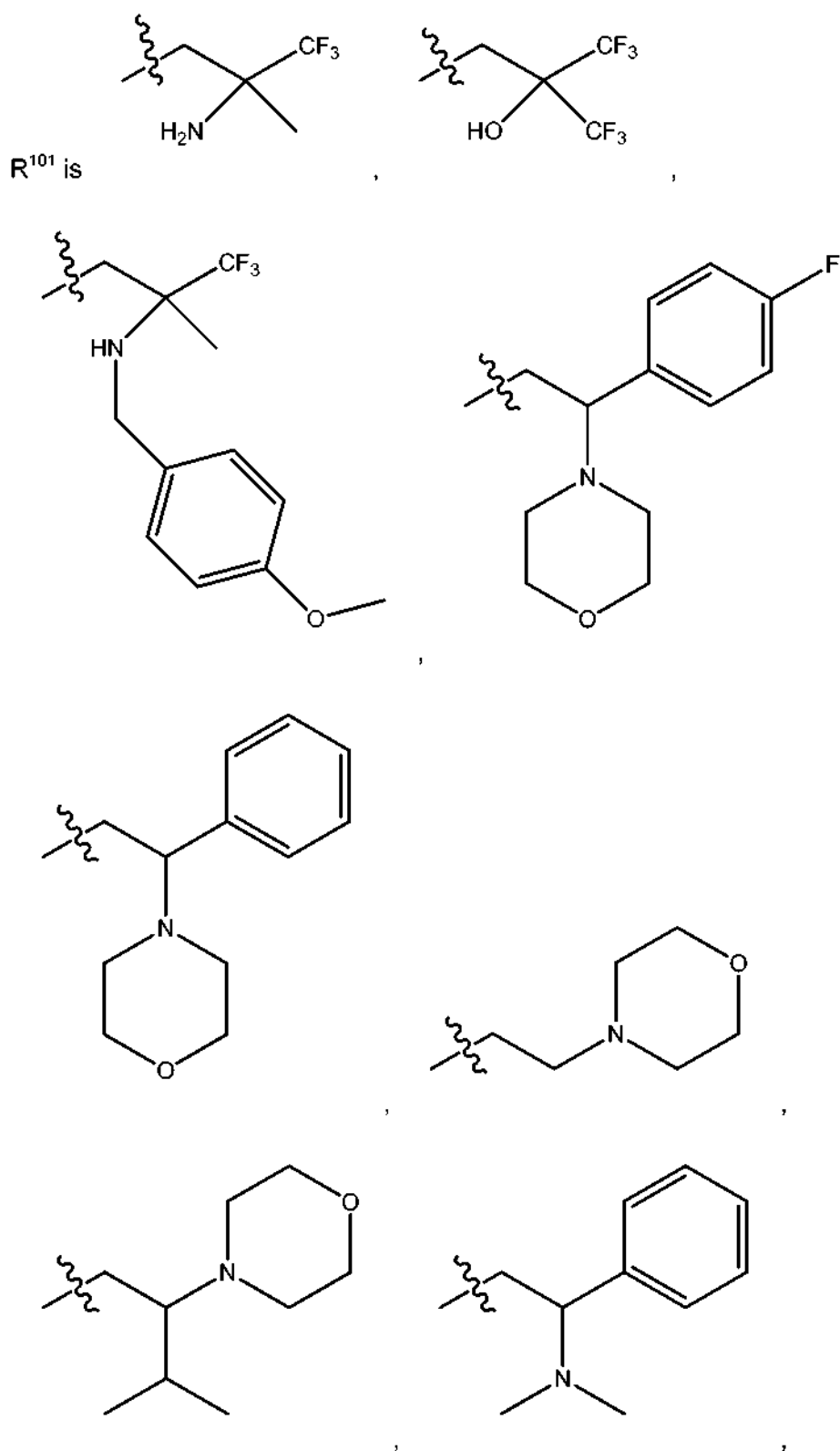
Embodiment 26: The compound according to embodiment 24, wherein

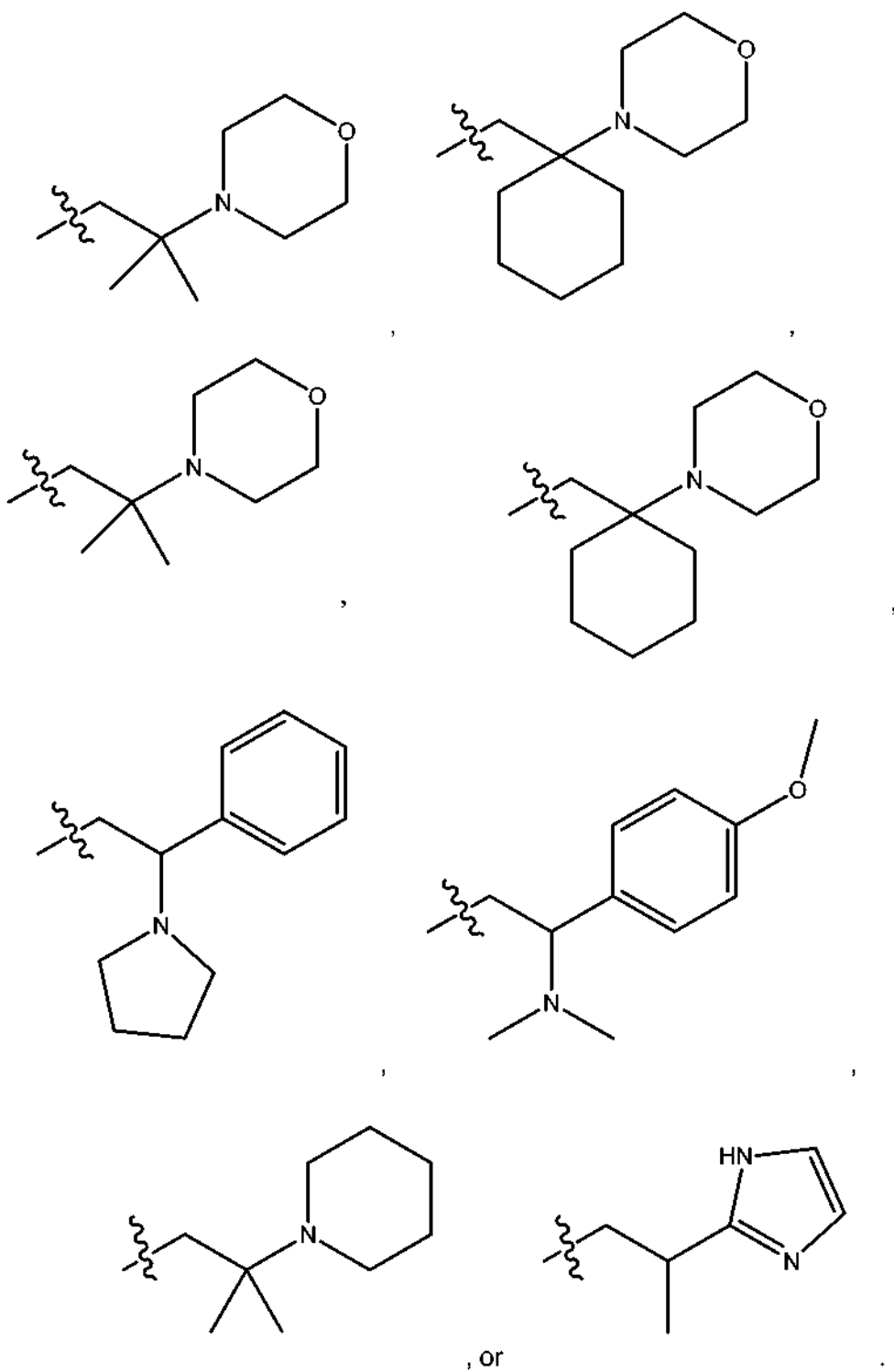
R^3 is H;



10 Embodiment 27: The compound according to embodiment 24, wherein

R^3 is H;

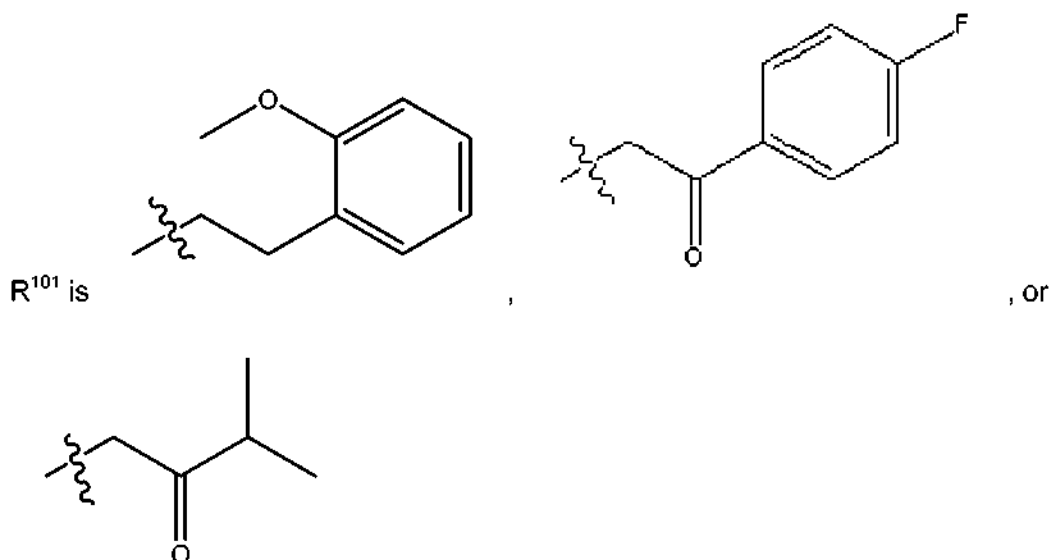




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Embodiment 28: The compound according to embodiment 24, wherein

R^3 is H;



5 Embodiment 29: The compound according to embodiment 1 to 16, wherein

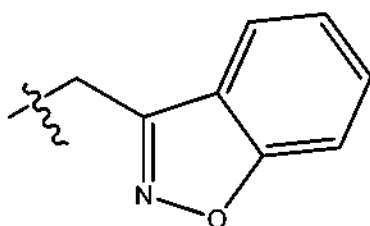
R^3 is H;

R^{101} is $-(C_1-C_2 \text{ alkyl})$ -5 to 10 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents.

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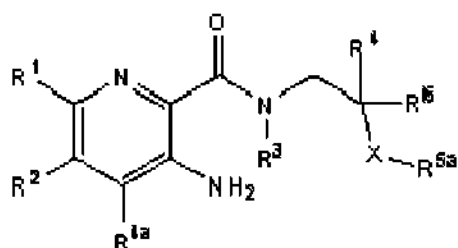
Embodiment 30: The compound according to embodiment 24 or 29, wherein

R^3 is H;



R^{101} is

15 Embodiment 31: The compound of formula III



III

or pharmaceutically acceptable salts thereof, wherein:

X is NR^y or O;

R^1 is $\text{C}_1\text{-C}_8$ alkyl optionally substituted by one or more halogen atoms; $\text{C}_3\text{-C}_{10}$ cycloalkyl;

- 5 $-\text{C}_1\text{-C}_4$ alkyl- $\text{C}_3\text{-C}_8$ cycloalkyl; $\text{C}_1\text{-C}_8$ alkoxy optionally substituted by one or more halogen atoms; halogen; CN; $\text{NR}^{11}\text{R}^{12}$; $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$; $\text{NR}^{13}\text{C}(\text{O})\text{R}^{15}$; CO_2R^{15} ; $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl; or $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-3 to 14 membered heterocyclic group}$, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the cycloalkyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z
- 10 substituents;

R^2 is $\text{C}_1\text{-C}_4$ haloalkyl;

R^3 is H or $\text{C}_1\text{-C}_8$ alkyl optionally substituted by one or more halogen atoms;

R^{4a} is selected from halogen; $\text{C}_2\text{-C}_8$ alkenyl and $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl;

R^4 is H, or $\text{C}_1\text{-C}_8$ alkyl optional substituted with one or more halogen;

- 15 R^{5a} is H, $\text{C}_1\text{-C}_8$ alkyl optional substituted with one or more halogen, $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl or $-\text{3 to 14 membered heterocyclic group}$, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl and $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-3 to 14 membered heterocyclic group}$ are each optionally substituted by one or more Z substituents;

- 20 R^y is H, $\text{C}_1\text{-C}_8$ alkyl optional substituted with one or more halogen, $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl or $-\text{3 to 14 membered heterocyclic group}$, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl and $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-3 to 14 membered heterocyclic group}$ are each optionally substituted by one or more Z substituents;

- 25 R^6 is $\text{C}_1\text{-C}_8$ alkyl optionally substituted by one or more halogen atoms; $\text{C}_3\text{-C}_{10}$ cycloalkyl; $-\text{C}_1\text{-C}_4$ alkyl- $\text{C}_3\text{-C}_8$ cycloalkyl; $\text{C}_1\text{-C}_8$ alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-C}_6\text{-C}_{14}$ aryl; or $-(\text{C}_0\text{-C}_4 \text{ alkyl})\text{-3 to 14 membered}$

heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the cycloalkyl, cycloalkenyl, $-(C_0-C_4 \text{ alkyl})-C_6-C_{14}$ aryl and $-(C_0-C_4 \text{ alkyl})$ -3 to 14 membered heterocyclic group are each optionally substituted by one or more Z substituents; or

- 5 R^4 and R^6 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

R^{5a} and R^6 together with the atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; or

- 10 R^{5a} and R^y together with the atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

R^{11} and R^{13} are each independently H, C_1-C_8 alkyl optionally substituted by one or more halogen atoms, C_3-C_{10} cycloalkyl or $-(C_1-C_4 \text{ alkyl})-C_3-C_8$ cycloalkyl;

- 15 R^{12} , R^{14} , and R^{15} are each independently H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyl; C_5-C_{10} cycloalkenyl; $-(C_1-C_4 \text{ alkyl})-C_3-C_8$ cycloalkyl; $-(C_0-C_4 \text{ alkyl})-C_6-C_{14}$ aryl; or $-(C_0-C_4 \text{ alkyl})$ -3 to 14

membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the cycloalkyl, cycloalkenyl, aryl and

- 20 heterocyclyl groups are each optionally substituted by one or more Z substituents; or R^{11} and R^{12} , and R^{13} and R^{14} together with the nitrogen atom to which they are attached may form a 4 to 14 membered heterocyclic group optionally substituted by one or more Z substituents;

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C_1-C_6 alkyl optionally substituted

- 25 by one or more OH groups or NH_2 groups, C_1-C_6 alkyl optionally substituted by one or more halogen atoms, C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, $NR^{18}(SO_2)R^{21}$, $(SO_2)NR^{19}R^{21}$, $(SO_2)R^{21}$, $NR^{18}C(O)R^{21}$, $C(O)NR^{19}R^{21}$, $NR^{18}C(O)NR^{19}R^{21}$, $NR^{18}C(O)OR^{19}$, $NR^{19}R^{21}$, $C(O)OR^{19}$, $C(O)R^{19}$, SR^{19} , OR^{19} , oxo, CN, NO_2 , halogen or a 3 to 14 membered heterocyclic group, wherein the heterocyclic group

- 30 contains at least one heteroatom selected from N, O and S;

R^{19} and R^{21} are each independently H; C_1-C_8 alkyl; C_3-C_8 cycloalkyl; C_1-C_4 alkoxy- C_1-C_4 alkyl; $(C_0-C_4 \text{ alkyl})$ -aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; $(C_0-C_4 \text{ alkyl})$ -3- to 14-membered heterocyclic group,

- the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C₁-C₆ alkyl and C(O)C₁-C₆ alkyl; (C₀-C₄ alkyl)-O-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; and (C₀-C₄ alkyl)-O-3- to 14-
- 5 membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C₁-C₆ alkyl or C(O)C₁-C₆ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C₁-C₄ alkoxy, C(O)NH₂, C(O)NHC₁-C₆ alkyl or C(O)N(C₁-C₆ alkyl)₂; or
- 10 R¹⁹ and R²¹ together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O
- 15 and S; S(O)₂-aryl; S(O)₂-C₁-C₆ alkyl; C₁-C₆ alkyl optionally substituted by one or more halogen atoms; C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy; and C(O)OC₁-C₆ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by C₁-C₆ alkyl, C₁-C₆ haloalkyl or C₁-C₆ alkoxy.
- 20 Embodiment 32: The compound according to embodiment 31, wherein
X is NR^y or O;
R¹ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms; C₁-C₄ alkoxy optionally substituted by one or more halogen atoms; halogen; -(C₀-C₄ alkyl)-C₆ aryl; or -(C₀-C₄ alkyl)-5 to 6 membered heterocyclic group, wherein the heterocyclic group
- 25 contains at least one heteroatom selected from N, O and S; wherein the cycloalkyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents;
R² is C₁-C₄ haloalkyl;
R³ is H;
R⁴ is H, or C₁-C₄ alkyl optional substituted with one or more halogen;
- 30 R^{5a} is H, C₁-C₄ alkyl optional substituted with one or more halogen, -(C₀-C₄ alkyl)-C₆ aryl or -5 to 8 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the -(C₀-C₄ alkyl)-C₆ aryl and -5 to 8

membered heterocyclic group are each optionally substituted by one or more Z substituents;

R^y is H, C_1 - C_4 alkyl optional substituted with one or more halogen, $-(C_0$ - C_4 alkyl)- C_6 aryl or -5 to 8 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the $-(C_0$ - C_4 alkyl)- C_6 aryl and -5 to 8 membered heterocyclic group are each optionally substituted by one or more Z substituents;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms; OH; CN; $-(C_0$ - C_4 alkyl)- C_6 aryl; or -5 to 8 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the $-C_6$ aryl and -5 to 8 membered heterocyclic group are each optionally substituted by one or more Z substituents; or R^4 and R^6 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

R^{5a} and R^6 together with the atoms to which they are bound a 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from N, O and S, wherein the heterocyclic group is optionally substituted by one or more Z substituents; or R^{5a} and R^y together with the atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

Z is independently OH, aryl, O-aryl, C_1 - C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1 - C_6 alkyl optionally substituted by one or more halogen atoms, C_1 - C_6 alkoxy optionally substituted by one or more OH groups or C_1 - C_4 alkoxy, $NR^{18}C(O)R^{21}$, $C(O)NR^{19}R^{21}$, $NR^{19}R^{21}$, $C(O)OR^{19}$, $C(O)R^{19}$, SR^{19} , OR^{19} , oxo, CN, NO_2 , halogen or a 5 to 8 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the heterocyclic group is option substituted by halogen, C_1 - C_4 alkyl optionally substituted by halogen, C_1 - C_4 alkoxy or -CN;

R^{18} is H or C_1 - C_4 alkyl;

R^{19} and R^{21} are each independently H; C_1 - C_8 alkyl; C_3 - C_8 cycloalkyl; C_1 - C_4 alkoxy- C_1 - C_4 alkyl; $(C_0$ - C_4 alkyl)-aryl optionally substituted by one or more groups selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy and halogen; $(C_0$ - C_4 alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S,

optionally substituted by one or more groups selected from halogen, oxo, C₁-C₆ alkyl and C(O)C₁-C₆ alkyl; (C₀-C₄ alkyl)-O-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; and (C₀-C₄ alkyl)-O-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C₁-C₆ alkyl or C(O)C₁-C₆ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C₁-C₄ alkoxy, C(O)NH₂, C(O)NHC₁-C₆ alkyl or C(O)N(C₁-C₆ alkyl)₂; or

R¹⁹ and R²¹ together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(O)₂-aryl; S(O)₂-C₁-C₆ alkyl; C₁-C₆ alkyl optionally substituted by one or more halogen atoms; C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy; and C(O)OC₁-C₆ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by C₁-C₆ alkyl, C₁-C₆ haloalkyl or C₁-C₆ alkoxy.

Embodiment 33: The compound according to embodiment 31 or 32, wherein

X is NR^y or O;

R¹ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms; C₁-C₄ alkoxy optionally substituted by one or more halogen atoms; or halogen;

R² is CF₃;

R³ is H;

R⁴ is H, or C₁-C₄ alkyl optional substituted with one or more halogen;

R^{5a} is H, C₁-C₄ alkyl optional substituted with one or more halogen,

R^y is H, C₁-C₄ alkyl optional substituted with one or more halogen,

R⁶ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms; C₁-C₄ alkoxy optionally substituted by one or more halogen atoms; OH; CN; or

R⁴ and R⁶ together with the carbon atoms to which they are bound form a 3 to 6 membered carbocyclic ring system; or

- R^{5a} and R⁶ together with the atoms to which they are bound a 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from N, O and S, wherein the heterocyclic group is optionally substituted by one or more Z substituents; or R^{5a} and R⁷ together with the atoms to which they are bound a 5 to 8 membered
- 5 heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; Z is independently OH, C₁-C₆ alkyl optionally substituted by one or more OH groups or NH₂ groups, C₁-C₆ alkyl optionally substituted by one or more halogen atoms, C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy, NR¹⁹R²¹,
- 10 C(O)OR¹⁹, C(O)R¹⁹, SR¹⁹, OR¹⁹, oxo, CN, NO₂, or halogen; R¹⁹ is H; C₁-C₈ alkyl; (C₀-C₄ alkyl)-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; (C₀-C₄ alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen,
- 15 oxo, C₁-C₆ alkyl and C(O)C₁-C₆ alkyl; (C₀-C₄ alkyl)-O-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; and (C₀-C₄ alkyl)- O- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C₁-C₆ alkyl or C(O)C₁-C₆ alkyl; wherein the alkyl groups are
- 20 optionally substituted by one or more halogen atoms, C₁-C₄ alkoxy, C(O)NH₂, C(O)NHC₁-C₆ alkyl or C(O)N(C₁-C₆ alkyl)₂; or R¹⁹ and R²¹ together with the nitrogen atom to which they attached form a 5- to 6-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally
- 25 substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(O)₂-aryl; S(O)₂-C₁-C₆ alkyl; C₁-C₆ alkyl optionally substituted by one or more halogen atoms; C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy; and C(O)OC₁-C₆ alkyl, wherein the aryl and heterocyclic substituent groups are
- 30 themselves optionally substituted by C₁-C₆ alkyl, C₁-C₆ haloalkyl or C₁-C₆ alkoxy.

Embodiment 34: The compound according to embodiment 31 to 33, wherein X is NR⁷ or O;

R¹ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms; C₁-C₄ alkoxy optionally substituted by one or more halogen atoms; or halogen;

R² is CF₃;

R³ is H;

5 R⁴ is H, or C₁-C₄ alkyl optional substituted with one or more halogen;

R^{5a} is H, C₁-C₄ alkyl optional substituted with one or more halogen,

R^y is H, C₁-C₄ alkyl optional substituted with one or more halogen,

R⁶ is C₁-C₄ alkyl optionally substituted by one or more halogen atoms; C₁-C₄ alkoxy optionally substituted by one or more halogen atoms; OH; CN; or

10 R^{5a} and R⁶ together with the atoms to which they are bound a 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from N, O and S, wherein the heterocyclic group is optionally substituted by one or more Z substituents; or R^{5a} and R^y together with the atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S,

15 wherein the ring system is optionally substituted by one or more Z substituents;

Z is independently OH, C₁-C₆ alkyl optionally substituted by one or more OH groups or NH₂ groups, C₁-C₆ alkyl optionally substituted by one or more halogen atoms, C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy, oxo, CN, NO₂, or halogen;

20

Embodiment 35: The compound according to any proceeding embodiment, wherein R² is CF₃CF₂-, (CF₃)₂CH-, CH₃-CF₂-, CF₃CF₂-, CF₃, CF₂H-, CH₃-CCl₂-, CF₃CFCClH-, CBr₃, CBr₂H-CF₃CF₂CHCF₃ or CF₃CF₂CF₂CF₂-.

25 Embodiment 36: The compound according to any one of embodiments 1 to 35, wherein R² is CF₃.

Embodiment 37: The compound according to any one of embodiments 1 to 36, wherein
30 the compound is a substantially pure enantiomer with the S configuration.

Embodiment 38: The compound according to any one of embodiments 1 to 36, wherein the compound is a substantially pure enantiomer with the R configuration.

Embodiment 39: The compound according to embodiment 5, 24 or 31, wherein the compound is represented by:

(S)-3-Amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide;

(S)-3-Amino-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoro methyl)-4-vinylpicolinamide; and

3-Amino-6-methoxy-4-phenyl-5-trifluoromethyl-pyridine-2-carboxylic acid ((S)-3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide.

Embodiment 40: Use of a compound according to any one of embodiments 1 to 39 in the manufacture of a medicament for use in the treatment of an inflammatory or obstructive airways disease or mucosal hydration.

Embodiment 41: Use of a compound according to any one of embodiments 1 to 39 in the manufacture of a medicament for use in the treatment of a disease mediated by CFTR.

Embodiment 42: Use of a compound according to any one of embodiments 1 to 39 in the manufacture of a medicament for use in the treatment of a disease mediated by CFTR, wherein the disease is CF or COPD.

Embodiment 43: Use of a compound according to any one of embodiments 1 to 39 in the manufacture of a medicament for use in the treatment of cystic fibrosis.

Embodiment 44: A pharmaceutical composition for treating a disease or disorder mediated by CFTR, comprising:

the compound according to embodiment 1 to 39 and one or more pharmaceutically acceptable excipients.

Embodiment 45: A pharmaceutical composition, according to embodiment 44, wherein the disease or disorder is cystic fibrosis or COPD.

Embodiment 46: A pharmaceutical composition, according to embodiment 45, wherein the disease or disorder is cystic fibrosis.

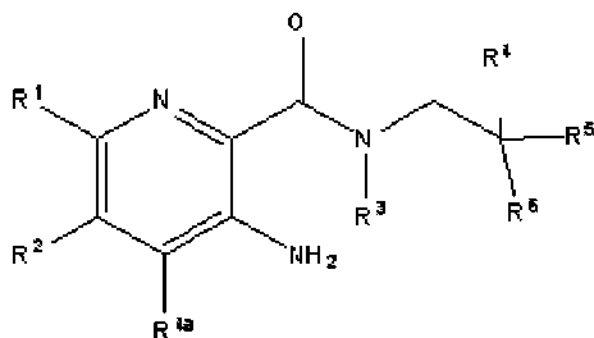
Embodiment 47: A pharmaceutical combination, comprising:

- 5 a first active comprising the compound according to any one of embodiments 1 to 39 and a second active selected from osmotic agents, ENaC blockers, anti-inflammatory agents, bronchodilatory agents, antihistamine agents, anti-tussive agents, antibiotic agents and DNase drug substances, wherein the first and second actives may be in the same or different pharmaceutical composition.

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Embodiment 48: A pharmaceutical combination according to embodiment 47, wherein the second active agent is an EnaC blocker.

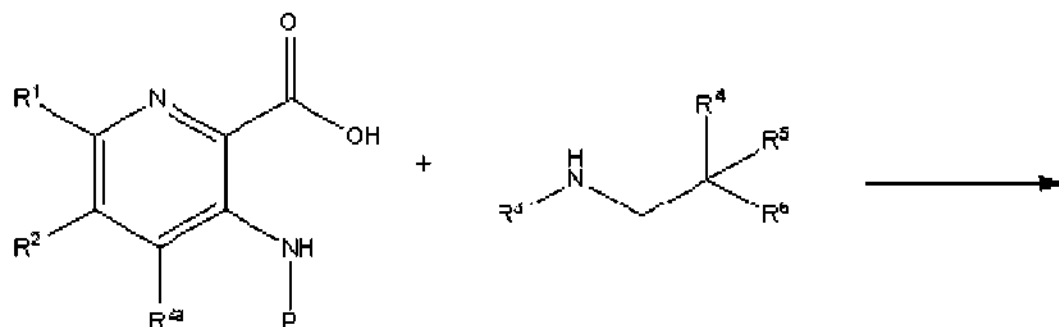
Embodiment 49: A process for the preparation of compounds of formula (I), comprising:



15

I

reacting a compound 1 with compound 2 in a peptide coupling reaction,



1

2

wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined herein and P is a suitable amino protecting group;

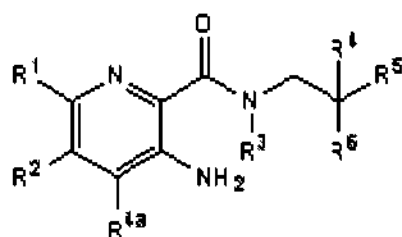
- 5 removing protecting groups and isolating the compound of formula I.

Embodiment 50: The process according to embodiment 49, wherein the peptide coupling condition is HATU in an aprotic solvent.

10

Claims

1. A compound of Formula I



I

5 wherein:

R¹ is H; C₁-C₈ alkyl optionally substituted by one or more halogen atoms; C₂-C₈ alkenyl; C₂-C₈ alkynyl; C₃-C₁₀ cycloalkyl; C₅-C₁₀ cycloalkenyl; -C₁-C₄ alkyl-C₃-C₈ cycloalkyl; C₁-C₈ alkoxy optionally substituted by one or more halogen atoms; halogen; SO₂NR⁸R⁹;

10 SO₂R¹⁰; S-C₁-C₈alkyl optionally substituted by one or more halogen atoms; S-C₆-C₁₄ aryl; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; CN; NR¹¹R¹²; CONR¹³R¹⁴; NR¹³SO₂R¹⁵; NR¹³C(O)R¹⁵ and CO₂R¹⁵, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more

15 Z substituents;

R² is C₁-C₄ haloalkyl;

R³ and R⁴ are each independently H or C₁-C₈ alkyl optionally substituted by one or more

20 halogen atoms;

R^{4a} is selected from halogen; C₂-C₈ alkenyl; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; -(C₀-C₄ alkyl)-3 to 14 membered heterocyclyl; and C₁-C₈ hydroxyalkyl; wherein the -(C₀-C₄ alkyl)-C₆-C₁₄ aryl and -(C₀-C₄ alkyl)-3 to 14 membered heterocyclyl groups are each optionally

25 substituted by one or more Z substituents;

R^5 and R^6 are each independently H; C_1 - C_8 alkyl optionally substituted by one or more halogen atoms; C_2 - C_8 alkenyl; C_2 - C_8 alkynyl; C_3 - C_{10} cycloalkyl; C_5 - C_{10} cycloalkenyl; $-C_1$ - C_4 alkyl- C_3 - C_8 cycloalkyl; C_1 - C_8 alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; $-(C_0$ - C_4 alkyl)- C_6 - C_{14} aryl; $-(C_0$ - C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; or $-(C_0$ - C_4 alkyl)- CO_2R^{15} , wherein the cycloalkyl, cycloalkenyl, $-(C_0$ - C_4 alkyl)- C_6 - C_{14} aryl and $-(C_0$ - C_4 alkyl)-3 to 14 membered heterocyclic group groups are each optionally substituted by one or more Z substituents; or

10 R^5 and R^6 are each independently a group of the formula:
 $-(CH_2)_m-NR^{17}R^{18}$; or

R^5 and R^6 are each independently a group of the formula:
 $-(CH_2)_m-OR^4$; or

15

R^4 and R^5 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

20 R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 8 membered carbocyclic ring system or a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

25 R^4 , R^5 and R^6 cannot all be the same;

m is 0, 1, 2 or 3;

30 R^8 , R^{11} , R^{13} and R^{17} are each independently H, C_1 - C_8 alkyl optionally substituted by one or more halogen atoms, C_3 - C_{10} cycloalkyl or $-(C_1$ - C_4 alkyl)- C_3 - C_8 cycloalkyl;

R^9 , R^{10} , R^{12} , R^{14} , R^{15} , R^{16} and R^{18} are each independently H; C_1 - C_8 alkyl optionally substituted by one or more halogen atoms; C_2 - C_8 alkenyl; C_2 - C_8 alkynyl; C_3 - C_{10} cycloalkyl; C_5 - C_{10} cycloalkenyl; $-C_1$ - C_4 alkyl- C_3 - C_8 cycloalkyl; $-(C_0$ - C_4 alkyl)- C_6 - C_{14} aryl; or

-(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

5

R⁶ and R⁹, R¹¹ and R¹², R¹³ and R¹⁴, and R¹⁷ and R¹⁸ together with the nitrogen atom to which they are attached may form a 4 to 14 membered heterocyclic group optionally substituted by one or more Z substituents;

- 10 Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C₁-C₆ alkyl optionally substituted by one or more OH groups or NH₂ groups, C₁-C₆ alkyl optionally substituted by one or more halogen atoms, C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy, NR¹⁸(SO₂)R²¹, (SO₂)NR¹⁹R²¹, (SO₂)R²¹, NR¹⁸C(O)R²¹, C(O)NR¹⁹R²¹, NR¹⁸C(O)NR¹⁹R²¹, NR¹⁸C(O)OR¹⁹, NR¹⁹R²¹, C(O)OR¹⁹, C(O)R¹⁹, SR¹⁹, OR¹⁹, oxo, CN, NO₂, halogen or a 3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S;

- 15 R¹⁹ and R²¹ are each independently H; C₁-C₈ alkyl; C₃-C₈ cycloalkyl; C₁-C₄ alkoxy-C₁-C₄ alkyl; (C₀-C₄ alkyl)-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; (C₀-C₄ alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C₁-C₆ alkyl and C(O)C₁-C₆ alkyl; (C₀-C₄ alkyl)-O-aryl optionally substituted by one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen; and (C₀-C₄ alkyl)- O-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C₁-C₆ alkyl or C(O)C₁-C₆ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C₁-C₄ alkoxy, C(O)NH₂, C(O)NHC₁-C₆ alkyl or C(O)N(C₁-C₆ alkyl)₂; or

30

R¹⁹ and R²¹ together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally

substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(O)₂-aryl; S(O)₂-C₁-C₆ alkyl; C₁-C₆ alkyl optionally substituted by one or more halogen atoms; C₁-C₆ alkoxy optionally substituted by one or more OH groups or C₁-C₄ alkoxy; and C(O)OC₁-C₆ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by C₁-C₆ alkyl, C₁-C₆ haloalkyl or C₁-C₆ alkoxy; or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 or 2, wherein R^{4a} is selected from halogen; C₂-C₈ alkenyl; -(C₀-C₄ alkyl)-C₆-C₁₄ aryl; -(C₀-C₄ alkyl)-3 to 14 membered heterocyclyl; C₁-C₈ hydroxyalkyl.

3. The compound according to claim 1 or 2, wherein R¹ is C₁-C₈ alkoxy optionally substituted by one or more halogen atoms; or halogen.

4. The compound according to any one of claims 1 to 3, wherein R¹ is C₁-C₄ alkoxy optionally substituted by one or more halogen atoms; or halogen.

5. The compound according to any one of claims 1 to 3, wherein R¹ is aryl, wherein aryl is phenyl optionally substituted by one or more Z substituents.

6. The compound according to any one of claims 1 to 5, wherein R² is CF₃.

7. The compound according to any one of claims 1 to 6, wherein R⁴ is H or C₁-C₄ alkyl optionally substituted by one or more halogen atoms; R⁵ is C₁-C₄ alkoxy optionally substituted by one or more halogen atoms; -(CH₂)_m-NR¹⁷R¹⁸, -(CH₂)_m-OR¹; or -(C₀-C₄ alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl heterocyclyl groups is optionally substituted by one or more Z substituents;

R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms; C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms; or $-(C_0$ - C_4 alkyl)- C_6 - C_{14} aryl wherein the aryl is optionally substituted by one or more Z substituents; or

R^4 and R^6 together with the carbon atoms to which they are bound form a 3 to 6

5 membered carbocyclic ring system; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

10 m is 0 or 1;

R^{17} and R^{18} are each independently H; C_1 - C_8 alkyl optionally substituted by one or more halogen atoms.

8. The compound according to any one of claims 1 to 7, wherein

15 R^1 is or C_1 - C_4 alkoxy optionally substituted by one or more halogen atoms;

R^2 is CF_3 ;

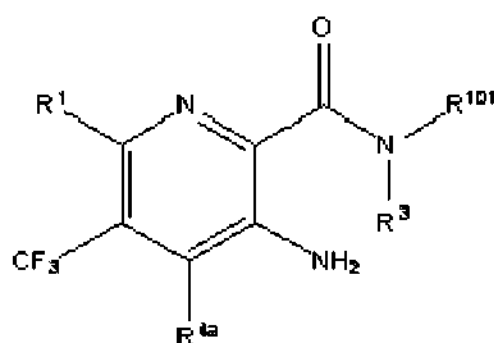
R^3 is H, CH_3 or CF_3 ;

R^4 is H or Me;

R^5 is $-NR^{17}R^{18}$ or OH, and

20 R^6 is C_1 - C_4 alkyl optionally substituted by one or more halogen atoms.

9. The compound according to claim 1, represented by formula II,

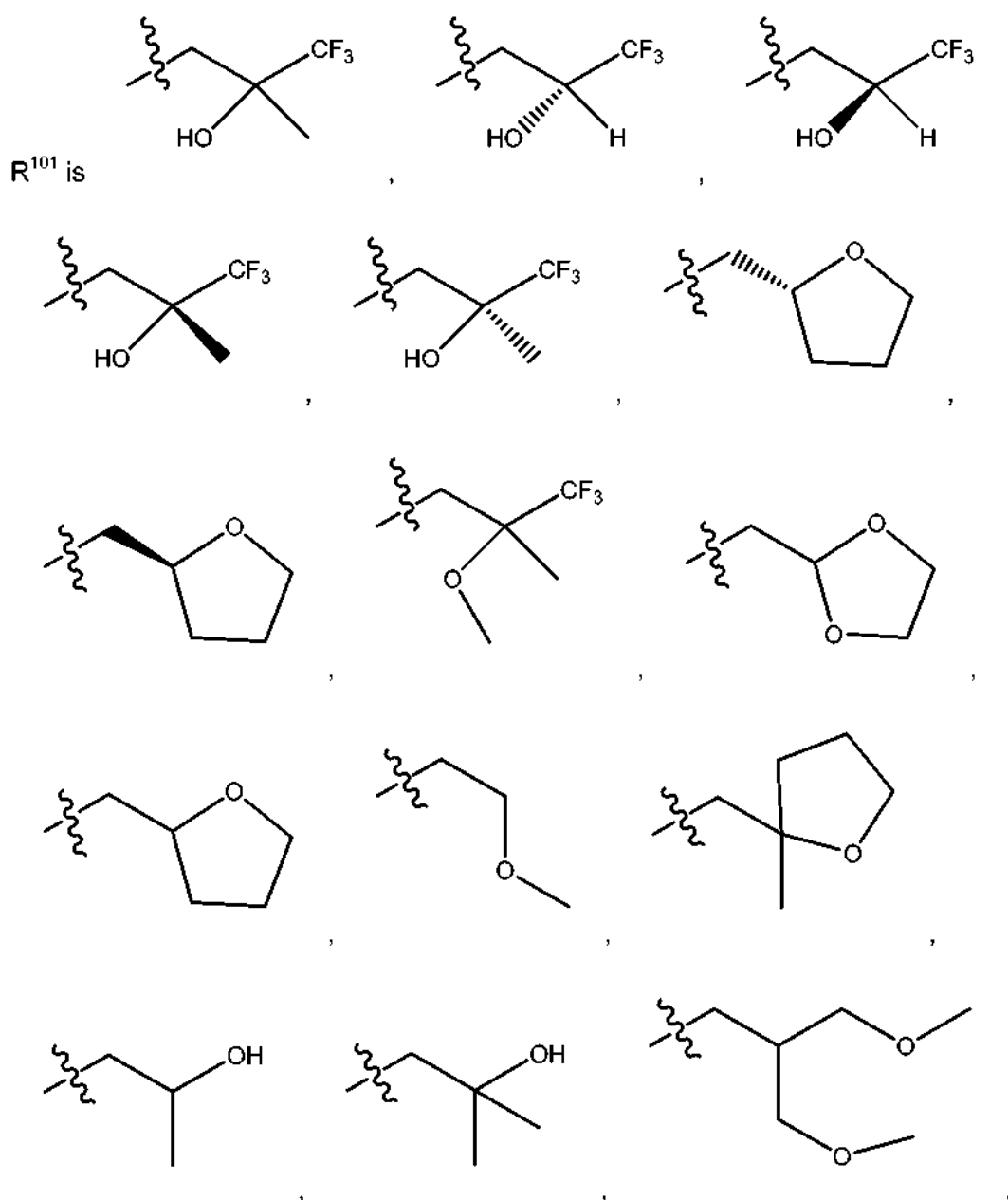


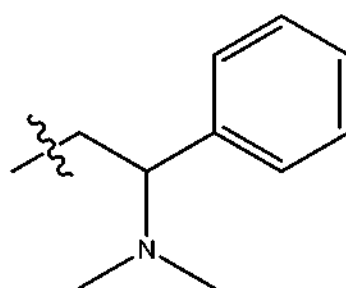
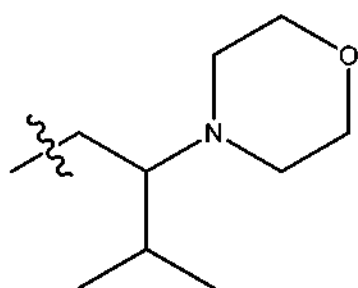
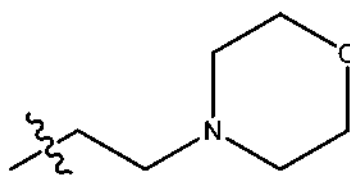
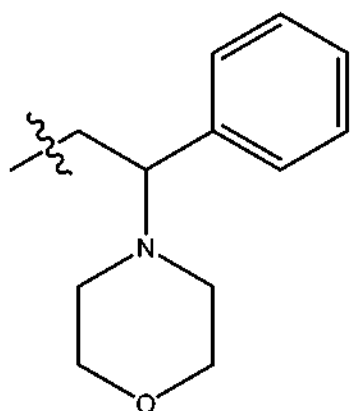
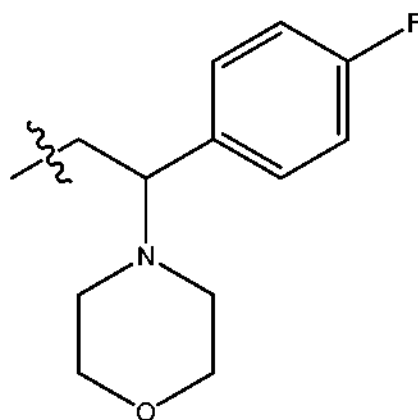
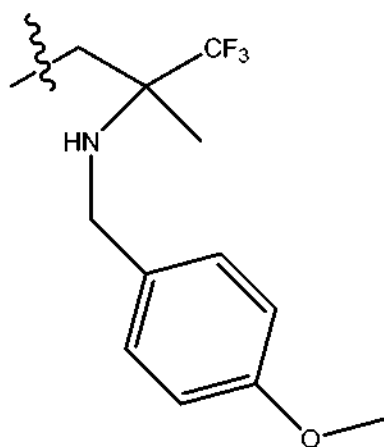
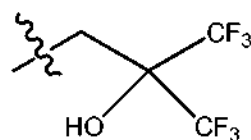
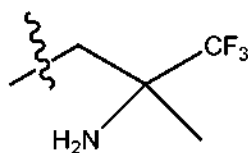
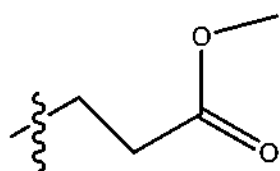
II

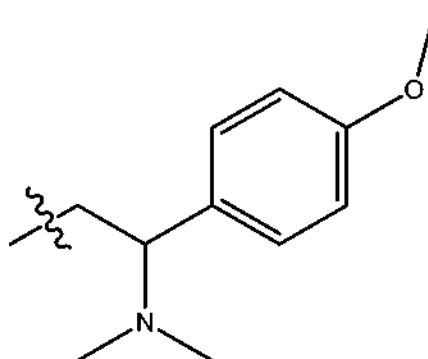
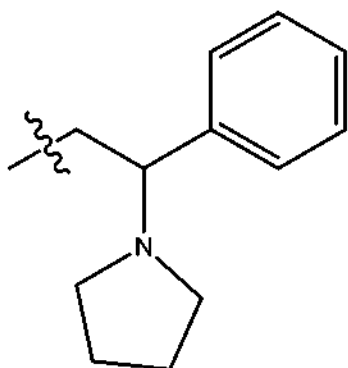
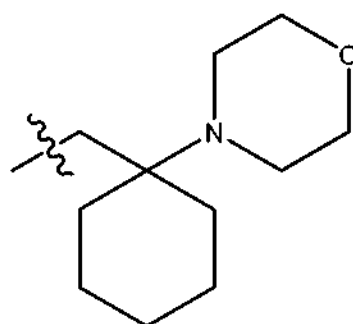
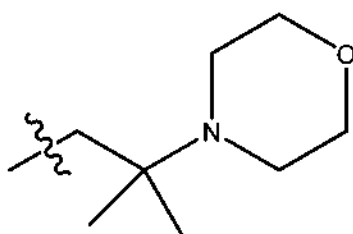
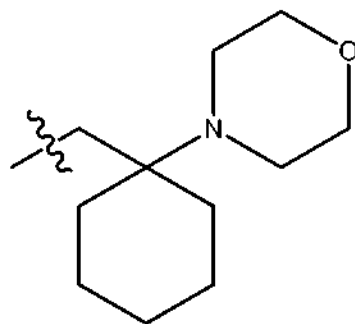
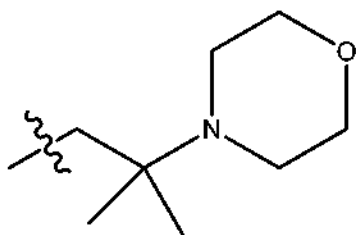
or a pharmaceutically acceptable salt thereof, wherein

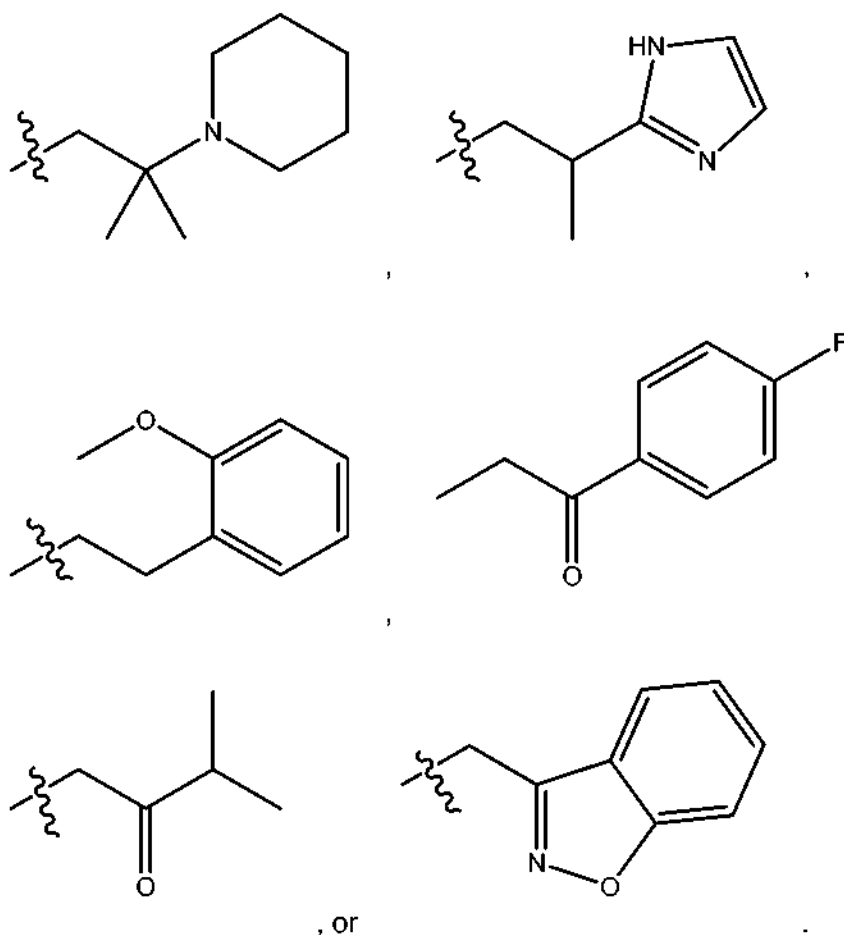
25 R^1 is C_1 - C_8 alkoxy optionally substituted by one or more halogen atoms; or halogen;;

R_3 is H or CH_3 ;









- 5 10. The compound according to any one of claims 1 to 10 selected from
 (S)-3-Amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-
 (trifluoromethyl)picolinamide;
 (S)-3-Amino-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoro methyl)-
 4-vinylpicolinamide; and
- 10 3-Amino-6-methoxy-4-phenyl-5-trifluoromethyl-pyridine-2-carboxylic acid ((S)-3,3,3-
 trifluoro-2-hydroxy-2-methyl-propyl)-amide.
11. A compound according to any of Claims 1 to 10 for use as a pharmaceutical.
- 15 12. A compound according to any of Claims 1 to 10 for use in the treatment of an
 inflammatory or obstructive airways disease or mucosal hydration.

13. Use of a compound according to any of Claims 1 to 10 in the manufacture of a medicament for use in the treatment of an inflammatory or obstructive airways disease or mucosal hydration.

5

14. A pharmaceutical composition, comprising:
the compound according to any of Claims 1 to 10 and
one or more pharmaceutically acceptable excipients.

10

15. A pharmaceutical combination, comprising:
a first active comprising the compound according to any of Claims 1 to 10 and
a second active selected from osmotic agents, ENaC blockers, anti-inflammatory agents, bronchodilatory agents, antihistamine agents, anti-tussive agents, antibiotic agents and DNase drug substances, wherein the first and second actives may be in the same or
15 different pharmaceutical composition.

15

16. A pharmaceutical combination, comprising:
a first active comprising the compound according to any of Claims 1 to 10 and
a second active which is a CFTR corrector, wherein the first and second actives may be
20 in the same or different pharmaceutical composition.

20

17. A method for treating CFTR mediated condition or disease, comprising:
administering an effective amount of at least one compound according to any of claims 1
to 10 to a subject in need of such treatment.

25

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2012/054801

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/81 A61K31/44 A61P11/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WO 2011/113894 A1 (NOVARTIS AG [CH]; BAETTIG URS [GB]; BALA KAMLESH JAGDIS [GB]; BUDD EMM) 22 September 2011 (2011-09-22) claims 1,15	1-17
A	----- WO 2008/141119 A2 (VERTEX PHARMA [US]; HADIDA RUAH SARA [US]; GROOTENHUIS PETER D J [US];) 20 November 2008 (2008-11-20) claim 1 -----	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011113894 A1	22-09-2011	AR 080765 A1	09-05-2012
		AU 2011229022 A1	04-10-2012
		CA 2793392 A1	22-09-2011
		CR 20120468 A	31-10-2012
		US 2011230483 A1	22-09-2011
		US 2012277232 A1	01-11-2012
		WO 2011113894 A1	22-09-2011

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		CA 2686838 A1	20-11-2008
		CN 101687842 A	31-03-2010
		EP 2164840 A2	24-03-2010
		JP 2010526831 A	05-08-2010
		NZ 581259 A	27-07-2012
		WO 2008141119 A2	20-11-2008

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(72) Inventors; and

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Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HETEROCYCLIC MODULATORS OF ATP-BINDING CASSETTE TRANSPORTERS

(57) Abstract: Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful as modulators of ATP-Binding Cassette ("ABC") transporters or fragments thereof, including Cystic Fibrosis Transmembrane Conductance Regulator ("CFTR"). The present invention also relates to methods of treating ABC transporter mediated diseases using compounds of the present invention.



WO 2007/056341 A1

HETEROCYCLIC MODULATORS OF ATP-BINDING CASSETTE TRANSPORTERS**CROSS-REFERENCE TO RELATED APPLICATIONS**

[00100] The present application claims the benefit under 35 U.S.C. § 119 of United States Provisional Application No. 60/734,506, filed on November 8, 2005, United States Provisional Application No. 60/754,086, filed on December 27, 2005, and United States Provisional Application No. 60/802,458, filed on May 22, 2006, the entire contents of each of the above applications being incorporated herein by reference.

TECHNICAL FIELD OF THE INVENTION

[00101] The present invention relates to modulators of ATP-Binding Cassette ("ABC") transporters or fragments thereof, including Cystic Fibrosis Transmembrane Conductance Regulator ("CFTR"), compositions thereof, and methods therewith. The present invention also relates to methods of treating ABC transporter mediated diseases using such modulators.

BACKGROUND OF THE INVENTION

[00102] ABC transporters are a family of membrane transporter proteins that regulate the transport of a wide variety of pharmacological agents, potentially toxic drugs, and xenobiotics, as well as anions. ABC transporters are homologous membrane proteins that bind and use cellular adenosine triphosphate (ATP) for their specific activities. Some of these transporters were discovered as multi-drug resistance proteins (like the MDR1-P glycoprotein, or the multi-drug resistance protein, MRP1), defending malignant cancer cells against chemotherapeutic agents. To date, 48 ABC Transporters have been identified and grouped into 7 families based on their sequence identity and function.

[00103] ABC transporters regulate a variety of important physiological roles within the body and provide defense against harmful environmental compounds. Because of this, they represent important potential drug targets for the treatment of diseases associated with defects in the transporter, prevention of drug transport out of the target cell, and intervention in other diseases in which modulation of ABC transporter activity may be beneficial.

[00104] One member of the ABC transporter family commonly associated with disease is the cAMP/ATP-mediated anion channel, CFTR. CFTR is expressed in a variety of cells types, including absorptive and secretory epithelia cells, where it regulates anion flux across the membrane, as well as the activity of other ion channels and proteins. In epithelia cells, normal functioning of CFTR is critical for the maintenance of electrolyte transport

throughout the body, including respiratory and digestive tissue. CFTR is composed of approximately 1480 amino acids that encode a protein made up of a tandem repeat of transmembrane domains, each containing six transmembrane helices and a nucleotide binding domain. The two transmembrane domains are linked by a large, polar, regulatory (R)-domain with multiple phosphorylation sites that regulate channel activity and cellular trafficking.

[00105] The gene encoding CFTR has been identified and sequenced (See Gregory, R. J. et al. (1990) *Nature* 347:382-386; Rich, D. P. et al. (1990) *Nature* 347:358-362), (Riordan, J. R. et al. (1989) *Science* 245:1066-1073). A defect in this gene causes mutations in CFTR resulting in Cystic Fibrosis ("CF"), the most common fatal genetic disease in humans. Cystic Fibrosis affects approximately one in every 2,500 infants in the United States. Within the general United States population, up to 10 million people carry a single copy of the defective gene without apparent ill effects. In contrast, individuals with two copies of the CF associated gene suffer from the debilitating and fatal effects of CF, including chronic lung disease.

[00106] In patients with cystic fibrosis, mutations in CFTR endogenously expressed in respiratory epithelia leads to reduced apical anion secretion causing an imbalance in ion and fluid transport. The resulting decrease in anion transport contributes to enhanced mucus accumulation in the lung and the accompanying microbial infections that ultimately cause death in CF patients. In addition to respiratory disease, CF patients typically suffer from gastrointestinal problems and pancreatic insufficiency that, if left untreated, results in death. In addition, the majority of males with cystic fibrosis are infertile and fertility is decreased among females with cystic fibrosis. In contrast to the severe effects of two copies of the CF associated gene, individuals with a single copy of the CF associated gene exhibit increased resistance to cholera and to dehydration resulting from diarrhea – perhaps explaining the relatively high frequency of the CF gene within the population.

[00107] Sequence analysis of the CFTR gene of CF chromosomes has revealed a variety of disease causing mutations (Cutting, G. R. et al. (1990) *Nature* 346:366-369; Dean, M. et al. (1990) *Cell* 61:863-870; and Kerem, B-S. et al. (1989) *Science* 245:1073-1080; Kerem, B-S et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:8447-8451). To date, > 1000 disease causing mutations in the CF gene have been identified (<http://www.genet.sickkids.on.ca/cftr/>). The most prevalent mutation is a deletion of phenylalanine at position 508 of the CFTR amino acid sequence, and is commonly referred to as $\Delta F508$ -CFTR. This mutation occurs in approximately 70% of the cases of cystic fibrosis and is associated with a severe disease.

[00108] The deletion of residue 508 in $\Delta F508$ -CFTR prevents the nascent protein from folding correctly. This results in the inability of the mutant protein to exit the ER, and traffic to the plasma membrane. As a result, the number of channels present in the membrane is far less than observed in cells expressing wild-type CFTR. In addition to impaired trafficking, the mutation results in defective channel gating. Together, the reduced number of channels in the membrane and the defective gating lead to reduced anion transport across epithelia leading to defective ion and fluid transport. (Quinton, P. M. (1990), *FASEB J.* 4: 2709-2727). Studies have shown, however, that the reduced numbers of $\Delta F508$ -CFTR in the membrane are functional, albeit less than wild-type CFTR. (Dalemans et al. (1991), *Nature Lond.* 354: 526-528; Denning et al., *supra*; Pasyk and Foskett (1995), *J. Cell. Biochem.* 270: 12347-50). In addition to $\Delta F508$ -CFTR, other disease causing mutations in CFTR that result in defective trafficking, synthesis, and/or channel gating could be up- or down-regulated to alter anion secretion and modify disease progression and/or severity.

[00109] Although CFTR transports a variety of molecules in addition to anions, it is clear that this role (the transport of anions) represents one element in an important mechanism of transporting ions and water across the epithelium. The other elements include the epithelial Na^+ channel, ENaC, $\text{Na}^+/\text{2Cl}^-/\text{K}^+$ co-transporter, $\text{Na}^+-\text{K}^+-\text{ATPase}$ pump and the basolateral membrane K^+ channels, that are responsible for the uptake of chloride into the cell.

[00110] These elements work together to achieve directional transport across the epithelium via their selective expression and localization within the cell. Chloride absorption takes place by the coordinated activity of ENaC and CFTR present on the apical membrane and the $\text{Na}^+-\text{K}^+-\text{ATPase}$ pump and Cl^- channels expressed on the basolateral surface of the cell. Secondary active transport of chloride from the luminal side leads to the accumulation of intracellular chloride, which can then passively leave the cell via Cl^- channels, resulting in a vectorial transport. Arrangement of $\text{Na}^+/\text{2Cl}^-/\text{K}^+$ co-transporter, $\text{Na}^+-\text{K}^+-\text{ATPase}$ pump and the basolateral membrane K^+ channels on the basolateral surface and CFTR on the luminal side coordinate the secretion of chloride via CFTR on the luminal side. Because water is probably never actively transported itself, its flow across epithelia depends on tiny transepithelial osmotic gradients generated by the bulk flow of sodium and chloride.

[00111] In addition to Cystic Fibrosis, modulation of CFTR activity may be beneficial for other diseases not directly caused by mutations in CFTR, such as secretory diseases and other protein folding diseases mediated by CFTR. These include, but are not limited to, chronic obstructive pulmonary disease (COPD), dry eye disease, and Sjögren's Syndrome.

[00112] COPD is characterized by airflow limitation that is progressive and not fully reversible. The airflow limitation is due to mucus hypersecretion, emphysema, and bronchiolitis. Activators of mutant or wild-type CFTR offer a potential treatment of mucus hypersecretion and impaired mucociliary clearance that is common in COPD. Specifically, increasing anion secretion across CFTR may facilitate fluid transport into the airway surface liquid to hydrate the mucus and optimized periciliary fluid viscosity. This would lead to enhanced mucociliary clearance and a reduction in the symptoms associated with COPD. Dry eye disease is characterized by a decrease in tear aqueous production and abnormal tear film lipid, protein and mucin profiles. There are many causes of dry eye, some of which include age, Lasik eye surgery, arthritis, medications, chemical/thermal burns, allergies, and diseases, such as Cystic Fibrosis and Sjögren's syndrome. Increasing anion secretion via CFTR would enhance fluid transport from the corneal endothelial cells and secretory glands surrounding the eye to increase corneal hydration. This would help to alleviate the symptoms associated with dry eye disease. Sjögren's syndrome is an autoimmune disease in which the immune system attacks moisture-producing glands throughout the body, including the eye, mouth, skin, respiratory tissue, liver, vagina, and gut. Symptoms, include, dry eye, mouth, and vagina, as well as lung disease. The disease is also associated with rheumatoid arthritis, systemic lupus, systemic sclerosis, and polymyositis/dermatomyositis. Defective protein trafficking is believed to cause the disease, for which treatment options are limited. Modulators of CFTR activity may hydrate the various organs afflicted by the disease and help to alleviate the associated symptoms.

[00113] As discussed above, it is believed that the deletion of residue 508 in $\Delta F508$ -CFTR prevents the nascent protein from folding correctly, resulting in the inability of this mutant protein to exit the ER, and traffic to the plasma membrane. As a result, insufficient amounts of the mature protein are present at the plasma membrane and chloride transport within epithelial tissues is significantly reduced. In fact, this cellular phenomenon of defective ER processing of ABC transporters by the ER machinery has been shown to be the underlying basis not only for CF disease, but for a wide range of other isolated and inherited diseases. The two ways that the ER machinery can malfunction is either by loss of coupling to ER export of the proteins leading to degradation, or by the ER accumulation of these defective/misfolded proteins [Aridor M, *et al.*, *Nature Med.*, 5(7), pp 745- 751 (1999); Shastry, B.S., *et al.*, *Neurochem. International*, 43, pp 1-7 (2003); Rutishauser, J., *et al.*, *Swiss Med Wkly*, 132, pp 211-222 (2002); Morello, JP *et al.*, *TIPS*, 21, pp. 466- 469 (2000); Bross P., *et al.*, *Human Mut.*, 14, pp. 186-198 (1999)]. The diseases associated with the first class of ER malfunction are

Cystic fibrosis (due to misfolded $\Delta F508$ -CFTR as discussed above), Hereditary emphysema (due to $\alpha 1$ -antitrypsin; non Piz variants), Hereditary hemochromatosis, Coagulation-Fibrinolysis deficiencies, such as Protein C deficiency, Type 1 hereditary angioedema, Lipid processing deficiencies, such as Familial hypercholesterolemia, Type 1 chylomicronemia, Abetalipoproteinemia, Lysosomal storage diseases, such as I-cell disease/Pseudo-Hurler, Mucopolysaccharidoses (due to Lysosomal processing enzymes), Sandhof/Tay-Sachs (due to β -Hexosaminidase), Crigler-Najjar type II (due to UDP-glucuronyl-sialyl-transferase), Polyendocrinopathy/Hyperinsulemia, Diabetes mellitus (due to Insulin receptor), Laron dwarfism (due to Growth hormone receptor), Myeloperoxidase deficiency, Primary hypoparathyroidism (due to Preproparathyroid hormone), Melanoma (due to Tyrosinase). The diseases associated with the latter class of ER malfunction are Glycanosis CDG type 1, Hereditary emphysema (due to $\alpha 1$ -Antitrypsin (PiZ variant), Congenital hyperthyroidism, Osteogenesis imperfecta (due to Type I, II, IV procollagen), Hereditary hypofibrinogenemia (due to Fibrinogen), ACT deficiency (due to $\alpha 1$ -Antichymotrypsin), Diabetes insipidus (DI), Neurophyseal DI (due to Vasopressin hormone/V2-receptor), Neprogenic DI (due to Aquaporin II), Charcot-Marie Tooth syndrome (due to Peripheral myelin protein 22), Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease (due to β APP and presenilins), Parkinson's disease, Amyotrophic lateral sclerosis, Progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders such as Huntington, Spinocerebellar ataxia type I, Spinal and bulbar muscular atrophy, Dentatorubal pallidoluyian, and Myotonic dystrophy, as well as Spongiform encephalopathies, such as Hereditary Creutzfeldt-Jakob disease (due to Prion protein processing defect), Fabry disease (due to lysosomal α -galactosidase A) and Straussler-Scheinker syndrome (due to Prp processing defect).

[00114] In addition to up-regulation of CFTR activity, reducing anion secretion by CFTR modulators may be beneficial for the treatment of secretory diarrheas, in which epithelial water transport is dramatically increased as a result of secretagogue activated chloride transport. The mechanism involves elevation of cAMP and stimulation of CFTR.

[00115] Although there are numerous causes of diarrhea, the major consequences of diarrheal diseases, resulting from excessive chloride transport are common to all, and include dehydration, acidosis, impaired growth and death.

[00116] Acute and chronic diarrheas represent a major medical problem in many areas of the world. Diarrhea is both a significant factor in malnutrition and the leading cause of death (5,000,000 deaths/year) in children less than five years old.

[00117] Secretory diarrheas are also a dangerous condition in patients of acquired immunodeficiency syndrome (AIDS) and chronic inflammatory bowel disease (IBD). 16 million travelers to developing countries from industrialized nations every year develop diarrhea, with the severity and number of cases of diarrhea varying depending on the country and area of travel.

[00118] Diarrhea in barn animals and pets such as cows, pigs, and horses, sheep, goats, cats and dogs, also known as scours, is a major cause of death in these animals. Diarrhea can result from any major transition, such as weaning or physical movement, as well as in response to a variety of bacterial or viral infections and generally occurs within the first few hours of the animal's life.

[00119] The most common diarrhea causing bacteria is enterotoxogenic E-coli (ETEC) having the K99 pilus antigen. Common viral causes of diarrhea include rotavirus and coronavirus. Other infectious agents include cryptosporidium, giardia lamblia, and salmonella, among others.

[00120] Symptoms of rotaviral infection include excretion of watery feces, dehydration and weakness. Coronavirus causes a more severe illness in the newborn animals, and has a higher mortality rate than rotaviral infection. Often, however, a young animal may be infected with more than one virus or with a combination of viral and bacterial microorganisms at one time. This dramatically increases the severity of the disease.

[00121] Accordingly, there is a need for modulators of an ABC transporter activity, and compositions thereof, that can be used to modulate the activity of the ABC transporter in the cell membrane of a mammal.

[00122] There is a need for methods of treating ABC transporter mediated diseases using such modulators of ABC transporter activity.

[00123] There is a need for methods of modulating an ABC transporter activity in an *ex vivo* cell membrane of a mammal.

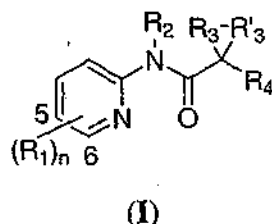
[00124] There is a need for modulators of CFTR activity that can be used to modulate the activity of CFTR in the cell membrane of a mammal.

[00125] There is a need for methods of treating CFTR-mediated diseases using such modulators of CFTR activity.

[00126] There is a need for methods of modulating CFTR activity in an *ex vivo* cell membrane of a mammal.

SUMMARY OF THE INVENTION

[00127] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are useful as modulators of ABC transporter activity. These compounds have the general formula (I):



or a pharmaceutically acceptable salt thereof, wherein R_1 , R_2 , R_3 , R'_3 , R_4 , and n are described herein.

[00128] These compounds and pharmaceutically acceptable compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, cystic fibrosis, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes Mellitus, Laron dwarfism, myeloperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, hereditary emphysema, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes Insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear plasy, Pick's disease, several polyglutamine neurological disorders asuch as Huntington, spinocerebullar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidolulsian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease, Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, and Sjogren's disease.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

[00129] As used herein, the following definitions shall apply unless otherwise indicated.

[00130] The term "ABC-transporter" as used herein means an ABC-transporter protein or a fragment thereof comprising at least one binding domain, wherein said protein or fragment thereof is present *in vivo* or *in vitro*. The term "binding domain" as used herein means a domain on the ABC-transporter that can bind to a modulator. See, e.g., Hwang, T. C. *et al.*, J. Gen. Physiol. (1998): 111(3), 477-90.

[00131] The term "CFTR" as used herein means cystic fibrosis transmembrane conductance regulator or a mutation thereof capable of regulator activity, including, but not limited to, $\Delta F508$ CFTR and G551D CFTR (see, e.g., <http://www.genet.sickkids.on.ca/cftr/>, for CFTR mutations).

[00132] The term "modulating" as used herein means increasing or decreasing, e.g. activity, by a measurable amount. Compounds that modulate ABC Transporter activity, such as CFTR activity, by increasing the activity of the ABC Transporter, e.g., a CFTR anion channel, are called agonists. Compounds that modulate ABC Transporter activity, such as CFTR activity, by decreasing the activity of the ABC Transporter, e.g., CFTR anion channel, are called antagonists. An agonist interacts with an ABC Transporter, such as CFTR anion channel, to increase the ability of the receptor to transduce an intracellular signal in response to endogenous ligand binding. An antagonist interacts with an ABC Transporter, such as CFTR, and competes with the endogenous ligand(s) or substrate(s) for binding site(s) on the receptor to decrease the ability of the receptor to transduce an intracellular signal in response to endogenous ligand binding.

[00133] The phrase "treating or reducing the severity of an ABC Transporter mediated disease" refers both to treatments for diseases that are directly caused by ABC Transporter and/or CFTR activities and alleviation of symptoms of diseases not directly caused by ABC Transporter and/or CFTR anion channel activities. Examples of diseases whose symptoms may be affected by ABC Transporter and/or CFTR activity include, but are not limited to, Cystic fibrosis, Hereditary emphysema, Hereditary hemochromatosis, Coagulation-Fibrinolysis deficiencies, such as Protein C deficiency, Type 1 hereditary angioedema, Lipid processing deficiencies, such as Familial hypercholesterolemia, Type 1 chylomicronemia, Abetalipoproteinemia, Lysosomal storage diseases, such as I-cell disease/Pseudo-Hurler, Mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, Polyendocrinopathy/Hyperinsulemia, Diabetes mellitus, Laron dwarfism, Myeloperoxidase deficiency, Primary hypoparathyroidism, Melanoma, Glycanosis CDG type 1, Hereditary emphysema, Congenital hyperthyroidism, Osteogenesis imperfecta, Hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), Neurophyseal DI, Neprogenic

DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders as such as Huntington, Spinocerebellar ataxia type I, Spinal and bulbar muscular atrophy, Dentatorubal pallidolusian, and Myotonic dystrophy, as well as Spongiform encephalopathies, such as Hereditary Creutzfeldt-Jakob disease, Fabry disease, Strausler-Scheinker syndrome, COPD, dry-eye disease, and Sjogren's disease.

[00134] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[00135] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001.

[00136] As used herein the term "aliphatic" encompasses the terms alkyl, alkenyl, alkynyl, each of which being optionally substituted as set forth below.

[00137] As used herein, an "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-8 (e.g., 1-6 or 1-4) carbon atoms. An alkyl group can be straight or branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-heptyl, or 2-ethylhexyl. An alkyl group can be substituted (i.e., optionally substituted) with one or more substituents such as halo, cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], heterocycloaliphatic [e.g., heterocycloalkyl or heterocycloalkenyl], aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl [e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl], nitro, cyano, amido [e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino], amino [e.g., aliphaticamino, cycloaliphaticamino, or heterocycloaliphaticamino], sulfonyl [e.g., aliphaticsulfonyl], sulfinyl,

sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, alkoxycarbonyl, alkylcarbonyloxy, or hydroxy. Without limitation, some examples of substituted alkyls include carboxyalkyl (such as HOOC-alkyl, alkoxycarbonylalkyl, and alkylcarbonyloxyalkyl), cyanoalkyl, hydroxyalkyl, alkoxyalkyl, acylalkyl, hydroxyalkyl, aralkyl, (alkoxyaryl)alkyl, (sulfonylamino)alkyl (such as (alkylsulfonylamino)alkyl), aminoalkyl, amidoalkyl, (cycloaliphatic)alkyl, cyanoalkyl, or haloalkyl.

[00138] As used herein, an “alkenyl” group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-6 or 2-4) carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to, allyl, isoprenyl, 2-butenyl, and 2-hexenyl. An alkenyl group can be optionally substituted with one or more substituents such as halo, cycloaliphatic, heterocycloaliphatic, aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl [e.g., (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl], nitro, cyano, acyl [e.g., aliphaticcarbonyl, cycloaliphaticcarbonyl, arylcarbonyl, heterocycloaliphaticcarbonyl or heteroarylcarbonyl], amido [e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl], amino [e.g., aliphaticamino, or aliphaticsulfonylamino], sulfonyl [e.g., alkylsulfonyl, cycloaliphaticsulfonyl, or arylsulfonyl], sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, alkoxycarbonyl, alkylcarbonyloxy, or hydroxy.

[00139] As used herein, an “alkynyl” group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-6 or 2-4) carbon atoms and has at least one triple bond. An alkynyl group can be straight or branched. Examples of an alkynyl group include, but are not limited to, propargyl and butynyl. An alkynyl group can be optionally substituted with one or more substituents such as aroyl, heteroaroyl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, nitro, carboxy, cyano, halo, hydroxy, sulfo, mercapto, sulfanyl [e.g., aliphatic sulfanyl or cycloaliphatic sulfanyl], sulfinyl [e.g., aliphatic sulfinyl or cycloaliphatic sulfinyl], sulfonyl [e.g., aliphatic sulfonyl, aliphaticaminosulfonyl, or cycloaliphatic sulfonyl], amido [e.g., aminocarbonyl, alkylaminocarbonyl, alkylcarbonylamino, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, cycloalkylcarbonylamino,

arylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (cycloalkylalkyl)carbonylamino, heteroaralkylcarbonylamino, heteroarylcarbonylamino or heteroarylamino, urea, thiourea, sulfamoyl, sulfamide, alkoxycarbonyl, alkylcarbonyloxy, cycloaliphatic, heterocycloaliphatic, aryl, heteroaryl, acyl [e.g., (cycloaliphatic)carbonyl or (heterocycloaliphatic)carbonyl], amino [e.g., aliphaticamino], sulfoxy, oxo, carboxy, carbamoyl, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, or (heteroaryl)alkoxy.

[00140] As used herein, an "amido" encompasses both "aminocarbonyl" and "carbonylamino". These terms when used alone or in connection with another group refers to an amido group such as $N(R^X R^Y)-C(O)-$ or $R^Y C(O)-N(R^X)-$ when used terminally and $-C(O)-N(R^X)-$ or $-N(R^X)-C(O)-$ when used internally, wherein R^X and R^Y are defined below. Examples of amido groups include alkylamido (such as alkylcarbonylamino or alkylcarbonylamino), (heterocycloaliphatic)amido, (heteroaralkyl)amido, (heteroaryl)amido, (heterocycloalkyl)alkylamido, arylamido, aralkylamido, (cycloalkyl)alkylamido, or cycloalkylamido.

[00141] As used herein, an "amino" group refers to $-NR^X R^Y$ wherein each of R^X and R^Y is independently hydrogen, alkyl, cycloaliphatic, (cycloaliphatic)aliphatic, aryl, araliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, heteroaryl, carboxy, sulfanyl, sulfinyl, sulfonyl, (aliphatic)carbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, arylcarbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, (heteroaryl)carbonyl, or (heteroaraliphatic)carbonyl, each of which being defined herein and being optionally substituted. Examples of amino groups include alkylamino, dialkylamino, or arylamino. When the term "amino" is not the terminal group (e.g., alkylcarbonylamino), it is represented by $-NR^X-$. R^X has the same meaning as defined above.

[00142] As used herein, an "aryl" group used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl" refers to monocyclic (e.g., phenyl); bicyclic (e.g., indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl); and tricyclic (e.g., fluorenyl, tetrahydrofluorenyl, or tetrahydroanthracenyl, anthracenyl) ring systems in which the monocyclic ring system is aromatic or at least one of the rings in a bicyclic or tricyclic ring system is aromatic. The bicyclic and tricyclic ring systems include benzofused 2-3 membered carbocyclic rings. For example, a benzofused group includes phenyl fused with two or more C_{4-8} carbocyclic moieties. An aryl is optionally substituted with one or more substituents including aliphatic [e.g., alkyl, alkenyl, or alkynyl]; cycloaliphatic; (cycloaliphatic)aliphatic;

heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic ring of a benzofused bicyclic or tricyclic aryl); nitro; carboxy; amido; acyl [e.g., aliphaticcarbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl]; sulfonyl [e.g., aliphaticsulfonyl or aminosulfonyl]; sulfinyl [e.g., aliphaticsulfinyl or cycloaliphaticsulfinyl]; sulfanyl [e.g., aliphatic sulfanyl]; cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, an aryl can be unsubstituted.

[00143] Non-limiting examples of substituted aryls include haloaryl [e.g., mono-, di (such as *p,m*-dihaloaryl), and (trihalo)aryl]; (carboxy)aryl [e.g., (alkoxycarbonyl)aryl, ((aralkyl)carbonyloxy)aryl, and (alkoxycarbonyl)aryl]; (amido)aryl [e.g., (aminocarbonyl)aryl, (((alkylamino)alkyl)aminocarbonyl)aryl, (alkylcarbonyl)aminoaryl, (arylaminocarbonyl)aryl, and (((heteroaryl)amino)carbonyl)aryl]; aminoaryl [e.g., ((alkylsulfonyl)amino)aryl or ((dialkyl)amino)aryl]; (cyanoalkyl)aryl; (alkoxy)aryl; (sulfamoyl)aryl [e.g., (aminosulfonyl)aryl]; (alkylsulfonyl)aryl; (cyano)aryl; (hydroxyalkyl)aryl; ((alkoxy)alkyl)aryl; (hydroxy)aryl, ((carboxy)alkyl)aryl; (((dialkyl)amino)alkyl)aryl; (nitroalkyl)aryl; (((alkylsulfonyl)amino)alkyl)aryl; ((heterocycloaliphatic)carbonyl)aryl; ((alkylsulfonyl)alkyl)aryl; (cyanoalkyl)aryl; (hydroxyalkyl)aryl; (alkylcarbonyl)aryl; alkylaryl; (trihaloalkyl)aryl; *p*-amino-*m*-alkoxycarbonylaryl; *p*-amino-*m*-cyanoaryl; *p*-halo-*m*-aminoaryl; or (*m*-(heterocycloaliphatic)-*o*-(alkyl))aryl.

[00144] As used herein, an "araliphatic" such as an "aralkyl" group refers to an aliphatic group (e.g., a C₁₋₄ alkyl group) that is substituted with an aryl group. "Aliphatic," "alkyl," and "aryl" are defined herein. An example of an araliphatic such as an aralkyl group is benzyl.

[00145] As used herein, an "aralkyl" group refers to an alkyl group (e.g., a C₁₋₄ alkyl group) that is substituted with an aryl group. Both "alkyl" and "aryl" have been defined above. An example of an aralkyl group is benzyl. An aralkyl is optionally substituted with one or more substituents such as aliphatic [e.g., alkyl, alkenyl, or alkynyl, including carboxyalkyl, hydroxyalkyl, or haloalkyl such as trifluoromethyl], cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amido

[e.g., aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, or heteroaralkylcarbonylamino], cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[00146] As used herein, a “bicyclic ring system” includes 8-12 (e.g., 9, 10, or 11) membered structures that form two rings, wherein the two rings have at least one atom in common (e.g., 2 atoms in common). Bicyclic ring systems include bicycloaliphatics (e.g., bicycloalkyl or bicycloalkenyl), bicycloheteroaliphatics, bicyclic aryls, and bicyclic heteroaryls.

[00147] As used herein, a “cycloaliphatic” group encompasses a “cycloalkyl” group and a “cycloalkenyl” group, each of which being optionally substituted as set forth below.

[00148] As used herein, a “cycloalkyl” group refers to a saturated carbocyclic mono- or bicyclic (fused or bridged) ring of 3-10 (e.g., 5-10) carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, norbornyl, cubyl, octahydro-indenyl, decahydro-naphthyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2]decyl, bicyclo[2.2.2]octyl, adamantyl, azacycloalkyl, or ((aminocarbonyl)cycloalkyl)cycloalkyl. A “cycloalkenyl” group, as used herein, refers to a non-aromatic carbocyclic ring of 3-10 (e.g., 4-8) carbon atoms having one or more double bonds. Examples of cycloalkenyl groups include cyclopentenyl, 1,4-cyclohexa-dienyl, cycloheptenyl, cyclooctenyl, hexahydro-indenyl, octahydro-naphthyl, cyclohexenyl, cyclopentenyl, bicyclo[2.2.2]octenyl, or bicyclo[3.3.1]nonenyl. A cycloalkyl or cycloalkenyl group can be optionally substituted with one or more substituents such as aliphatic [e.g., alkyl, alkenyl, or alkynyl], cycloaliphatic, (cycloaliphatic) aliphatic, heterocycloaliphatic, (heterocycloaliphatic) aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido [e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic)aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic)aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino], nitro, carboxy [e.g., HOOC-, alkoxycarbonyl, or alkylcarbonyloxy], acyl [e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic) aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl], cyano, halo, hydroxy, mercapto, sulfonyl [e.g., alkylsulfonyl and arylsulfonyl], sulfinyl [e.g., alkylsulfinyl], sulfanyl [e.g., alkylsulfanyl], sulfoxy, urea,

thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[00149] As used herein, "cyclic moiety" includes cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been defined previously.

[00150] As used herein, the term "heterocycloaliphatic" encompasses a heterocycloalkyl group and a heterocycloalkenyl group, each of which being optionally substituted as set forth below.

[00151] As used herein, a "heterocycloalkyl" group refers to a 3-10 membered mono- or bicyclic (fused or bridged) (e.g., 5- to 10-membered mono- or bicyclic) saturated ring structure, in which one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof). Examples of a heterocycloalkyl group include piperidyl, piperazyl, tetrahydropyranyl, tetrahydrofuryl, 1,4-dioxolanyl, 1,4-dithianyl, 1,3-dioxolanyl, oxazolidyl, isoxazolidyl, morpholinyl, thiomorpholyl, octahydrobenzofuryl, octahydrochromenyl, octahydrothiochromenyl, octahydroindolyl, octahydropyrindinyl, decahydroquinolinyl, octahydrobenzo[*b*]thiophenyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.0^{3,7}]nonyl. A monocyclic heterocycloalkyl group can be fused with a phenyl moiety such as tetrahydroisoquinoline. A "heterocycloalkenyl" group, as used herein, refers to a mono- or bicyclic (e.g., 5- to 10-membered mono- or bicyclic) non-aromatic ring structure having one or more double bonds, and wherein one or more of the ring atoms is a heteroatom (e.g., N, O, or S). Monocyclic and bicycloheteroaliphatics are numbered according to standard chemical nomenclature.

[00152] A heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with one or more substituents such as aliphatic [e.g., alkyl, alkenyl, or alkynyl], cycloaliphatic, (cycloaliphatic)aliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido [e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic)aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic)aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino], nitro, carboxy [e.g., HOOC-, alkoxycarbonyl, or alkylcarbonyloxy], acyl [e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl], nitro, cyano, halo, hydroxy, mercapto, sulfonyl [e.g., alkylsulfonyl or arylsulfonyl], sulfinyl [e.g., alkylsulfinyl],

sulfanyl [e.g., alkylsulfanyl], sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[00153] A "heteroaryl" group, as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system having 4 to 15 ring atoms wherein one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof) and in which the monocyclic ring system is aromatic or at least one of the rings in the bicyclic or tricyclic ring systems is aromatic. A heteroaryl group includes a benzofused ring system having 2 to 3 rings. For example, a benzofused group includes benzo fused with one or two 4 to 8 membered heterocycloaliphatic moieties (e.g., indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furyl, benzo[b]thiophenyl, quinolinyl, or isoquinolinyl). Some examples of heteroaryl are azetidiny, pyridyl, 1H-indazolyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, tetrazolyl, benzofuryl, isoquinolinyl, benzthiazolyl, xanthene, thioxanthene, phenothiazine, dihydroindole, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, puryl, cinnolyl, quinolyl, quinazolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, isoquinolyl, 4H-quinolizyl, benzo-1,2,5-thiadiazolyl, or 1,8-naphthyridyl.

[00154] Without limitation, monocyclic heteroaryls include furyl, thiophenyl, 2H-pyrrolyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4-H-pyranyl, pyridyl, pyridazyl, pyrimidyl, pyrazolyl, pyrazyl, or 1,3,5-triazyl. Monocyclic heteroaryls are numbered according to standard chemical nomenclature.

[00155] Without limitation, bicyclic heteroaryls include indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furyl, benzo[b]thiophenyl, quinolinyl, isoquinolinyl, indolizyl, isoindolyl, indolyl, benzo[b]furyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizyl, quinolyl, isoquinolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, 1,8-naphthyridyl, or pteridyl. Bicyclic heteroaryls are numbered according to standard chemical nomenclature.

[00156] A heteroaryl is optionally substituted with one or more substituents such as aliphatic [e.g., alkyl, alkenyl, or alkynyl]; cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic or heterocyclic ring of a bicyclic or tricyclic heteroaryl); carboxy; amido; acyl [e.g., aliphaticcarbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl;

or (heteroaraliphatic)carbonyl]; sulfonyl [e.g., aliphaticsulfonyl or aminosulfonyl]; sulfinyl [e.g., aliphaticsulfinyl]; sulfanyl [e.g., aliphaticsulfanyl]; nitro; cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, a heteroaryl can be unsubstituted.

[00157] Non-limiting examples of substituted heteroaryls include (halo)heteroaryl [e.g., mono- and di-(halo)heteroaryl]; (carboxy)heteroaryl [e.g., (alkoxycarbonyl)heteroaryl]; cyanoheteroaryl; aminoheteroaryl [e.g., ((alkylsulfonyl)amino)heteroaryl and((dialkyl)amino)heteroaryl]; (amido)heteroaryl [e.g., aminocarbonylheteroaryl, ((alkylcarbonyl)amino)heteroaryl, (((alkyl)amino)alkyl)aminocarbonyl)heteroaryl, (((heteroaryl)amino)carbonyl)heteroaryl, ((heterocycloaliphatic)carbonyl)heteroaryl, and ((alkylcarbonyl)amino)heteroaryl]; (cyanoalkyl)heteroaryl; (alkoxy)heteroaryl; (sulfamoyl)heteroaryl [e.g., (aminosulfonyl)heteroaryl]; (sulfonyl)heteroaryl [e.g., (alkylsulfonyl)heteroaryl]; (hydroxyalkyl)heteroaryl; (alkoxyalkyl)heteroaryl; (hydroxy)heteroaryl; ((carboxy)alkyl)heteroaryl; [((dialkyl)amino)alkyl]heteroaryl; (heterocycloaliphatic)heteroaryl; (cycloaliphatic)heteroaryl; (nitroalkyl)heteroaryl; (((alkylsulfonyl)amino)alkyl)heteroaryl; ((alkylsulfonyl)alkyl)heteroaryl; (cyanoalkyl)heteroaryl; (acyl)heteroaryl [e.g., (alkylcarbonyl)heteroaryl]; (alkyl)heteroaryl, and (haloalkyl)heteroaryl [e.g., trihaloalkylheteroaryl].

[00158] A "heteroaraliphatic" (such as a heteroaralkyl group) as used herein, refers to an aliphatic group (e.g., a C₁₋₄ alkyl group) that is substituted with a heteroaryl group. "Aliphatic," "alkyl," and "heteroaryl" have been defined above.

[00159] A "heteroaralkyl" group, as used herein, refers to an alkyl group (e.g., a C₁₋₄ alkyl group) that is substituted with a heteroaryl group. Both "alkyl" and "heteroaryl" have been defined above. A heteroaralkyl is optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[00160] As used herein, "cyclic moiety" includes cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, each of which has been defined previously.

[00161] As used herein, an "acyl" group refers to a formyl group or $R^X-C(O)-$ (such as $-alkyl-C(O)-$, also referred to as "alkylcarbonyl") where R^X and "alkyl" have been defined previously. Acetyl and pivaloyl are examples of acyl groups.

[00162] As used herein, an "aroyl" or "heteroaroyl" refers to an $aryl-C(O)-$ or a $heteroaryl-C(O)-$. The aryl and heteroaryl portion of the aroyl or heteroaroyl is optionally substituted as previously defined.

[00163] As used herein, an "alkoxy" group refers to an $alkyl-O-$ group where "alkyl" has been defined previously.

[00164] As used herein, a "carbamoyl" group refers to a group having the structure $-O-CO-NR^X R^Y$ or $-NR^X-CO-O-R^Z$ wherein R^X and R^Y have been defined above and R^Z can be aliphatic, aryl, araliphatic, heterocycloaliphatic, heteroaryl, or heteroaraliphatic.

[00165] As used herein, a "carboxy" group refers to $-COOH$, $-COOR^X$, $-OC(O)H$, $-OC(O)R^X$ when used as a terminal group; or $-OC(O)-$ or $-C(O)O-$ when used as an internal group.

[00166] As used herein, a "haloaliphatic" group refers to an aliphatic group substituted with 1, 2, or 3 halogen. For instance, the term haloalkyl includes the group $-CF_3$.

[00167] As used herein, a "mercapto" group refers to $-SH$.

[00168] As used herein, a "sulfo" group refers to $-SO_3H$ or $-SO_3R^X$ when used terminally or $-S(O)_3-$ when used internally.

[00169] As used herein, a "sulfamide" group refers to the structure $-NR^X-S(O)_2-NR^Y R^Z$ when used terminally and $-NR^X-S(O)_2-NR^Y-$ when used internally, wherein R^X , R^Y , and R^Z have been defined above.

[00170] As used herein, a "sulfamoyl" group refers to the structure $-S(O)_2-NR^X R^Y$ or $-NR^X-S(O)_2-R^Z$ when used terminally; or $-S(O)_2-NR^X-$ or $-NR^X-S(O)_2-$ when used internally, wherein R^X , R^Y , and R^Z are defined above.

[00171] As used herein a "sulfanyl" group refers to $-S-R^X$ when used terminally and $-S-$ when used internally, wherein R^X has been defined above. Examples of sulfanyls include alkylsulfanyl.

[00172] As used herein a "sulfinyl" group refers to $-S(O)-R^X$ when used terminally and $-S(O)-$ when used internally, wherein R^X has been defined above.

[00173] As used herein, a "sulfonyl" group refers to $-S(O)_2-R^X$ when used terminally and $-S(O)_2-$ when used internally, wherein R^X has been defined above.

[00174] As used herein, a "sulfoxy" group refers to $-O-SO-R^X$ or $-SO-O-R^X$, when used terminally and $-O-S(O)-$ or $-S(O)-O-$ when used internally, where R^X has been defined above.

[00175] As used herein, a "halogen" or "halo" group refers to fluorine, chlorine, bromine or iodine.

[00176] As used herein, an "alkoxycarbonyl," which is encompassed by the term carboxy, used alone or in connection with another group refers to a group such as alkyl- $O-C(O)-$.

[00177] As used herein, an "alkoxyalkyl" refers to an alkyl group such as alkyl- O -alkyl-, wherein alkyl has been defined above.

[00178] As used herein, a "carbonyl" refer to $-C(O)-$.

[00179] As used herein, an "oxo" refers to $=O$.

[00180] As used herein, an "aminoalkyl" refers to the structure $(R^X R^Y)N$ -alkyl-.

[00181] As used herein, a "cyanoalkyl" refers to the structure (NC) -alkyl-.

[00182] As used herein, a "urea" group refers to the structure $-NR^X-CO-NR^Y R^Z$ and a "thiourea" group refers to the structure $-NR^X-CS-NR^Y R^Z$ when used terminally and $-NR^X-CO-NR^Y-$ or $-NR^X-CS-NR^Y-$ when used internally, wherein R^X , R^Y , and R^Z have been defined above.

[00183] As used herein, a "guanidino" group refers to the structure $-N=C(N(R^X R^Y))N(R^X R^Y)$ wherein R^X and R^Y have been defined above.

[00184] As used herein, the term "amidino" group refers to the structure $-C=(NR^X)N(R^X R^Y)$ wherein R^X and R^Y have been defined above.

[00185] In general, the term "vicinal" refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to adjacent carbon atoms.

[00186] In general, the term "geminal" refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to the same

carbon atom.

[00187] The terms "terminally" and "internally" refer to the location of a group within a substituent. A group is terminal when the group is present at the end of the substituent not further bonded to the rest of the chemical structure. Carboxyalkyl, i.e., $R^XO(O)C$ -alkyl is an example of a carboxy group used terminally. A group is internal when the group is present in the middle of a substituent to at the end of the substituent bound to the rest of the chemical structure. Alkylcarboxy (e.g., alkyl- $C(O)O$ - or alkyl- $OC(O)$ -) and alkylcarboxyaryl (e.g., alkyl- $C(O)O$ -aryl- or alkyl- $O(CO)$ -aryl-) are examples of carboxy groups used internally.

[00188] As used herein, the term "amidino" group refers to the structure $-C=(NR^X)N(R^XR^Y)$ wherein R^X and R^Y have been defined above.

[00189] As used herein, "cyclic group" includes mono-, bi-, and tri-cyclic ring systems including cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been previously defined.

[00190] As used herein, a "bridged bicyclic ring system" refers to a bicyclic heterocycloaliphatic ring system or bicyclic cycloaliphatic ring system in which the rings are bridged. Examples of bridged bicyclic ring systems include, but are not limited to, adamantanyl, norbornanyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.2.3]nonyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.0^{3,7}]nonyl. A bridged bicyclic ring system can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[00191] As used herein, an "aliphatic chain" refers to a branched or straight aliphatic group (e.g., alkyl groups, alkenyl groups, or alkynyl groups). A straight aliphatic chain has the structure $-[CH_2]_v-$, where v is 1-6. A branched aliphatic chain is a straight aliphatic chain that is substituted with one or more aliphatic groups. A branched aliphatic chain

has the structure $-\text{[CHQ]}_n-$ where Q is hydrogen or an aliphatic group; however, Q shall be an aliphatic group in at least one instance. The term aliphatic chain includes alkyl chains, alkenyl chains, and alkynyl chains, where alkyl, alkenyl, and alkynyl are defined above.

[00192] The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." As described herein, compounds of the invention can optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. As described herein, the variables R_1 , R_2 , R_3 , and R_4 , and other variables contained therein formulae I encompass specific groups, such as alkyl and aryl. Unless otherwise noted, each of the specific groups for the variables R_1 , R_2 , R_3 , and R_4 , and other variables contained therein can be optionally substituted with one or more substituents described herein. Each substituent of a specific group is further optionally substituted with one to three of halo, cyano, oxoalkoxy, hydroxy, amino, nitro, aryl, haloalkyl, and alkyl. For instance, an alkyl group can be substituted with alkylsulfanyl and the alkylsulfanyl can be optionally substituted with one to three of halo, cyano, oxoalkoxy, hydroxy, amino, nitro, aryl, haloalkyl, and alkyl. As an additional example, the cycloalkyl portion of a (cycloalkyl)carbonylamino can be optionally substituted with one to three of halo, cyano, alkoxy, hydroxy, nitro, haloalkyl, and alkyl. When two alkoxy groups are bound to the same atom or adjacent atoms, the two alkoxy groups can form a ring together with the atom(s) to which they are bound.

[00193] In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, can be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[00194] The phrase "up to", as used herein, refers to zero or any integer number that is equal or less than the number following the phrase. For example, "up to 3" means any one of 0, 1, 2, and 3.

[00195] The phrase “stable or chemically feasible,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40° C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[00196] As used herein, an effective amount is defined as the amount required to confer a therapeutic effect on the treated patient, and is typically determined based on age, surface area, weight, and condition of the patient. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich et al., *Cancer Chemother. Rep.*, 50: 219 (1966). Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, New York, 537 (1970). As used herein, “patient” refers to a mammal, including a human.

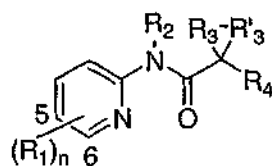
[00197] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

COMPOUNDS

[00198] Compounds of the present invention are useful modulators of ABC transporters and are useful in the treatment of ABC transport mediated diseases.

A. Generic Compounds

[00199] The present invention includes a compound of formula (I),



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Each R_1 is an optionally substituted C_{1-6} aliphatic, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted C_{3-10} cycloaliphatic, an optionally substituted 3 to 10 membered heterocycloaliphatic, carboxy [e.g., hydroxycarbonyl or alkoxycarbonyl], amido [e.g., aminocarbonyl], amino, halo, or hydroxy;

provided that at least one R_1 is an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl attached to the 5- or 6- position of the pyridyl ring;

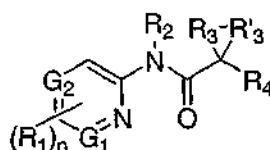
Each R_2 is hydrogen, an optionally substituted C_{1-6} aliphatic, an optionally substituted C_{3-6} cycloaliphatic, an optionally substituted phenyl, or an optionally substituted heteroaryl;

Each R_3 and R'_3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7} cycloaliphatic or an optionally substituted heterocycloaliphatic;

Each R_4 is an optionally substituted aryl or an optionally substituted heteroaryl; and

Each n is 1, 2, 3 or 4.

[00200] In another aspect, the present invention includes compounds of formula (I'):



or a pharmaceutically acceptable salt thereof,

wherein:

one of G_1 and G_2 is a nitrogen, and the other is a carbon; and

R_1 , R_2 , R_3 , R'_3 , R_4 , and n are defined above.

Specific Embodiments

A. Substituent R_1

[00201] Each R_1 is independently an optionally substituted C_{1-6} aliphatic, an

optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted C₃₋₁₀ membered cycloaliphatic, an optionally substituted 3 to 10 membered heterocycloaliphatic, carboxy [e.g., hydroxycarbonyl or alkoxycarbonyl], amido [e.g., aminocarbonyl], amino, halo, or hydroxy.

[00202] In some embodiments, one R₁ is an optionally substituted C₁₋₆ aliphatic. In several examples, one R₁ is an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, or an optionally substituted C₂₋₆ alkynyl. In several examples, one R₁ is C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl.

[00203] In several embodiments, one R₁ is an aryl or heteroaryl with 1, 2, or 3 substituents. In several examples, one R₁ is a monocyclic aryl or heteroaryl. In several embodiments, R₁ is an aryl or heteroaryl with 1, 2, or 3 substituents. In several examples, R₁ is a monocyclic aryl or heteroaryl.

[00204] In several embodiments, at least one R₁ is an optionally substituted aryl or an optionally substituted heteroaryl and R₁ is bonded to the core structure at the 6 position on the pyridine ring.

[00205] In several embodiments, at least one R₁ is an optionally substituted aryl or an optionally substituted heteroaryl and R₁ is bonded to the core structure at the 5 position on the pyridine ring.

[00206] In several embodiments, one R₁ is phenyl with up to 3 substituents. In several embodiments, R₁ is phenyl with up to 3 substituents.

[00207] In several embodiments, one R₁ is a heteroaryl ring with up to 3 substituents. In certain embodiments, one R₁ is a monocyclic heteroaryl ring with up to 3 substituents. In other embodiments, one R₁ is a bicyclic heteroaryl ring with up to 3 substituents. In several embodiments, R₁ is a heteroaryl ring with up to 3 substituents. In certain embodiments, R₁ is a monocyclic heteroaryl ring with up to 3 substituents. In other embodiments, R₁ is a bicyclic heteroaryl ring with up to 3 substituents.

[00208] In several embodiments, one R₁ is carboxy [e.g., hydroxycarbonyl or alkoxycarbonyl]. Or, one R₁ is amido [e.g., aminocarbonyl]. Or, one R₁ is amino. Or, is halo. Or, is cyano. Or, hydroxyl.

[00209] In some embodiments, R₁ is hydrogen, methyl, ethyl, i-propyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, allyl, F, Cl, methoxy, ethoxy, i-propoxy, t-butoxy, CF₃, OCF₃, CN, hydroxyl, or amino. In several examples, R₁ is hydrogen, methyl,

methoxy, F, CF₃ or OCF₃. In several examples, R₁ can be hydrogen. Or, R₁ can be methyl. Or, R₁ can be CF₃. Or, R₁ can be methoxy.

[00210] In several embodiments, R₁ is substituted with no more than three substituents selected from halo, oxo, or optionally substituted aliphatic, cycloaliphatic, heterocycloaliphatic, amino [e.g., (aliphatic)amino], amido [e.g., aminocarbonyl, ((aliphatic)amino)carbonyl, and ((aliphatic)₂amino)carbonyl], carboxy [e.g., alkoxycarbonyl and hydroxycarbonyl], sulfamoyl [e.g., aminosulfonyl, ((aliphatic)₂amino)sulfonyl, ((cycloaliphatic)aliphatic)aminosulfonyl, and ((cycloaliphatic)amino)sulfonyl], cyano, alkoxy, aryl, heteroaryl [e.g., monocyclic heteroaryl and bicycloheteroaryl], sulfonyl [e.g., aliphaticsulfonyl or (heterocycloaliphatic)sulfonyl], sulfinyl [e.g., aliphaticsulfinyl], aroyl, heteroaroyl, or heterocycloaliphaticcarbonyl.

[00211] In several embodiments, R₁ is substituted with halo. Examples of R₁ substituents include F, Cl, and Br. In several examples, R₁ is substituted with F.

[00212] In several embodiments, R₁ is substituted with an optionally substituted aliphatic. Examples of R₁ substituents include optionally substituted alkoxyaliphatic, heterocycloaliphatic, aminoalkyl, hydroxyalkyl, (heterocycloalkyl)aliphatic, alkylsulfonylaliphatic, alkylsulfonylaminoaliphatic, alkylcarbonylaminoaliphatic, alkylaminoaliphatic, or alkylcarbonylaliphatic.

[00213] In several embodiments, R₁ is substituted with an optionally substituted amino. Examples of R₁ substituents include aliphaticcarbonylamino, aliphaticamino, arylamino, or aliphaticsulfonylamino.

[00214] In several embodiments, R₁ is substituted with a sulfonyl. Examples of R₁ substituents include heterocycloaliphaticsulfonyl, aliphatic sulfonyl, aliphaticaminosulfonyl, aminosulfonyl, aliphaticcarbonylaminosulfonyl, alkoxyalkylheterocycloalkylsulfonyl, alkylheterocycloalkylsulfonyl, alkylaminosulfonyl, cycloalkylaminosulfonyl, (heterocycloalkyl)alkylaminosulfonyl, and heterocycloalkylsulfonyl.

[00215] In several embodiments, R₁ is substituted with carboxy. Examples of R₁ substituents include alkoxycarbonyl and hydroxycarbonyl.

[00216] In several embodiments R₁ is substituted with amido. Examples of R₁ substituents include alkylaminocarbonyl, aminocarbonyl, ((aliphatic)₂amino)carbonyl, and [((aliphatic)aminoaliphatic)amino]carbonyl.

[00217] In several embodiments, R₁ is substituted with carbonyl. Examples of R₁

substituents include arylcarbonyl, cycloaliphaticcarbonyl, heterocycloaliphaticcarbonyl, and heteroarylcarbonyl.

[00218] In some embodiments, R_1 is hydrogen. In some embodiments, R_1 is $Z^A R_5$, wherein each Z^A is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^A are optionally and independently replaced by $-CO-$, $-CS-$, $-CONR^A-$, $-CONR^A NR^A-$, $-CO_2-$, $-OCO-$, $-NR^A CO_2-$, $-O-$, $-NR^A CONR^A-$, $-OCONR^A-$, $-NR^A NR^A-$, $-NR^A CO-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^A-$, $-SO_2 NR^A-$, $-NR^A SO_2-$, or $-NR^A SO_2 NR^A-$. Each R_5 is independently R^A , halo, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-CF_3$, or $-OCF_3$. Each R^A is independently a C_{1-8} aliphatic group, a cycloaliphatic, a heterocycloaliphatic, an aryl, or a heteroaryl, each of which is optionally substituted with 1, 2, or 3 of R^D . Each R^D is $-Z^D R_9$, wherein each Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-CO-$, $-CS-$, $-CONR^E-$, $-CONR^E NR^E-$, $-CO_2-$, $-OCO-$, $-NR^E CO_2-$, $-O-$, $-NR^E CONR^E-$, $-OCONR^E-$, $-NR^E NR^E-$, $-NR^E CO-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^E-$, $-SO_2 NR^E-$, $-NR^E SO_2-$, or $-NR^E SO_2 NR^E-$. Each R_9 is independently R^E , halo, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-CF_3$, or $-OCF_3$. Each R^E is independently hydrogen, an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

[00219] In some embodiments, each R^D is independently $-Z^D R_9$; wherein each Z^D can independently be a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-O-$, $-NHC(O)-$, $-C(O)NR^E-$, $-SO_2-$, $-NH SO_2-$, $-NHC(O)-$, $-NR^E SO_2-$, $-SO_2 NH-$, $-SO_2 NR^E-$, $-NH-$, or $-C(O)O-$. In some embodiments, one carbon unit of Z^D is replaced by $-O-$. Or, by $-NHC(O)-$. Or, by $-C(O)NR^E-$. Or, by $-SO_2-$. Or, by $-NH SO_2-$. Or, by $-NHC(O)-$. Or, by $-SO-$. Or, by $-NR^E SO_2-$. Or, by $-SO_2 NH-$. Or, by $-SO_2 NR^E-$. Or, by $-NH-$. Or, by $-C(O)O-$.

[00220] In some embodiments, R_9 is hydrogen. In some embodiments, R_9 is independently an optionally substituted aliphatic. In some embodiments, R_9 is an optionally substituted cycloaliphatic. Or, is an optionally substituted heterocycloaliphatic. Or, is an optionally substituted aryl. Or, is an optionally substituted heteroaryl. Or, halo.

[00221] In some embodiments, one R_1 is aryl or heteroaryl, each optionally substituted with 1, 2, or 3 of R^D , wherein R^D is defined above.

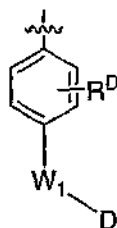
[00222] In several embodiments, one R_1 is carboxy [e.g., hydroxycarbonyl or alkoxy carbonyl]. Or, one R_1 is amido [e.g., aminocarbonyl]. Or, one R_1 is amino. Or, is halo.

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Or, is cyano. Or, hydroxyl.

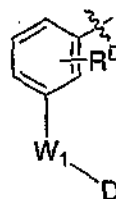
[00223] In some embodiments, one R_1 that is attached to 5- or 6- position of the pyridyl ring is aryl or heteroaryl, each optionally substituted with 1, 2, or 3 of R^D , wherein R^D is defined above. In some embodiments, the one R_1 attached to the 5- or 6- position of the pyridyl ring is phenyl optionally substituted with 1, 2, or 3 of R^D , wherein R^D is defined above. In some embodiments, the one R_1 attached to the 5- or 6- position of the pyridyl ring is heteroaryl optionally substituted with 1, 2, or 3 of R^D . In several embodiments, the one R_1 attached to the 5- or 6- position of the pyridyl ring is 5 or 6 membered heteroaryl having 1, 2, or 3 heteroatom independently selected from the group consisting of oxygen, nitrogen and sulfur. In other embodiments, the 5 or 6 membered heteroaryl is substituted with 1 R^D .

[00224] In some embodiments, one R_1 attached to the 5- or 6- position of the pyridyl ring is a phenyl substituted with 1 R^D . In some embodiments, one R_1 attached to the 5- or 6- position of the pyridyl ring is a phenyl substituted with 2 R^D . In some embodiments, one R_1 attached to the 5- or 6- position of the pyridyl ring is a phenyl substituted with 3 R^D .

[00225] In several embodiments, R_1 is:



(Z-1),



or (Z-2).

wherein

W_1 is $-C(O)-$, $-SO_2-$, or $-CH_2-$;

D is H, hydroxyl, or an optionally substituted group selected from aliphatic, cycloaliphatic, alkoxy, and amino; and

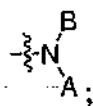
R^D is defined above.

[00226] In several embodiments, W_1 is $-C(O)-$. Or, W_1 is $-SO_2-$. Or, W_1 is $-CH_2-$.

[00227] In several embodiments, D is OH. Or, D is an optionally substituted C_{1-6} aliphatic or an optionally substituted C_3-C_8 cycloaliphatic. Or, D is an optionally substituted alkoxy. Or, D is an optionally substituted amino.

[00228]

In several examples, D is



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wherein each of A and B is independently H, an optionally substituted C₁₋₆ aliphatic, an optionally substituted C₃₋₈ cycloaliphatic, or

A and B, taken together, form an optionally substituted 3-7 membered heterocycloaliphatic ring.

[00229] In several embodiments, A is H and B is an optionally substituted C₁₋₆ aliphatic. In several embodiments, B is substituted with 1, 2, or 3 substituents. Or, both, A and B, are H. Exemplary substituents include oxo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, dialkylamino, or an optionally substituted group selected from cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl.

[00230] In several embodiments, A is H and B is an optionally substituted C₁₋₆ aliphatic. Or, both, A and B, are H. Exemplary substituents include oxo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, and an optionally substituted heterocycloaliphatic.

[00231] In several embodiments, B is C₁₋₆ alkyl, optionally substituted with oxo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, or an optionally substituted group selected from cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl. In several embodiments, B is substituted with oxo, C₁₋₆ alkyl, hydroxy, hydroxy-(C₁₋₆)alkyl, (C₁₋₆)alkoxy, (C₁₋₆)alkoxy(C₁₋₆)alkyl, C₃₋₈ cycloaliphatic, 3-8 membered heterocycloaliphatic, phenyl, and 5-10 membered heteroaryl. In one example, B is C₁₋₆ alkyl substituted with optionally substituted phenyl.

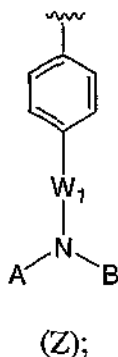
[00232] In several embodiments, A and B, taken together, form an optionally substituted 3-7 membered heterocycloaliphatic ring. In several examples, the heterocycloaliphatic ring is optionally substituted with 1, 2, or 3 substituents. Exemplary such rings include optionally substituted pyrrolidinyl, piperidinyl, morpholinyl, and piperazinyl. Exemplary substituents on such rings include halo, oxo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, acyl (e.g., alkylcarbonyl), amino, amido, and carboxy. In some embodiments, the substituent is halo, oxo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, amido, or carboxy.

[00233] In several embodiments, R^D is hydrogen, halo, or an optionally substituted group selected from aliphatic, cycloaliphatic, amino, hydroxy, alkoxy, carboxy, amido, carbonyl, cyano, aryl, or heteroaryl. In several examples, R^D is hydrogen, halo, an optionally substituted C₁₋₆ aliphatic, or an optionally substituted alkoxy. In several examples, R^D is hydrogen, F, Cl, an optionally substituted C₁₋₆ alkyl, or an optionally substituted -O(C₁₋₆ alkyl). Examples of R^D include hydrogen, F, Cl, methyl, ethyl, *i*-propyl, *t*-butyl, -OMe, -OEt, *i*-propoxy, *t*-butoxy, CF₃, or -OCF₃. In some examples, R^D is hydrogen, F, methyl, methoxy, CF₃,

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or -OCF₃. R^D can be hydrogen. R^D can be F. R^D can be methyl. R^D can be methoxy.

[00234] In several embodiments, R₁ is:



wherein:

W₁ is -C(O)-, -SO₂-, or -CH₂-;

Each of A and B is independently H, an optionally substituted C₁₋₆ aliphatic, an optionally substituted C₃₋₈ cycloaliphatic; or

A and B, taken together, form an optionally substituted 3-7 membered heterocycloaliphatic ring.

[00235] In some embodiments, one R₁ that is attached to the 5- or 6- position of the pyridyl ring is cycloaliphatic or heterocycloaliphatic, each optionally substituted with 1, 2, or 3 of R^D, wherein R^D is -Z^DR₉; wherein each Z^D is independently a bond or an optionally substituted branched or straight C₁₋₆ aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by -CO-, -CS-, -CONR^E-, -CONR^ENR^E-, -CO₂-, -OCO-, -NR^ECO₂-, -O-, -NR^ECONR^E-, -OCONR^E-, -NR^ENR^E-, -NR^ECO-, -S-, -SO-, -SO₂-, -NR^E-, -SO₂NR^E-, -NR^ESO₂-, or -NR^ESO₂NR^E-; each R₉ is independently R^E, halo, -OH, -NH₂, -NO₂, -CN, -CF₃, or -OCF₃; and each R^E is independently hydrogen, an optionally substituted C₁₋₈ aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

[00236] In several examples, one R₁ that is attached to the 5- or 6- position of the pyridyl ring is an optionally substituted C₃₋₈ cycloaliphatic.

[00237] In some embodiments, one R₁ that is attached to the 5- or 6- position of the pyridyl ring is an optionally substituted C₃₋₈ cycloalkyl or an optionally substituted C₃₋₈ cycloalkenyl.

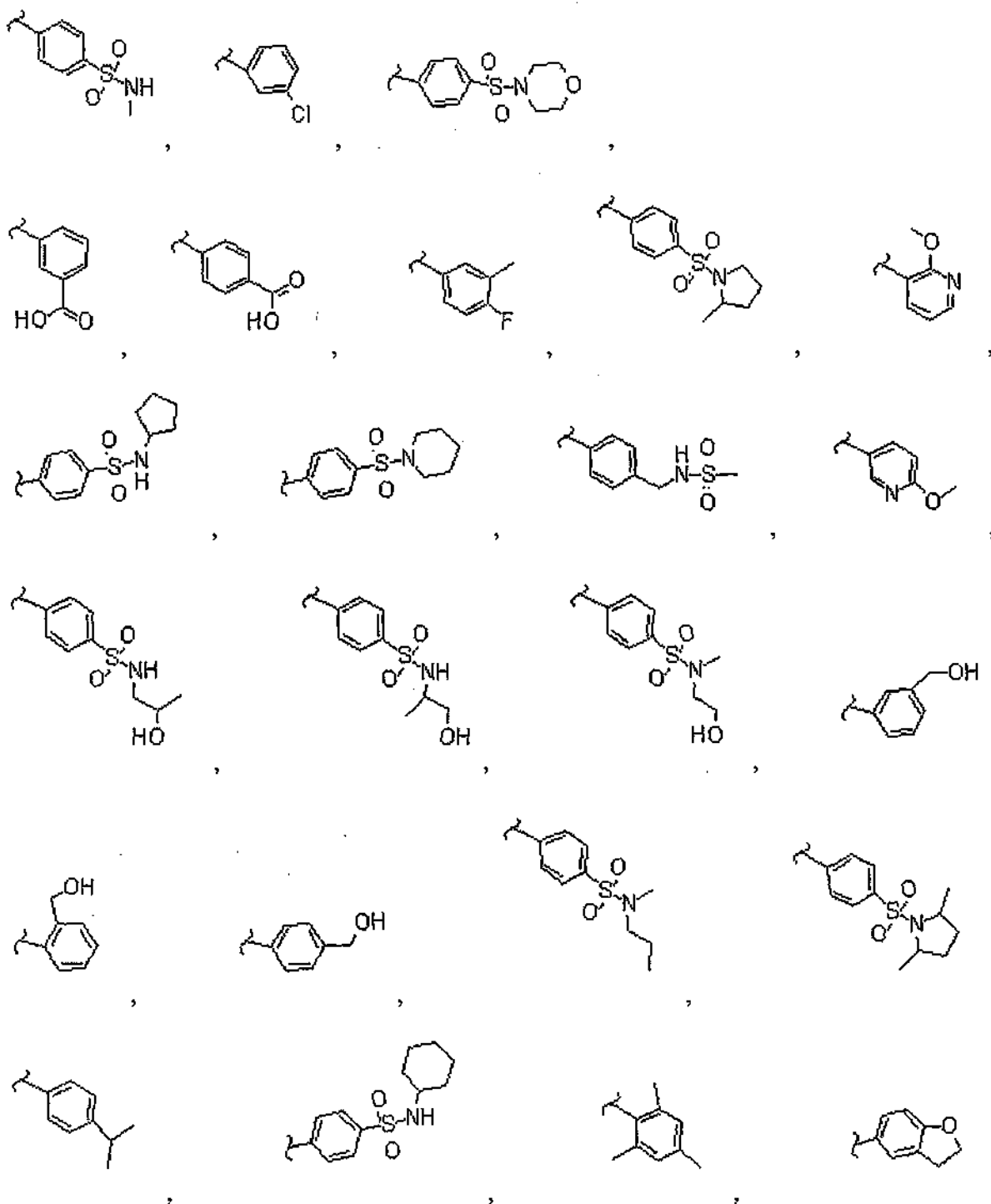
[00238] In several embodiments, one R₁ that is attached to the 5- or 6- position of the pyridyl ring is C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl. Examples of cycloalkyl and cycloalkenyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,

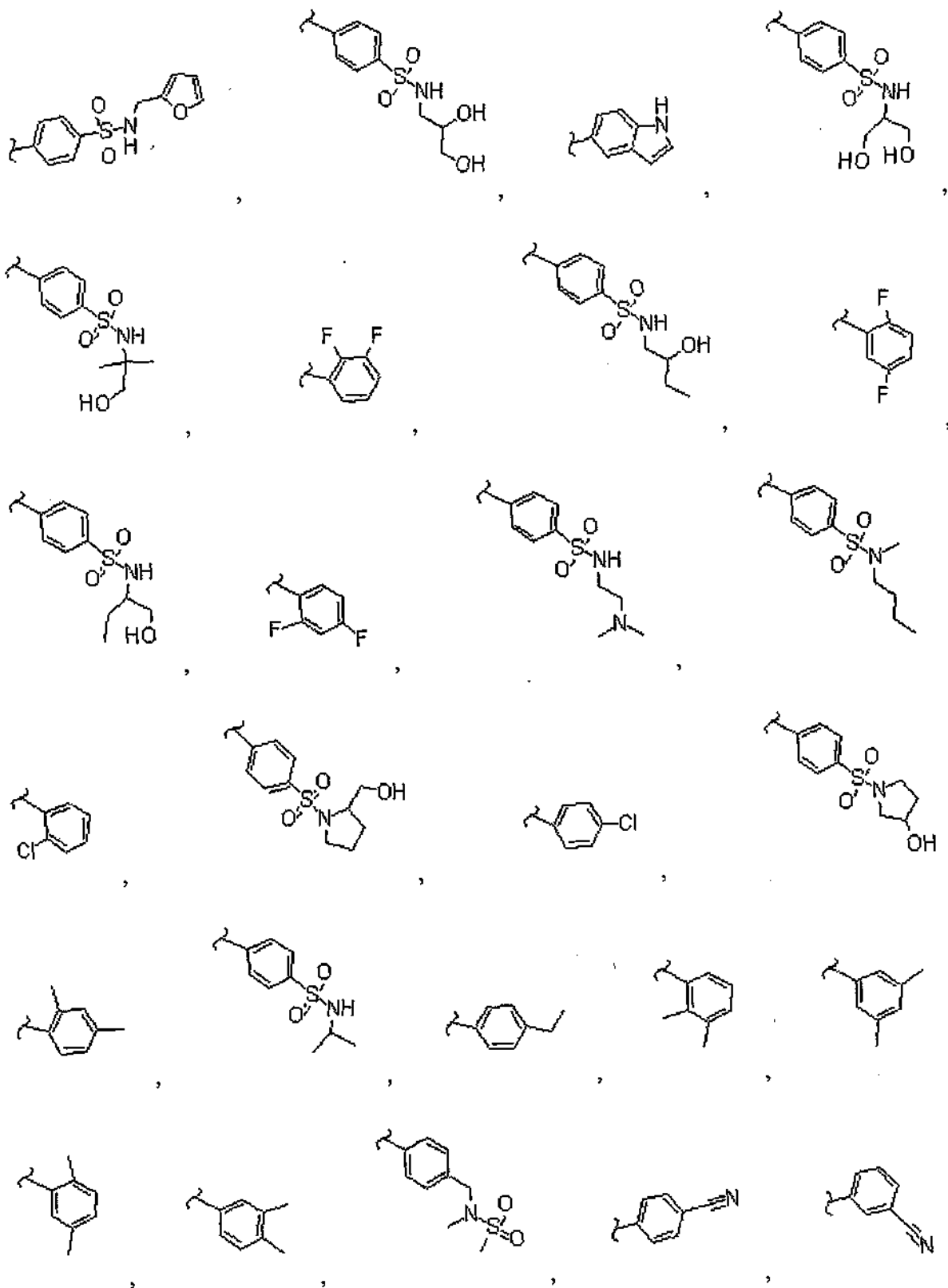
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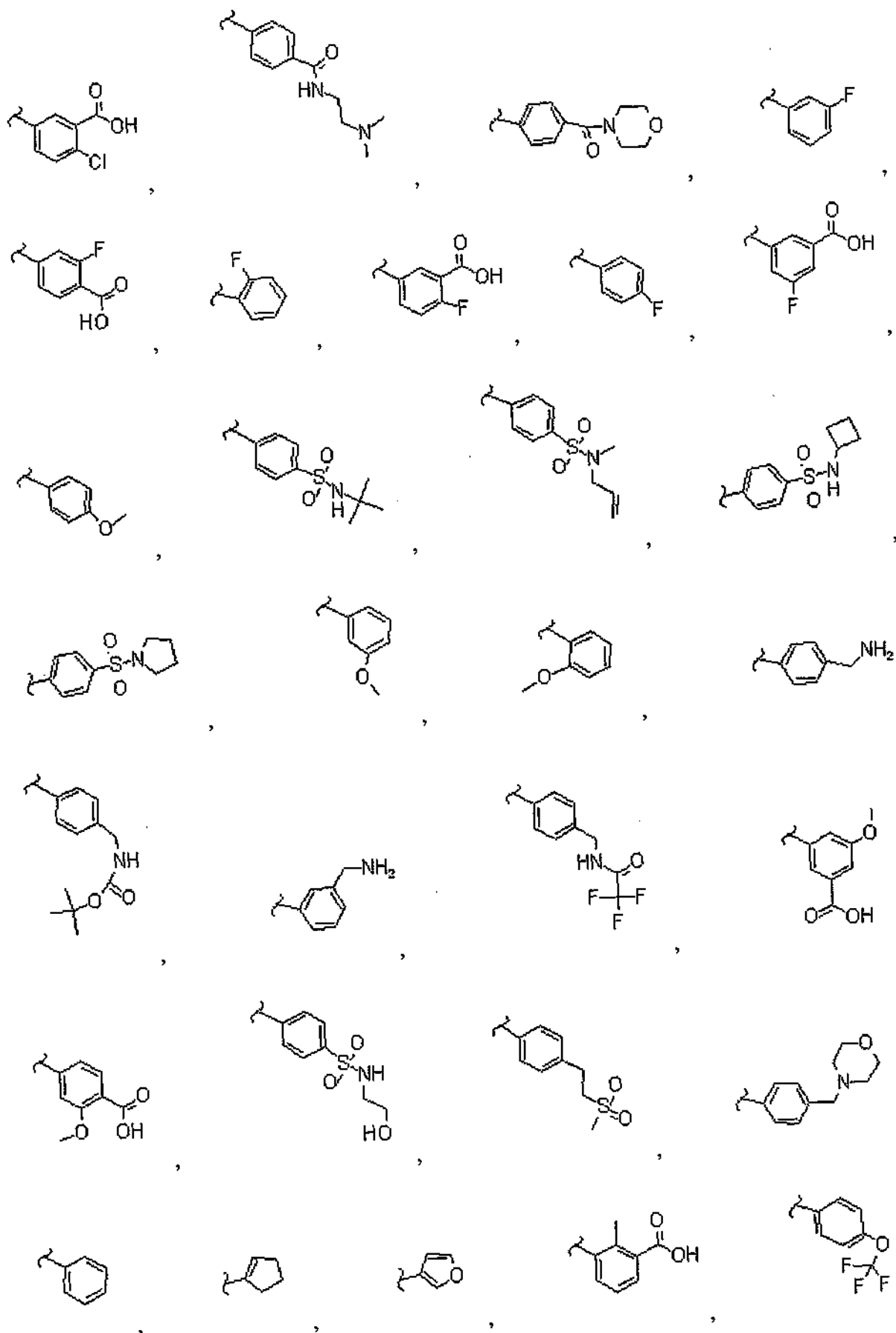
cyclopentenyl, cyclohexenyl, and cycloheptenyl.

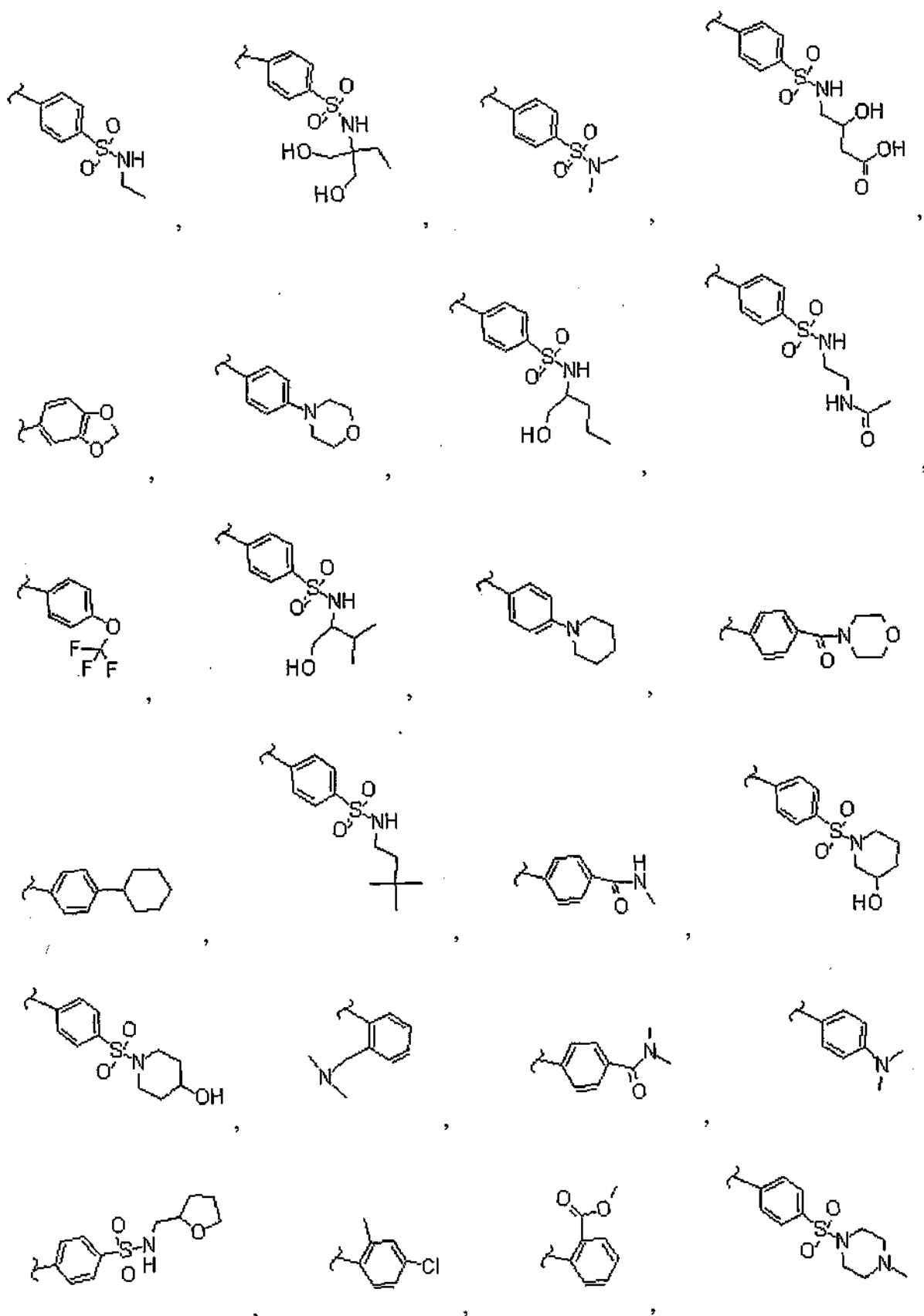
[00239]

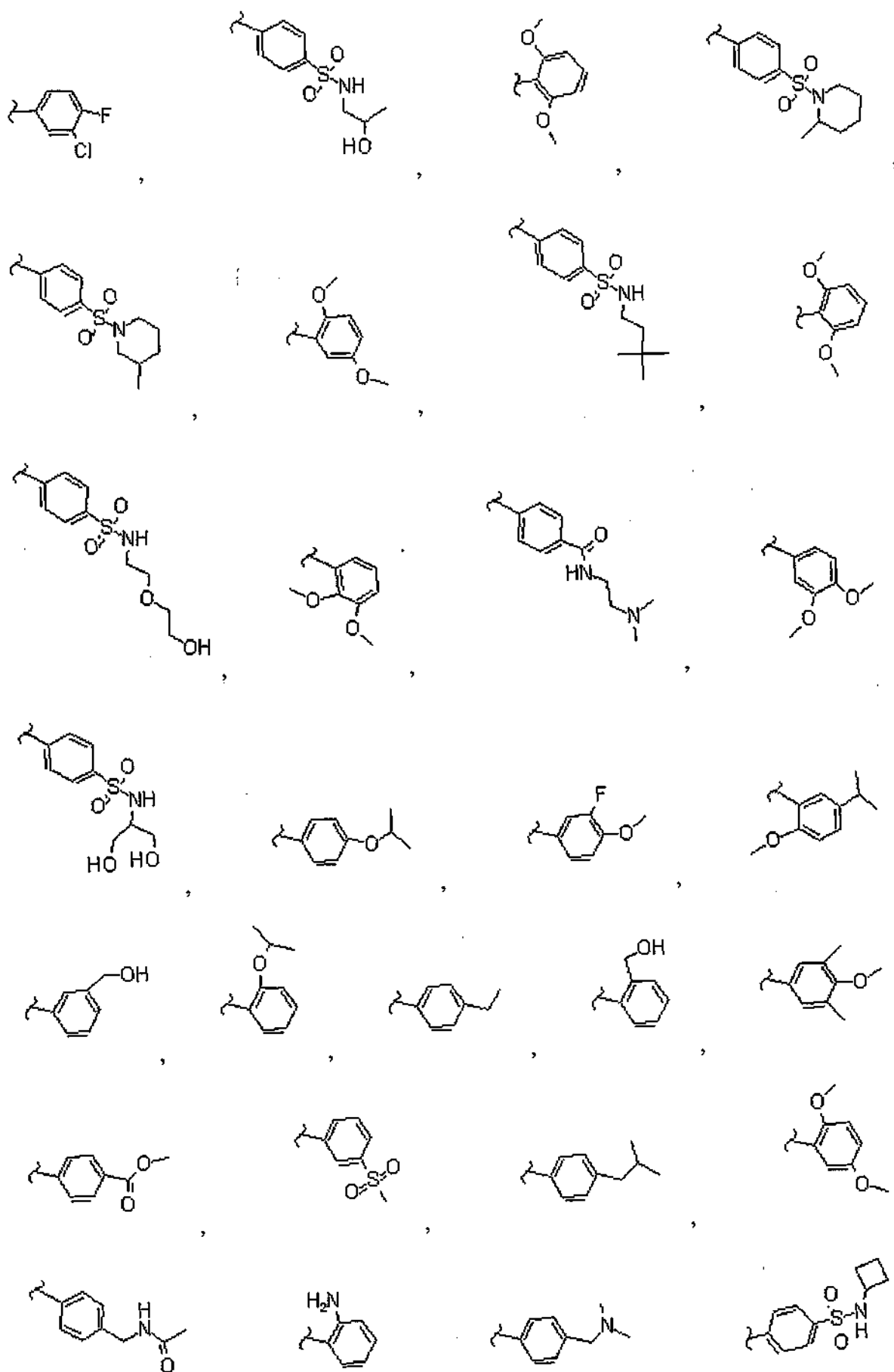
In some embodiments, R1 is:

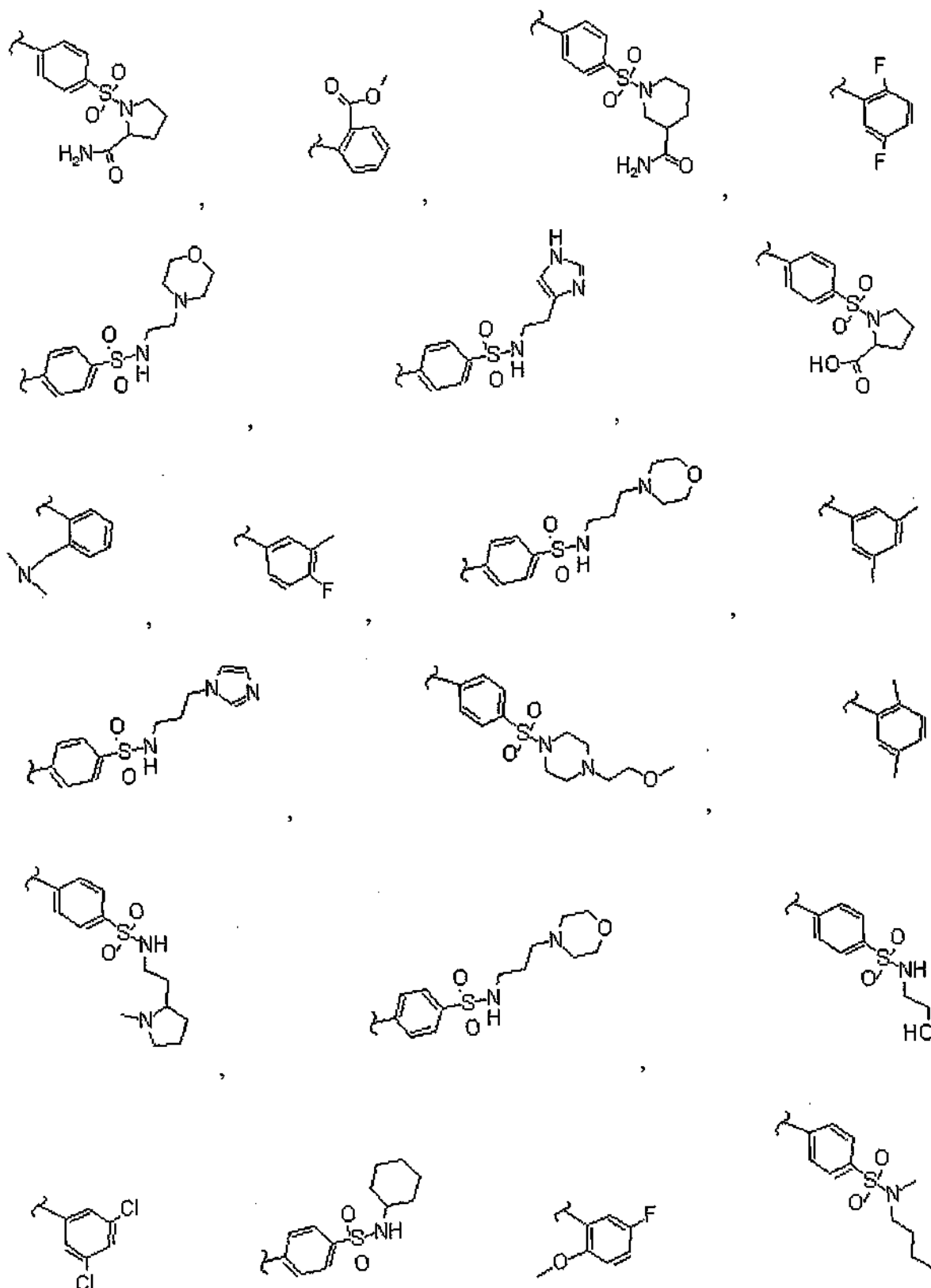


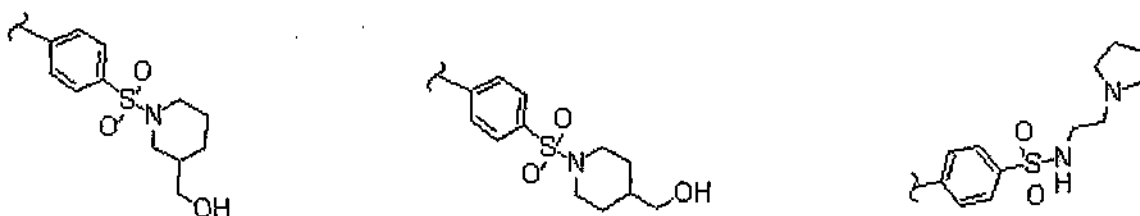
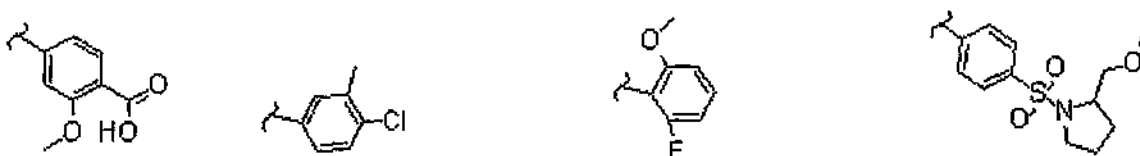
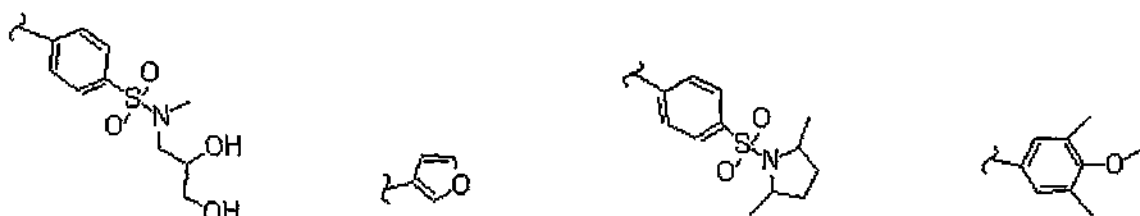
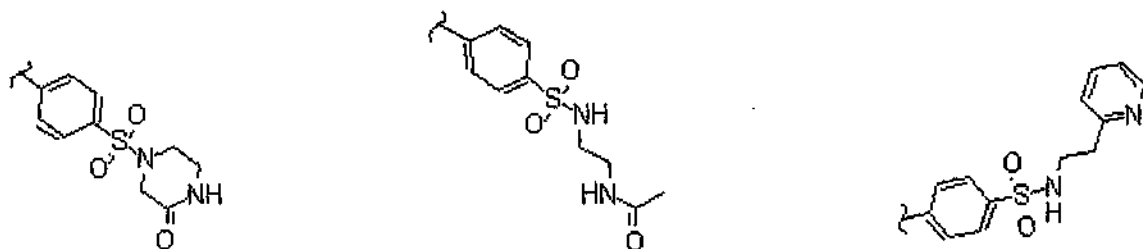
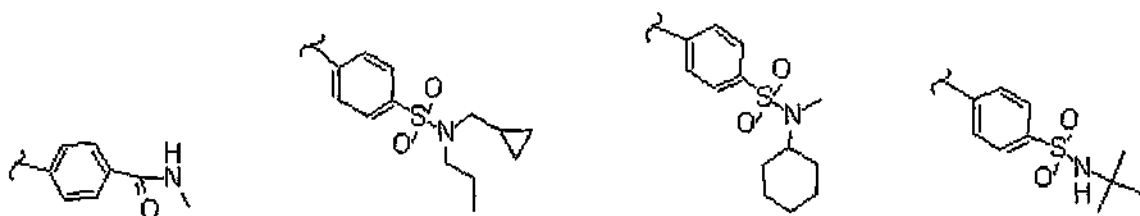


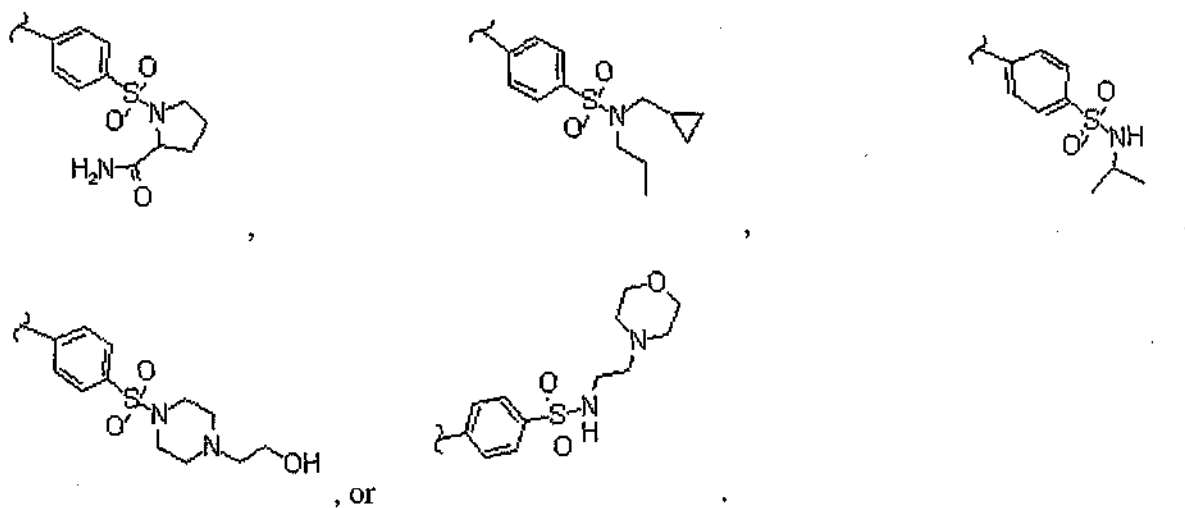




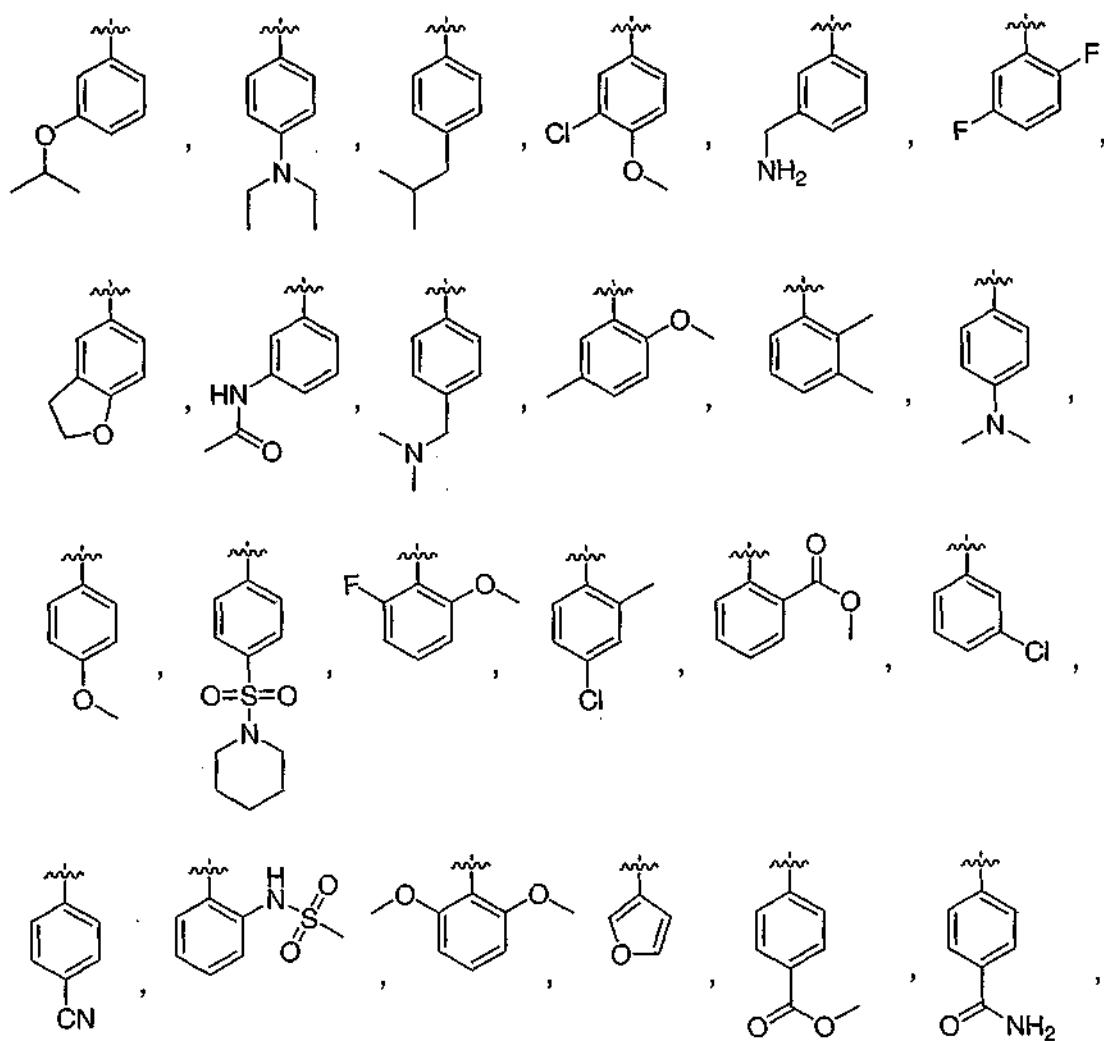






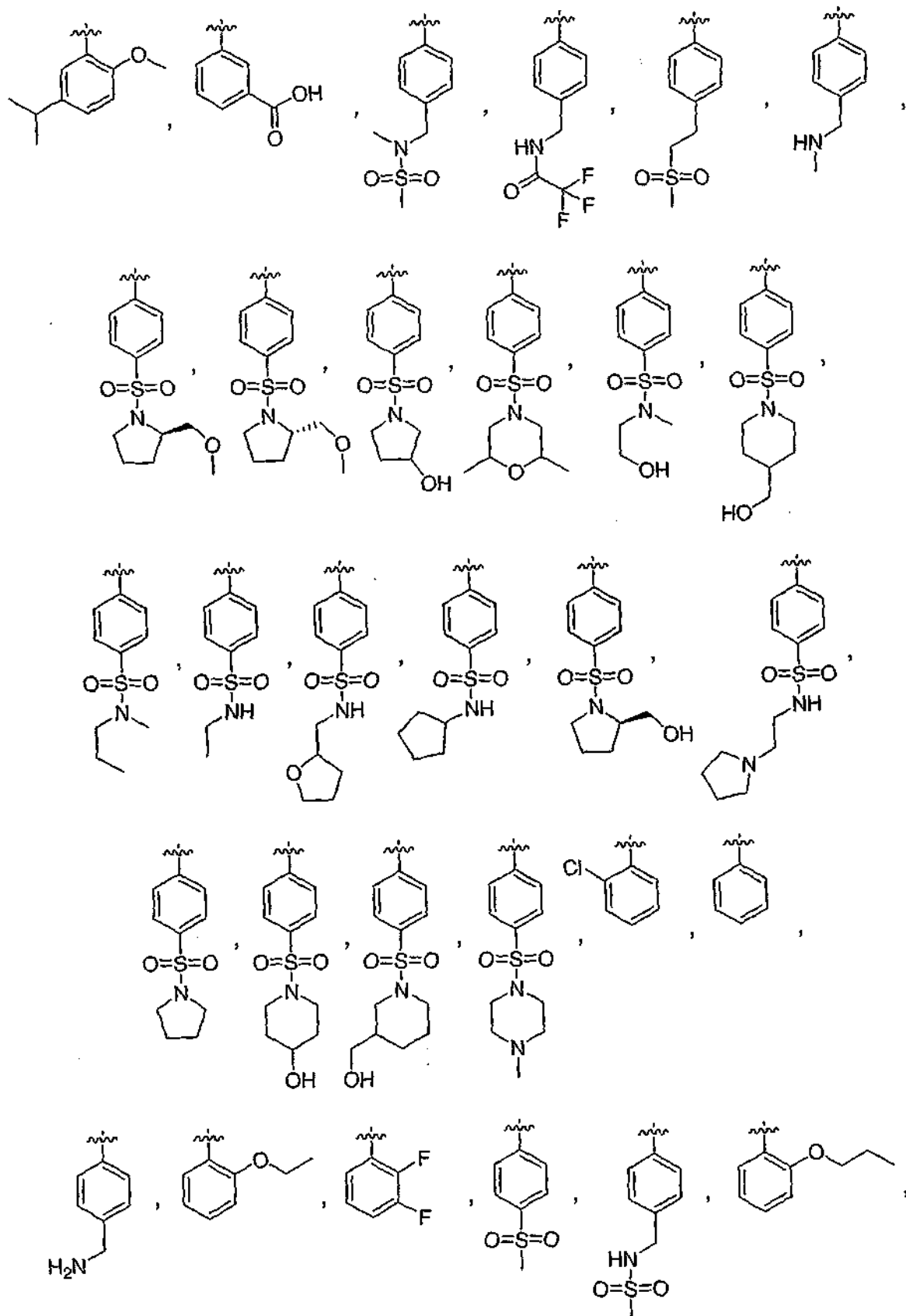


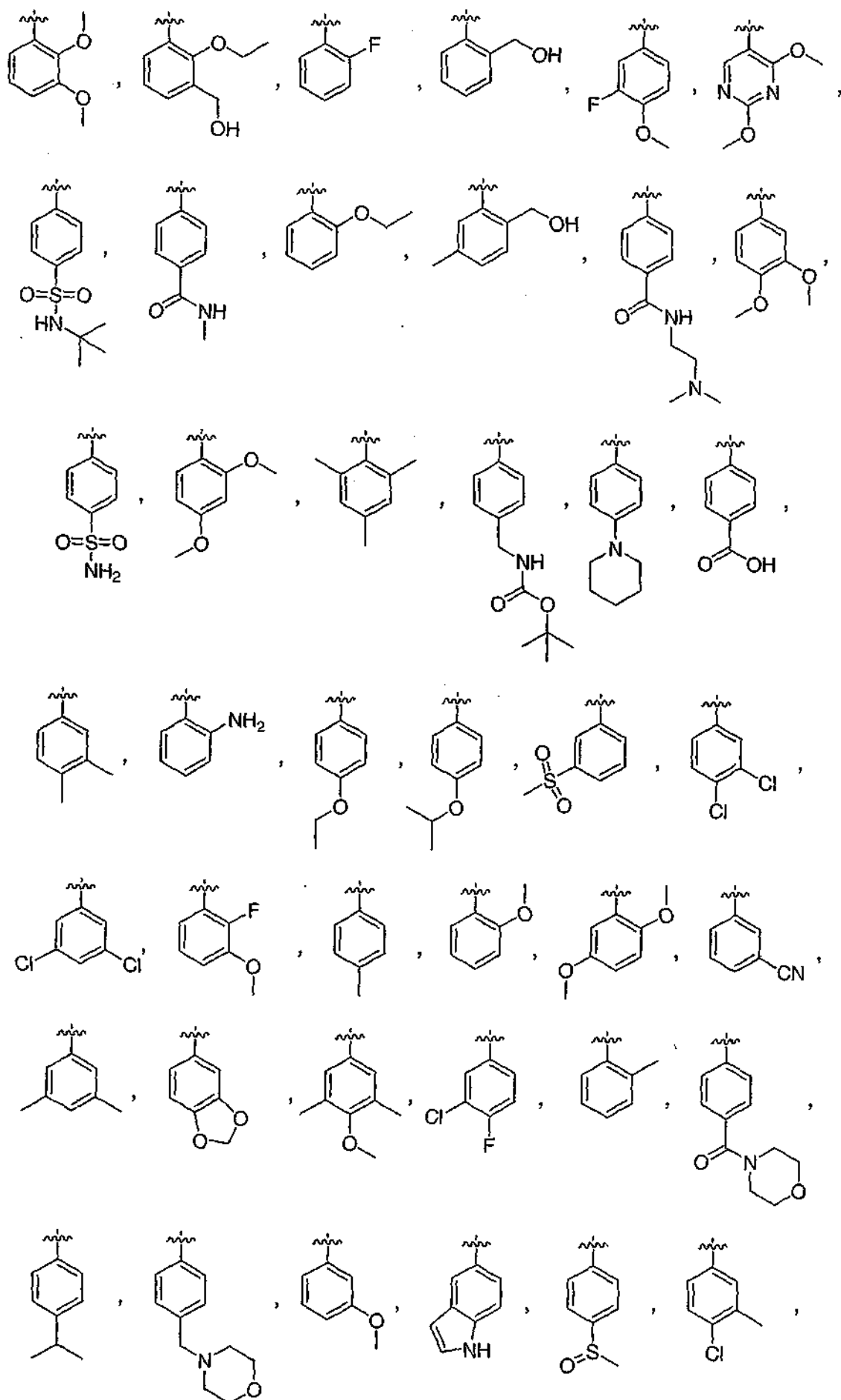
[00240] In several examples, R_1 is one selected from:

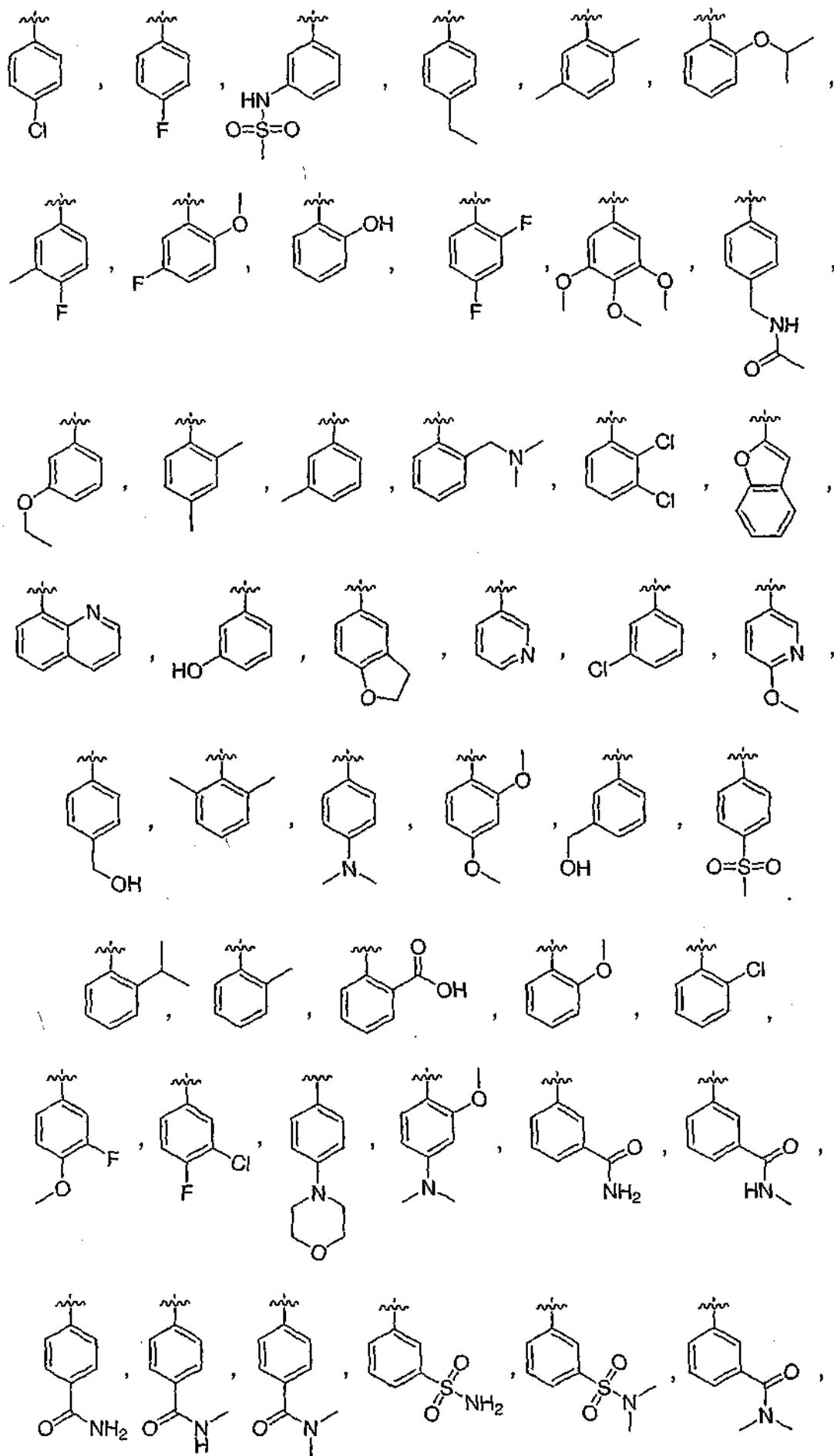


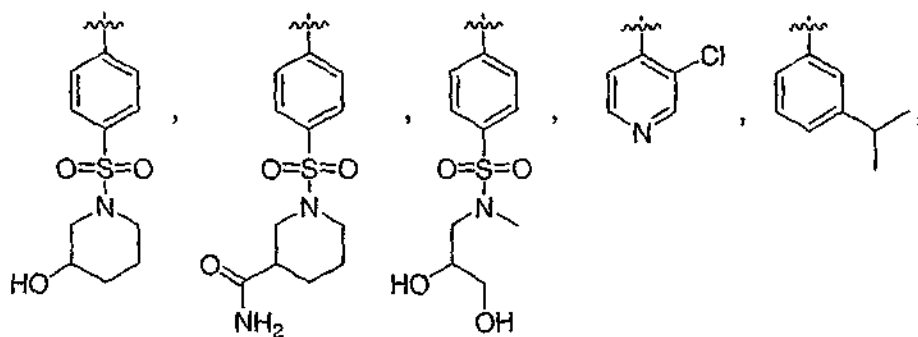
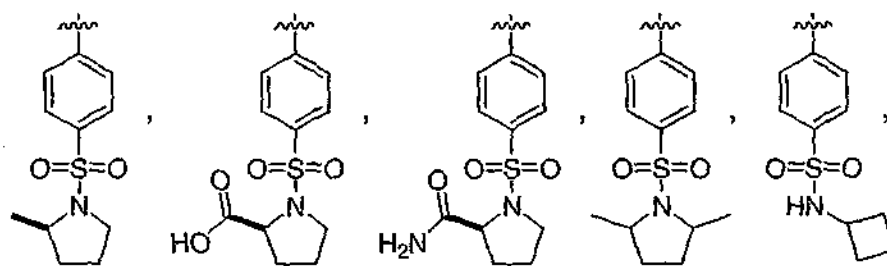
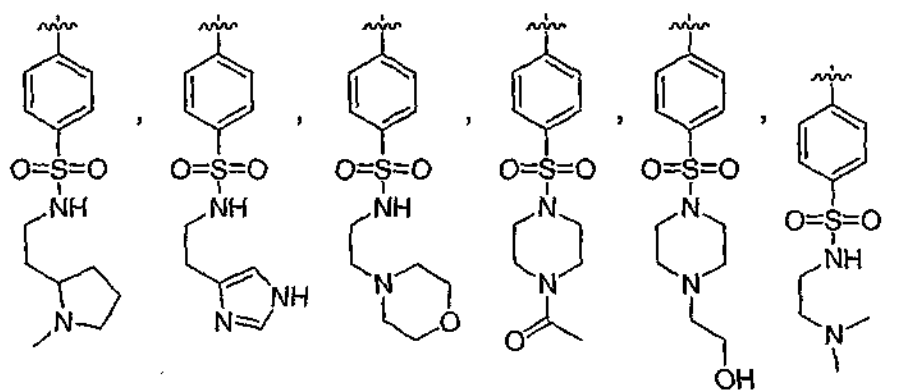
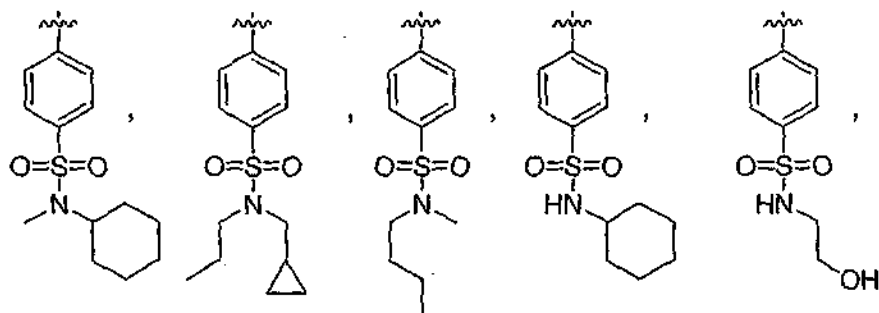
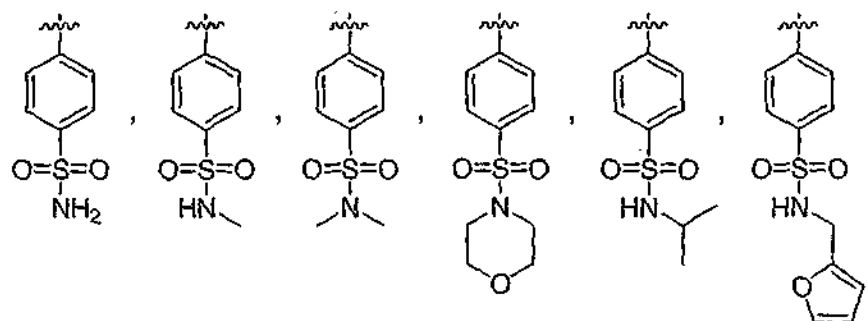
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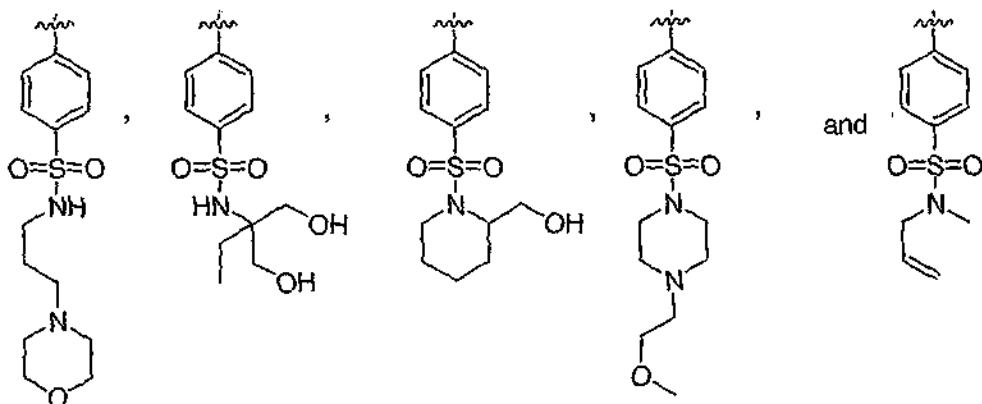






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B. Substituent R_2

[00241] Each R_2 can be hydrogen. Each R_2 can be an optionally substituted group selected from C_{1-6} aliphatic, C_{3-6} cycloaliphatic, phenyl, and heteroaryl.

[00242] In several embodiments, R_2 is a C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halo, C_{1-2} aliphatic, or alkoxy. In several examples, R_2 can be substituted methyl, ethyl, propyl, or butyl. In several examples, R_2 can be methyl, ethyl, propyl, or butyl.

[00243] In several embodiments, R_2 is hydrogen.

C. Substituents R_3 and R'_3

[00244] Each R_3 and R'_3 together with the carbon atom to which they are attached form a C_{3-7} cycloaliphatic or a heterocycloaliphatic, each of which is optionally substituted with 1, 2, or 3 substituents.

[00245] In several embodiments, R_3 and R'_3 together with the carbon atom to which they are attached form a C_{3-7} cycloaliphatic or a C_{3-7} heterocycloaliphatic, each of which is optionally substituted with 1, 2, or 3 of $-Z^B R_7$, wherein each Z^B is independently a bond, or an optionally substituted branched or straight C_{1-4} aliphatic chain wherein up to two carbon units of Z^B are optionally and independently replaced by $-\text{CO}-$, $-\text{CS}-$, $-\text{CONR}^B-$, $-\text{CONR}^B \text{NR}^B-$, $-\text{CO}_2-$, $-\text{OCO}-$, $-\text{NR}^B \text{CO}_2-$, $-\text{O}-$, $-\text{NR}^B \text{CONR}^B-$, $-\text{OCONR}^B-$, $-\text{NR}^B \text{NR}^B-$, $-\text{NR}^B \text{CO}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^B-$, $-\text{SO}_2 \text{NR}^B-$, $-\text{NR}^B \text{SO}_2-$, or $-\text{NR}^B \text{SO}_2 \text{NR}^B-$; each R_7 is independently R^B , halo, $-\text{OH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, or $-\text{OCF}_3$; and each R^B is independently hydrogen, an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

[00246] In several embodiments, R_3 and R'_3 together with the carbon atom to which they are attached form a 3, 4, 5, or 6 membered cycloaliphatic that is optionally substituted with 1, 2, or 3 substituents. In several examples, R_3 , R'_3 , and the carbon atom to which they are attached form an optionally substituted cyclopropyl group. In several alternative

examples, R_3 , R'_3 , and the carbon atom to which they are attached form an optionally substituted cyclobutyl group. In several other examples, R_3 , R'_3 , and the carbon atom to which they are attached form an optionally substituted cyclopentyl group. In other examples, R_3 , R'_3 , and the carbon atom to which they are attached form an optionally substituted cyclohexyl group. In more examples, R_3 and R'_3 together with the carbon atom to which they are attached form an unsubstituted cyclopropyl.

[00247] In several embodiments, R_3 and R'_3 together with the carbon atom to which they are attached form a 5, 6, or 7 membered optionally substituted heterocycloaliphatic. In other examples, R_3 , R'_3 , and the carbon atom to which they are attached form an optionally substituted tetrahydropyranyl group.

[00248] In some embodiments, R_3 and R'_3 together with the carbon atom to which they are attached form an unsubstituted C_{3-7} cycloaliphatic or an unsubstituted heterocycloaliphatic. In several examples, R_3 and R'_3 together with the carbon atom to which they are attached form an unsubstituted cyclopropyl, an unsubstituted cyclopentyl, or an unsubstituted cyclohexyl.

D. Substituent R_4

[00249] Each R_4 is independently an optionally substituted aryl or an optionally substituted heteroaryl.

[00250] In several embodiments, R_4 is an aryl having 6 to 10 members (e.g., 7 to 10 members) optionally substituted with 1, 2, or 3 substituents. Examples of R_4 include optionally substituted benzene, naphthalene, or indene. Or, examples of R_4 can be optionally substituted phenyl, optionally substituted naphthyl, or optionally substituted indenyl.

[00251] In several embodiments, R_4 is an optionally substituted heteroaryl. Examples of R_4 include monocyclic and bicyclic heteroaryl, such a benzofused ring system in which the phenyl is fused with one or two 4-8 membered heterocycloaliphatic groups.

[00252] In some embodiments, R_4 is an aryl or heteroaryl, each optionally substituted with 1, 2, or 3 of $-Z^C R_8$. In some embodiments, R_4 is an aryl optionally substituted with 1, 2, or 3 of $-Z^C R_8$. In some embodiments, R_4 is phenyl optionally substituted with 1, 2, or 3 of $-Z^C R_8$. Or, R_4 is a heteroaryl optionally substituted with 1, 2, or 3 of $-Z^C R_8$. Each Z^C is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^C are optionally and independently replaced by $-CO-$, $-CS-$, $-CONR^C-$, $-CONR^C NR^C-$, $-CO_2-$, $-OCO-$, $-NR^C CO_2-$, $-O-$, $-NR^C CONR^C-$, $-OCONR^C-$, $-NR^C NR^C-$, $-NR^C CO-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^C-$, $-SO_2 NR^C-$, $-NR^C SO_2-$; or $-NR^C SO_2 NR^C-$. Each R_8 is

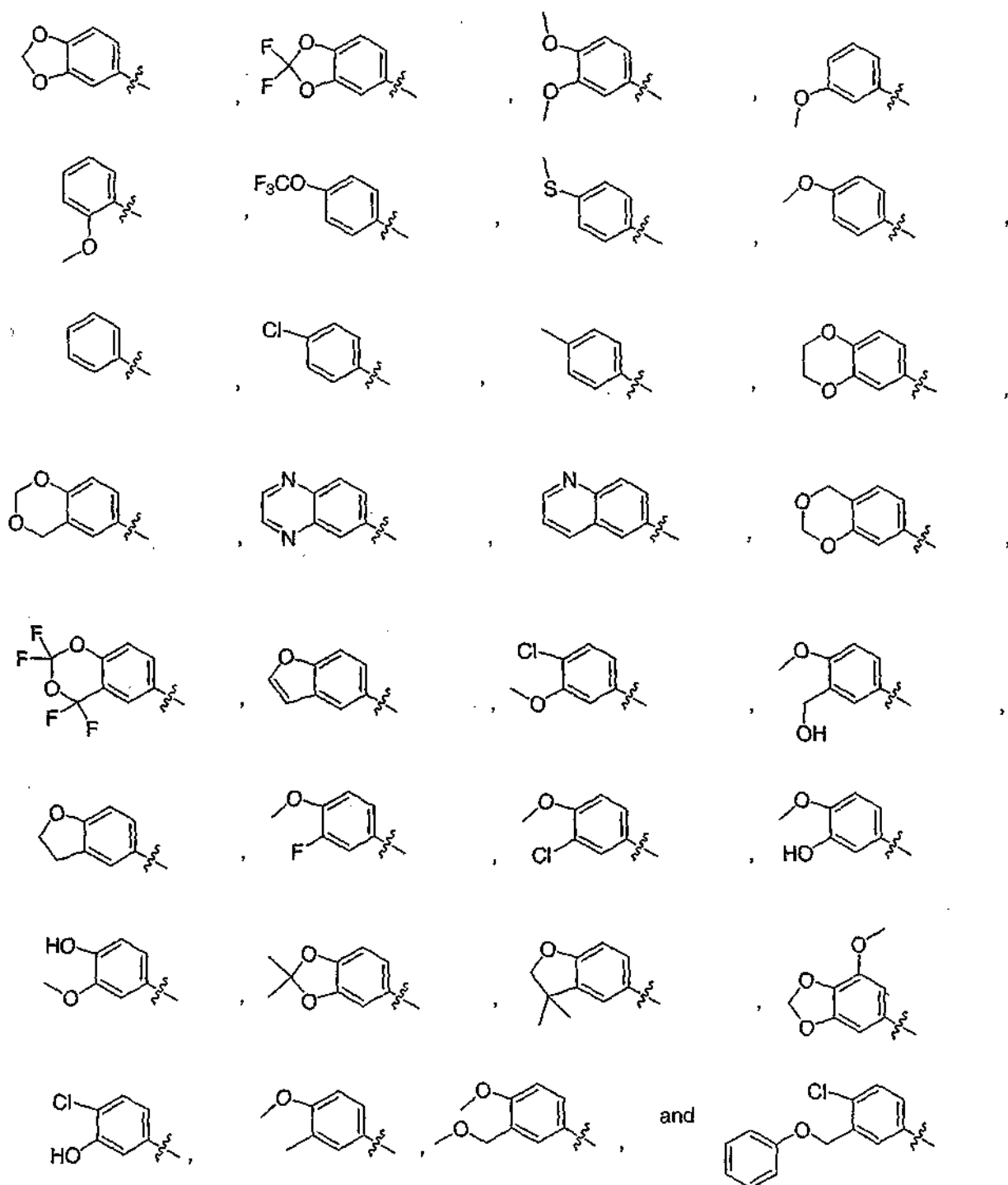
independently R^C , halo, -OH, -NH₂, -NO₂, -CN, -CF₃, or -OCF₃. Each R^C is independently hydrogen, an optionally substituted C₁₋₈ aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

[00253] In some embodiments, two occurrences of $-Z^C R_3$, taken together with carbons to which they are attached, form a 4-8 membered saturated, partially saturated, or aromatic ring with up to 3 ring atoms independently selected from the group consisting of O, NH, NR^C, and S; wherein R^C is defined herein.

[00254] In several embodiments, R₄ is one selected from

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E. Exemplary Compound Families

[00255] In several embodiments, R_1 is an optionally substituted cyclic group that is attached to the core structure at the 5 or 6 position of the pyridine ring.

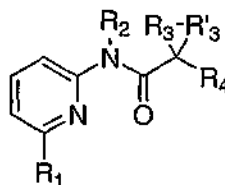
[00256] In several examples, R_1 is an optionally substituted aryl that is attached to the 5 position of the pyridine ring. In other examples, R_1 is an optionally substituted aryl that is attached to the 6 position of the pyridine ring.

[00257] In more examples, R_1 is an optionally substituted heteroaryl that is

attached to the 5 position of the pyridine ring. In still other examples, R_1 is an optionally substituted heteroaryl that is attached to the 6 position of the pyridine ring.

[00258] In other embodiments, R_1 is an optionally substituted cycloaliphatic or an optionally substituted heterocycloaliphatic that is attached to the pyridine ring at the 5 or 6 position.

[00259] Accordingly, another aspect of the present invention provides compounds of formula (II):



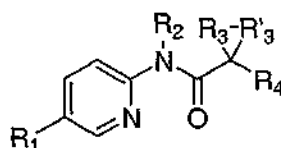
(II)

or a pharmaceutically acceptable salt thereof, wherein R_1 , R_2 , R_3 , R'_3 , and R_4 are defined in formula I.

[00260] In some embodiments, each R_1 is aryl or heteroaryl optionally substituted with 1, 2, or 3 of R^D , wherein R^D is $-Z^D R_9$, wherein each Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-CO-$, $-CS-$, $-CONR^E-$, $-CONR^E NR^E-$, $-CO_2-$, $-OCO-$, $-NR^E CO_2-$, $-O-$, $-NR^E CONR^E-$, $-OCONR^E-$, $-NR^E NR^E-$, $-NR^E CO-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^E-$, $-SO_2 NR^E-$, $-NR^E SO_2-$, or $-NR^E SO_2 NR^E-$; each R_9 is independently R^E , halo, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-CF_3$, or $-OCF_3$; each R^E is independently hydrogen, an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

[00261] In some embodiment, each R_1 is cycloaliphatic or heterocycloaliphatic optionally substituted with 1, 2, or 3 of R^D ; wherein R^D is defined above.

[00262] Another aspect of the present invention provides compounds of formula (III):



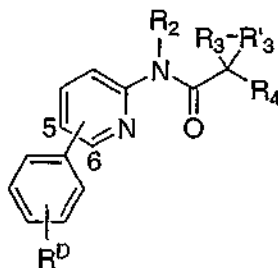
(III)

or a pharmaceutically acceptable salt thereof, wherein R_1 , R_2 , R_3 , R'_3 , and R_4 are defined in formula I.

[00263] In some embodiments, each R_1 is aryl or heteroaryl optionally substituted with 1, 2, or 3 of R^D , wherein R^D is $-Z^D R_9$, wherein each Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-\text{CO}-$, $-\text{CS}-$, $-\text{CONR}^E-$, $-\text{CONR}^E\text{NR}^E-$, $-\text{CO}_2-$, $-\text{OCO}-$, $-\text{NR}^E\text{CO}_2-$, $-\text{O}-$, $-\text{NR}^E\text{CONR}^E-$, $-\text{OCONR}^E-$, $-\text{NR}^E\text{NR}^E-$, $-\text{NR}^E\text{CO}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^E-$, $-\text{SO}_2\text{NR}^E-$, $-\text{NR}^E\text{SO}_2-$, or $-\text{NR}^E\text{SO}_2\text{NR}^E-$; each R_9 is independently R^E , halo, $-\text{OH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, or $-\text{OCF}_3$; each R^E is independently hydrogen, an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

[00264] In some embodiments, each R_1 is cycloaliphatic or heterocycloaliphatic optionally substituted with 1, 2, or 3 of R^D ; wherein R^D is defined above.

[00265] In another aspect, the present invention includes compounds of formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein R_2 , R_3 , R'_3 , and R_4 are defined in formula I.

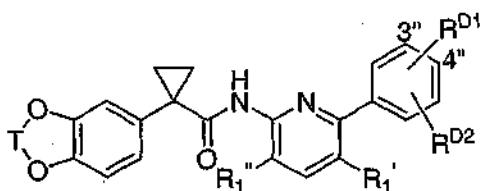
[00266] R^D is $-Z^D R_9$; wherein each Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-\text{CO}-$, $-\text{CS}-$, $-\text{CONR}^E-$, $-\text{CONR}^E\text{NR}^E-$, $-\text{CO}_2-$, $-\text{OCO}-$, $-\text{NR}^E\text{CO}_2-$, $-\text{O}-$, $-\text{NR}^E\text{CONR}^E-$, $-\text{OCONR}^E-$, $-\text{NR}^E\text{NR}^E-$, $-\text{NR}^E\text{CO}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^E-$, $-\text{SO}_2\text{NR}^E-$, $-\text{NR}^E\text{SO}_2-$, or $-\text{NR}^E\text{SO}_2\text{NR}^E-$.

[00267] R_9 is independently R^E , halo, $-\text{OH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, or $-\text{OCF}_3$.

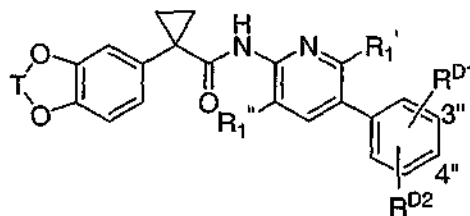
[00268] Each R^E is independently hydrogen, an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

[00269] In several embodiments, Z^D is independently a bond or is an optionally substituted branched or straight C_{1-6} aliphatic chain wherein one carbon unit of Z^D is optionally replaced by $-SO_2-$, $-CONR^E-$, $-NR^ESO_2-$, or $-SO_2NR^E-$. For example, Z^D is an optionally substituted branched or straight C_{1-6} aliphatic chain wherein one carbon unit of Z^D is optionally replaced by $-SO_2-$. In other examples, R_9 is an optionally substituted heteroaryl or an optionally substituted heterocycloaliphatic. In additional examples, R_9 is an optionally substituted heterocycloaliphatic having 1-2 nitrogen atoms, and R_9 attaches directly to $-SO_2-$ via a ring nitrogen.

[00270] In another aspect, the present invention includes compounds of formula V-A or formula V-B:



V-A



V-B

or a pharmaceutically acceptable salt thereof,

wherein:

T is an optionally substituted C_{1-2} aliphatic chain, wherein each of the carbon units is optionally and independently replaced by $-CO-$, $-CS-$, $-COCO-$, $-SO_2-$, $-B(OH)-$, or $-B(O(C_{1-6} \text{ alkyl}))-$;

Each of R_1' and R_1'' is independently a bond or an optionally substituted C_{1-6} aliphatic, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted 3 to 10 membered cycloaliphatic, an optionally substituted 3 to 10 membered heterocycloaliphatic, carboxy, amido, amino, halo, or hydroxy;

R^{D1} is attached to carbon 3" or 4";

each R^{D1} and R^{D2} is $-Z^D R_9$, wherein each Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-CO-$, $-CS-$, $-CONR^E-$, $-CONR^E NR^E-$, $-CO_2-$, $-OCO-$, $-NR^E CO_2-$, $-O-$, $-NR^E CONR^E-$, $-OCONR^E-$, $-NR^E NR^E-$, $-NR^E CO-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^E-$, $-SO_2 NR^E-$, $-NR^E SO_2-$, or $-NR^E SO_2 NR^E-$;

R_9 is independently R^E , halo, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-CF_3$, or $-OCF_3$;

or R^{D1} and R^{D2} , taken together with atoms to which they are attached, form a 3-8 membered saturated, partially unsaturated, or aromatic ring with up to 3 ring members independently selected from the group consisting of O, NH, NR^E , and S; and

each R^E is independently hydrogen, an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

[00271] In some embodiments, T is an optionally substituted $-CH_2-$. In some other embodiments, T is an optionally substituted $-CH_2CH_2-$.




[00272] In some embodiments, T is optionally substituted by $-Z^E R_{10}$; wherein each Z^E is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^E are optionally and independently replaced by $-CO-$, $-CS-$, $-CONR^F-$, $-CONR^F NR^F-$, $-CO_2-$, $-OCO-$, $-NR^F CO_2-$, $-O-$, $-NR^F CONR^F-$, $-OCONR^F-$, $-NR^F NR^F-$, $-NR^F CO-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^F-$, $-SO_2 NR^F-$, $-NR^F SO_2-$, or $-NR^F SO_2 NR^F-$; R_{10} is independently R^F , halo, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-CF_3$, or $-OCF_3$; each R^F is independently hydrogen, an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl. In one example, Z^E is $-O-$.


[00273] In some embodiments, R_{10} can be an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{3-7} cycloaliphatic, or an optionally substituted C_{6-10} aryl. In one embodiment, R_{10} is methyl, ethyl, *i*-propyl, or *t*-butyl.




[00274] In some embodiments, up to two carbon units of T are optionally substituted by $-CO-$, $-CS-$, $-B(OH)-$, or $-B(O(C_{1-6} \text{ alkyl})-$.


[00275] In some embodiments, T is selected from the group consisting of $-CH_2-$, -

CH_2CH_2- , $-CF_2-$, $-C(CH_3)_2-$, $-C(O)-$, , , , , $-C(Phenyl)_2-$, $-B(OH)-$,

and $-CH(OEt)-$. In some embodiments, T is $-CH_2-$, $-CF_2-$, $-C(CH_3)_2-$, , , ,

, or $-C(Phenyl)_2-$. In other embodiments, T is $-CH_2CH_2-$, $-C(O)-$, $-B(OH)-$, and -

$CH(OEt)-$. In several embodiments, T is $-CH_2-$, $-CF_2-$, $-C(CH_3)_2-$, , , , or

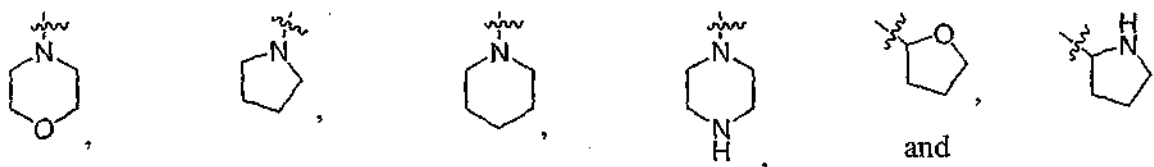
. More preferably, T is $-CH_2-$, $-CF_2-$, or $-C(CH_3)_2-$. In several embodiments, T is -

8 cycloaliphatic, 3-8 membered heterocycloaliphatic, C₆₋₁₀ aryl, and 5-10 membered heteroaryl. In several examples, R₉ is hydrogen, F, Cl, -OH, -CN, -CF₃, or -OCF₃. In some embodiments, R⁹ is C₁₋₆ aliphatic, C₃₋₈ cycloaliphatic, 3-8 membered heterocycloaliphatic, C₆₋₁₀ aryl, and 5-10 membered heteroaryl, each of which is optionally substituted by 1 or 2 substituents independently selected from the group consisting of R^E, oxo, halo, -OH, -NR^ER^E, -OR^E, -COOR^E, and -CONR^ER^E. In several examples, R₉ is optionally substituted by 1 or 2 substituents independently selected from the group consisting of oxo, F, Cl, methyl, ethyl, *i*-propyl, *t*-butyl, -CH₂OH, -CH₂CH₂OH, -C(O)OH, -C(O)NH₂, -CH₂O(C₁₋₆ alkyl), -CH₂CH₂O(C₁₋₆ alkyl), and -C(O)(C₁₋₆ alkyl).

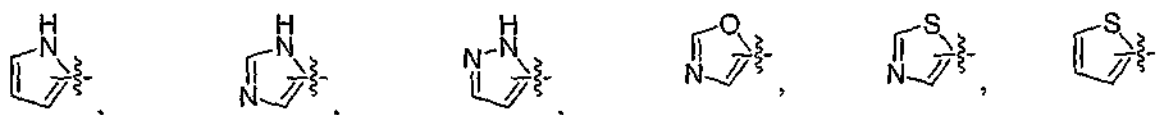
[00281] In one embodiment, R₉ is hydrogen. In some embodiments, R₉ is selected from the group consisting of C₁₋₆ straight or branched alkyl or C₂₋₆ straight or branched alkenyl; wherein said alkyl or alkenyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of R^E, oxo, halo, -OH, -NR^ER^E, -OR^E, -COOR^E, and -CONR^ER^E.

[00282] In other embodiments, R₉ is C₃₋₈ cycloaliphatic optionally substituted by 1 or 2 substituents independently selected from the group consisting of R^E, oxo, halo, -OH, -NR^ER^E, -OR^E, -COOR^E, and -CONR^ER^E. Examples of cycloaliphatic include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[00283] In yet other embodiments, R₉ is a 3-8 membered heterocyclic with 1 or 2 heteroatoms independently selected from the group consisting of O, NH, NR^E, and S; wherein said heterocyclic is optionally substituted by 1 or 2 substituents independently selected from the group R^E, oxo, halo, -OH, -NR^ER^E, -OR^E, -COOR^E, and -CONR^ER^E. Example of 3-8 membered heterocyclic include but are not limited to

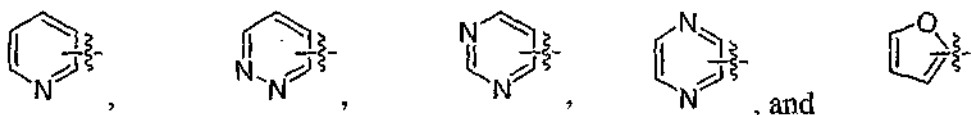


[00284] In yet some other embodiments, R₉ is an optionally substituted 5-8 membered heteroaryl with one or two ring atom independently selected from the group consisting of O, S, and NR^E. Examples of 5-8 membered heteroaryl include but are not limited to

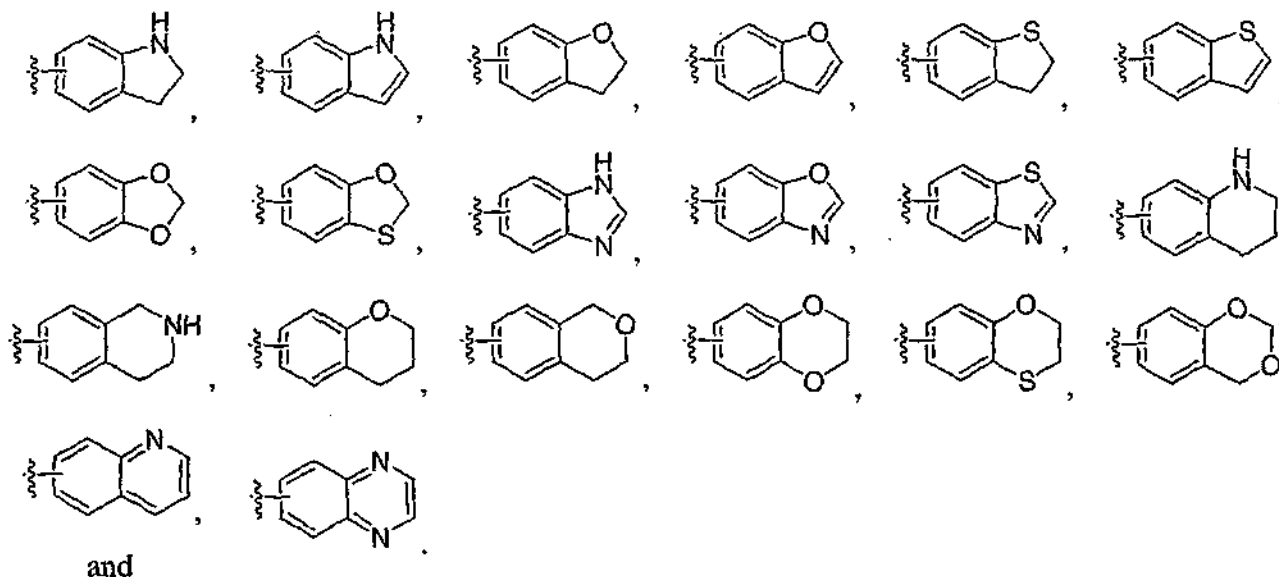


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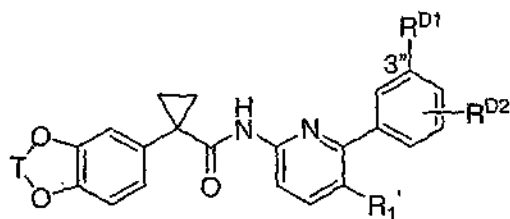
[00285] In some embodiments, R^{D1} and R^{D2} , taken together with carbons to which they are attached, form an optionally substituted 4-8 membered saturated, partially unsaturated, or aromatic ring with 0-2 ring atoms independently selected from the group consisting of O, NH, NR^E , and S. Examples of R^{D1} and R^{D2} , taken together with phenyl containing carbon atoms 3" and 4", include but are not limited to



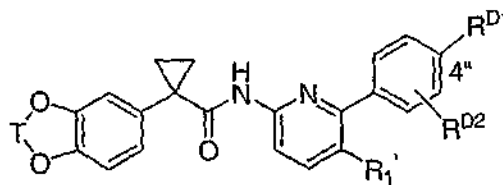
[00286] In some embodiments, R^{D2} is selected from the group consisting of H, R^E , halo, -OH, $-(CH_2)_rNR^E R^E$, $-(CH_2)_rOR^E$, $-SO_2R^E$, $-NR^E-SO_2R^E$, $-SO_2NR^E R^E$, $-C(O)R^E$, $-C(O)OR^E$, $-OC(O)OR^E$, $-NR^E C(O)OR^E$, and $-C(O)NR^E R^E$; wherein r is 0, 1, or 2. In other embodiments, R^{D2} is selected from the group consisting of H, C_{1-6} aliphatic, halo, -CN, $-NH_2$, $-NH(C_{1-6} \text{ aliphatic})$, $-N(C_{1-6} \text{ aliphatic})_2$, $-CH_2-N(C_{1-6} \text{ aliphatic})_2$, $-CH_2-NH(C_{1-6} \text{ aliphatic})$, $-CH_2NH_2$, -OH, $-O(C_{1-6} \text{ aliphatic})$, $-CH_2OH$, $-CH_2-O(C_{1-6} \text{ aliphatic})$, $-SO_2(C_{1-6} \text{ aliphatic})$, $-N(C_{1-6} \text{ aliphatic})-SO_2(C_{1-6} \text{ aliphatic})$, $-NH-SO_2(C_{1-6} \text{ aliphatic})$, $-SO_2NH_2$, $-SO_2NH(C_{1-6} \text{ aliphatic})$, $-SO_2N(C_{1-6} \text{ aliphatic})_2$, $-C(O)(C_{1-6} \text{ aliphatic})$, $-C(O)O(C_{1-6} \text{ aliphatic})$, $-C(O)OH$, $-OC(O)O(C_{1-6} \text{ aliphatic})$, $-NHC(O)(C_{1-6} \text{ aliphatic})$, $-NHC(O)O(C_{1-6} \text{ aliphatic})$, $-N(C_{1-6} \text{ aliphatic})C(O)O(C_{1-6} \text{ aliphatic})$, $-C(O)NH_2$, and $-C(O)N(C_{1-6} \text{ aliphatic})_2$. In several examples, R^{D2} is selected from the group consisting of H, C_{1-6} aliphatic, halo, -CN, $-NH_2$, $-CH_2NH_2$, -OH, $-O(C_{1-6} \text{ aliphatic})$, $-CH_2OH$, $-SO_2(C_{1-6} \text{ aliphatic})$, $-NH-SO_2(C_{1-6} \text{ aliphatic})$, $-C(O)O(C_{1-6} \text{ aliphatic})$, $-C(O)OH$, $-NHC(O)(C_{1-6} \text{ aliphatic})$, $-C(O)NH_2$, $-C(O)NH(C_{1-6} \text{ aliphatic})$, and $-C(O)N(C_{1-6} \text{ aliphatic})_2$. For examples, R^{D2} is selected from the group consisting of H, methyl, ethyl, n-propyl, i-propyl, t-butyl, F, Cl, CN, $-NH_2$, $-CH_2NH_2$, -OH, -OCH₃, -O-ethyl, -O-(i-propyl), -O-(n-propyl), -

CH₂OH, -SO₂CH₃, -NH-SO₂CH₃, -C(O)OCH₃, -C(O)OCH₂CH₃, -C(O)OH, -NHC(O)CH₃, -C(O)NH₂, and -C(O)N(CH₃)₂. In one embodiment, R^{D2} is hydrogen. In another embodiment, R^{D2} is methyl. Or, R^{D2} is ethyl. Or, R^{D2} is F. Or, R^{D2} is Cl. Or, -OCH₃.

[00287] In one embodiment, the present invention provides compounds of formula VI-A-i or formula VI-A-ii:



VI-A-i



VI-A-ii;

wherein T, R^{D1}, R^{D2}, and R₁' are as defined above.

[00288] In one embodiment, T is -CH₂-, -CF₂-, or -C(CH₃)₂-.

[00289] In one embodiment, R₁' is selected from the group consisting of H, C₁₋₆ aliphatic, halo, CF₃, CHF₂, -O(C₁₋₆ aliphatic), C3-C5 cycloalkyl, or C4-C6 heterocycloalkyl containing one oxygen atom. Exemplary embodiments include H, methyl, ethyl, *i*-propyl, *t*-butyl, F, Cl, CF₃, CHF₂, -OCH₃, -OCH₂CH₃, -O(*i*-propyl), -O(*t*-butyl), cyclopropyl, or oxetanyl. More preferably, R₁' is H. Or, R₁' is methyl. Or, ethyl. Or, CF₃. Or, oxetanyl.

[00290] In one embodiment, R^{D1} is Z^DR₉, wherein Z^D is selected from CONH, NHCO, SO₂NH, SO₂N(C₁₋₆ alkyl), NHSO₂, CH₂NHSO₂, CH₂N(CH₃)SO₂, CH₂NHCO, COO, SO₂, or CO. In one embodiment, R^{D1} is Z^DR₉, wherein Z^D is selected from CONH, SO₂NH, SO₂N(C₁₋₆ alkyl), CH₂NHSO₂, CH₂N(CH₃)SO₂, CH₂NHCO, COO, SO₂, or CO.

[00291] In one embodiment, Z^D is COO and R₉ is H. In one embodiment, Z^D is COO and R₉ is an optionally substituted straight or branched C₁₋₆ aliphatic. In one embodiment, Z^D is COO and R₉ is an optionally substituted straight or branched C₁₋₆ alkyl. In one embodiment, Z^D is COO and R₉ is C₁₋₆ alkyl. In one embodiment, Z^D is COO and R₉ is methyl.

[00292] In one embodiment, Z^D is CONH and R₉ is H. In one embodiment, Z^D is CONH and R₉ is an optionally substituted straight or branched C₁₋₆ aliphatic. In one embodiment, Z^D is CONH and R₉ is straight or branched C₁₋₆ alkyl. In one embodiment, Z^D is CONH and R₉ is methyl. In one embodiment, Z^D is CONH and R₉ is an optionally substituted straight or branched C₁₋₆ alkyl. In one embodiment, In one embodiment, Z^D is CONH and R₉ is 2-(dimethylamino)-ethyl.

[00293] In some embodiments, Z^D is CH_2NHCO and R_9 is an optionally substituted straight or branched C_{1-6} aliphatic or an optionally substituted alkoxy. In some embodiments, Z^D is CH_2NHCO and R_9 is straight or branched C_{1-6} alkyl optionally substituted with halo, oxo, hydroxyl, or an optionally substituted group selected from aliphatic, cyclic, aryl, heteroaryl, alkoxy, amino, carboxyl, or carbonyl. In one embodiment, Z^D is CH_2NHCO and R_9 is methyl. In one embodiment, Z^D is CH_2NHCO and R_9 is CF_3 . In one embodiment, Z^D is CH_2NHCO and R_9 is *t*-butoxy.

[00294] In one embodiment, Z^D is SO_2NH and R_9 is H. In some embodiments, Z^D is SO_2NH and R_9 is an optionally substituted straight or branched C_{1-6} aliphatic. In some embodiments, Z^D is SO_2NH and R_9 is straight or branched C_{1-6} alkyl optionally substituted with halo, oxo, hydroxyl, or an optionally substituted group selected from C_{1-6} aliphatic, 3-8 membered cyclic, C_{6-10} aryl, 5-8 membered heteroaryl, alkoxy, amino, amido, carboxyl, or carbonyl. In one embodiment, Z^D is SO_2NH and R_9 is methyl. In one embodiment, Z^D is SO_2NH and R_9 is ethyl. In one embodiment, Z^D is SO_2NH and R_9 is *i*-propyl. In one embodiment, Z^D is SO_2NH and R_9 is *t*-butyl. In one embodiment, Z^D is SO_2NH and R_9 is 3,3-dimethylbutyl. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}_2\text{CH}_2\text{OH}$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}(\text{CH}_2\text{OH})_2$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}_3$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{OH}$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{C}(\text{CH}_3)(\text{CH}_2\text{OH})_2$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{C}(\text{O})\text{OH}$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}_2\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}(\text{CH}(\text{CH}_3)_2)\text{CH}_2\text{OH}$. In one embodiment, Z^D is SO_2NH and R_9 is $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CH}_2\text{OH}$. In one embodiment, Z^D is SO_2NH and R_9 is 1-tetrahydrofuryl-methyl. In one embodiment, Z^D is SO_2NH and R_9 is furylmethyl. In one embodiment, Z^D is SO_2NH and R_9 is (5-methylfuryl)-methyl. In one embodiment, Z^D is SO_2NH and R_9 is 2-pyrrolidinylethyl. In one embodiment, Z^D is SO_2NH and R_9 is 2-(1-methylpyrrolidinyl)-ethyl. In one embodiment, Z^D is SO_2NH and R_9 is 2-(4-morpholinyl)-ethyl. In one embodiment, Z^D is SO_2NH and R_9 is 3-(4-morpholinyl)-propyl. In one embodiment, Z^D is SO_2NH and R_9 is $\text{C}(\text{CH}_2\text{CH}_3)(\text{CH}_2\text{OH})_2$. In one embodiment, Z^D is SO_2NH and R_9 is 2-(1*H*-imidazol-4-yl)ethyl. In one embodiment, Z^D is SO_2NH and R_9 is 3-(1*H*-imidazol-1-yl)-propyl. In one embodiment, Z^D is SO_2NH and R_9 is 2-

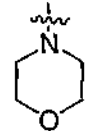
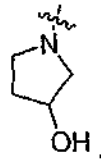
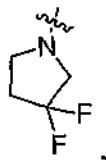
(2-pyridinyl)-ethyl.

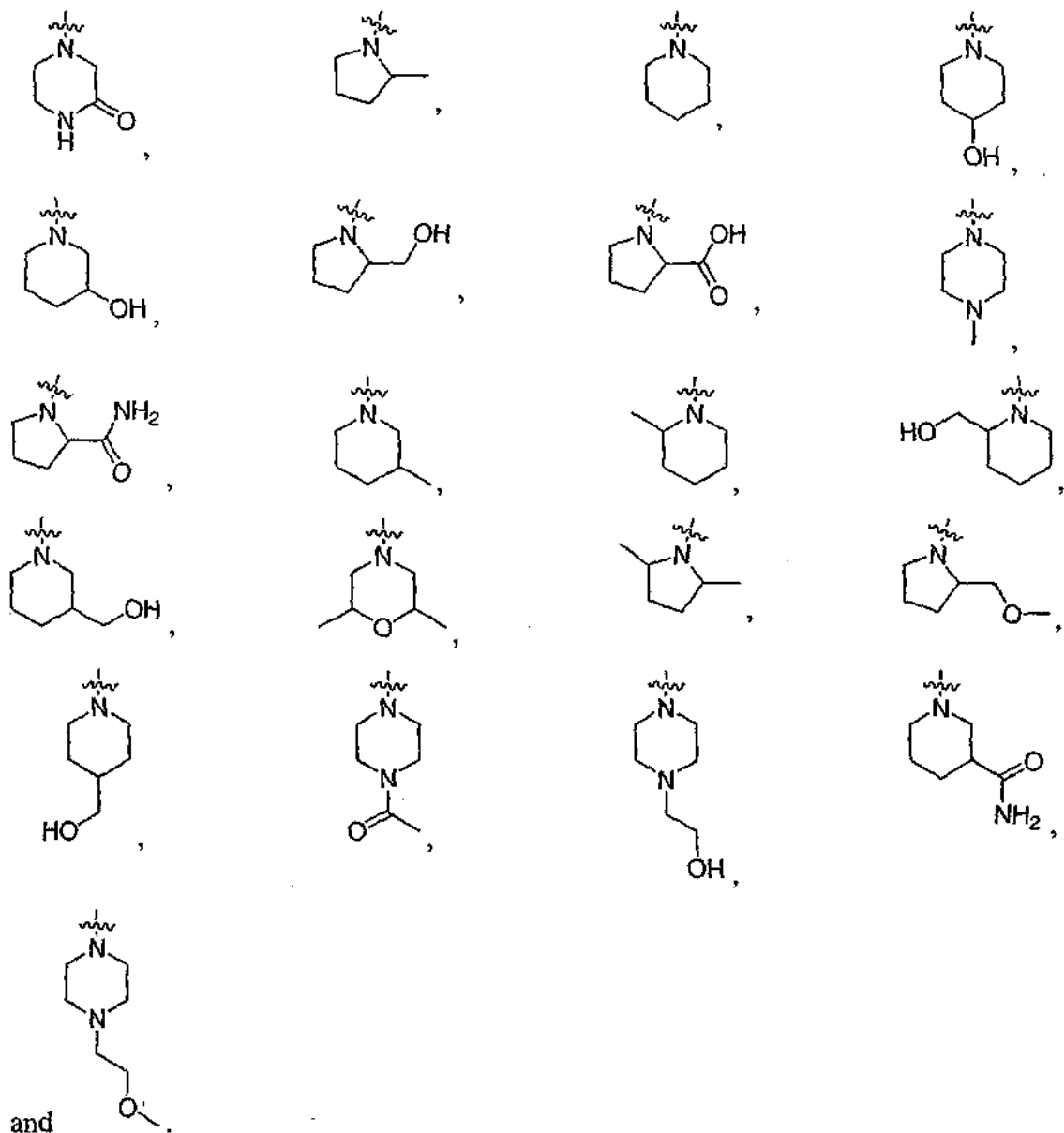
[00295] In some embodiment, Z^D is SO_2NH and R_9 is an optionally substituted C_{1-6} cycloaliphatic. In several examples, Z^D is SO_2NH and R_9 is an optionally substituted C_{1-6} cycloalkyl. In several examples, Z^D is SO_2NH and R_9 is C_{1-6} cycloalkyl. In one embodiment, Z^D is SO_2NH and R_9 is cyclobutyl. In one embodiment, Z^D is SO_2NH and R_9 is cyclopentyl. In one embodiment, Z^D is SO_2NH and R_9 is cyclohexyl.

[00296] In some embodiments, Z^D is $\text{SO}_2\text{N}(\text{C}_{1-6} \text{ alkyl})$ and R_9 is an optionally substituted straight or branched C_{1-6} aliphatic or an optionally substituted cycloaliphatic. In some embodiments, Z^D is $\text{SO}_2\text{N}(\text{C}_{1-6} \text{ alkyl})$ and R_9 is an optionally substituted straight or branched C_{1-6} aliphatic. In some embodiments, Z^D is $\text{SO}_2\text{N}(\text{C}_{1-6} \text{ alkyl})$ and R_9 is an optionally substituted straight or branched C_{1-6} alkyl or an optionally substituted straight or branched C_{1-6} alkenyl. In one embodiment, Z^D is $\text{SO}_2\text{N}(\text{CH}_3)$ and R_9 is methyl. In one embodiment, Z^D is $\text{SO}_2\text{N}(\text{CH}_3)$ and R_9 is n-propyl. In one embodiment, Z^D is $\text{SO}_2\text{N}(\text{CH}_3)$ and R_9 is n-butyl. In one embodiment, Z^D is $\text{SO}_2\text{N}(\text{CH}_3)$ and R_9 is cyclohexyl. In one embodiment, Z^D is $\text{SO}_2\text{N}(\text{CH}_3)$ and R_9 is allyl. In one embodiment, Z^D is $\text{SO}_2\text{N}(\text{CH}_3)$ and R_9 is $\text{CH}_2\text{CH}_2\text{OH}$. In one embodiment, Z^D is $\text{SO}_2\text{N}(\text{CH}_3)$ and R_9 is $\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$. In one embodiment, Z^D is $\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)$ and R_9 is cyclopropylmethyl.

[00297] In one embodiment, Z^D is $\text{CH}_2\text{NH}\text{SO}_2$ and R_9 is methyl. In one embodiment, Z^D is $\text{CH}_2\text{N}(\text{CH}_3)\text{SO}_2$ and R_9 is methyl.

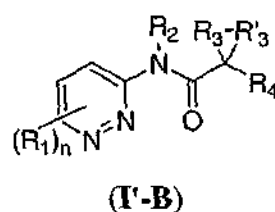
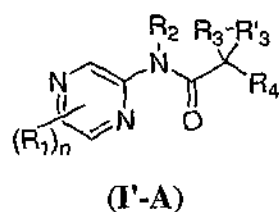
[00298] In some embodiments, Z^D is SO_2 and R_9 is an optionally substituted C_{1-6} straight or branched aliphatic or an optionally substituted 3-8 membered heterocyclic, having 1, 2, or 3 ring members selected from the group consisting of nitrogen, oxygen, sulfur, SO , or SO_2 . In some embodiments, Z^D is SO_2 and R_9 is straight or branched C_{1-6} alkyl or 3-8 membered heterocycloaliphatic each of which is optionally substituted with 1, 2, or 3 of oxo, halo, hydroxyl, or an optionally substituted group selected from C_{1-6} aliphatic, carbonyl, amino, and carboxy. In one embodiment, Z^D is SO_2 and R_9 is methyl. In some embodiments, Z^D is SO_2 and examples of R_9 include





[00299] In some embodiments, R^{D2} is H, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or NH_2 . In several examples, R^{D2} is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy. Examples of R^{D2} include H, F, Cl, methyl, ethyl, and methoxy.

[00300] In some embodiments, the present invention provides compounds of formula (I'-A) or formula (I'-B):



or a pharmaceutically acceptable salt thereof,

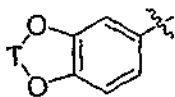
wherein R_1 , R_2 , R_3 , R'_3 , R_4 , and n are defined above.

[00301] In some embodiments, R_1 is an optionally substituted aryl. In several examples, R_1 is phenyl optionally substituted with 1, 2, or 3 of halo, OH, $-O(C_{1-6}$ aliphatic), amino, C_{1-6} aliphatic, C_{3-7} cycloaliphatic, 3-8 membered heterocycloaliphatic, C_{6-10} aryl, or 5-8 membered heteroaryl. In some embodiments, R_1 is phenyl optionally substituted with alkoxy, halo, or amino. In one embodiment, R_1 is phenyl. In one embodiment, R_1 is phenyl substituted with Cl, methoxy, ethoxy, or dimethylamino.

[00302] In some embodiments, R_2 is hydrogen. In some embodiments, R_2 is optionally substituted C_{1-6} aliphatic.

[00303] In some embodiments, R_3 , R'_3 , and the carbon atom to which they are attached form an optionally substituted C_{3-8} cycloaliphatic or an optionally substituted 3-8 membered heterocycloaliphatic. In some embodiments, R_3 , R'_3 , and the carbon atom to which they are attached form an optionally substituted C_{3-8} cycloalkyl. In one example, R_3 , R'_3 , and the carbon atom to which they are attached is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, each of which is optionally substituted. In one example, R_3 , R'_3 , and the carbon atom to which they are attached is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. In several examples, R_3 , R'_3 , and the carbon atom to which they are attached is cyclopropyl.

[00304] In some embodiments, R_4 is an optionally substituted aryl or an optionally substituted heteroaryl. In some embodiments, R_4 is an optionally substituted phenyl. In several embodiments, R_4 is phenyl fused to a 3, 4, 5, or 6 membered heterocyclic having 1, 2, or 3 ring membered selected from oxygen, sulfur and nitrogen. In several embodiments, R_4 is



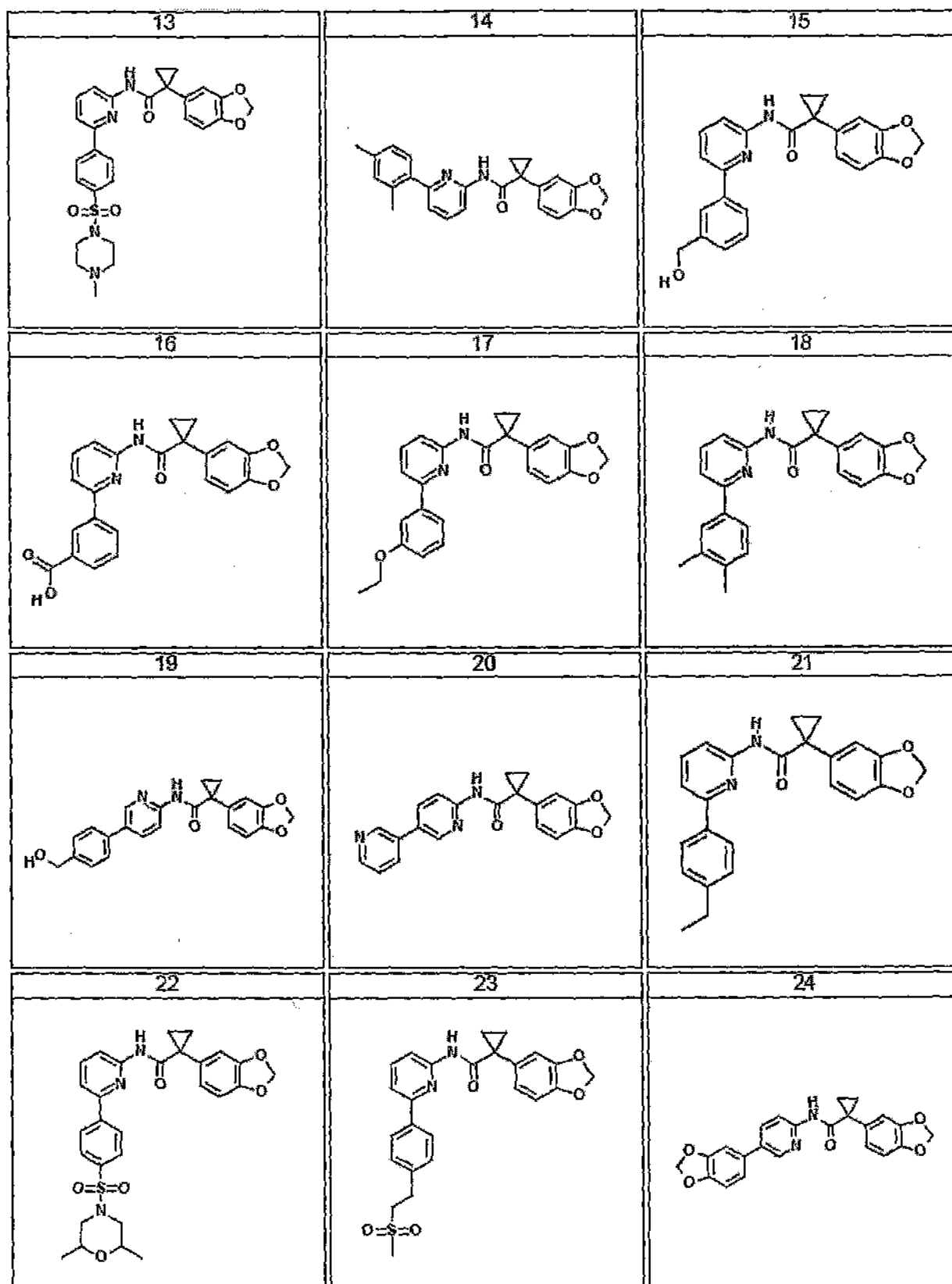
, wherein T is defined above. In several examples, T is $-CH_2-$.

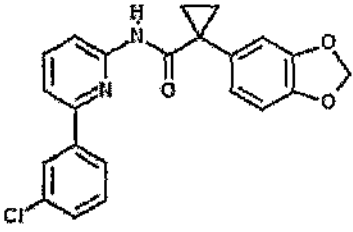
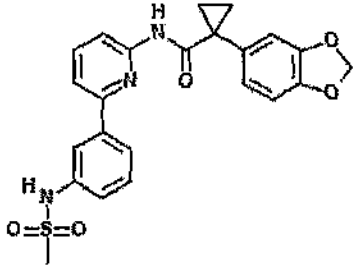
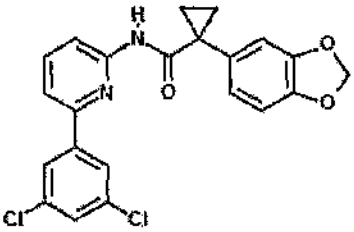
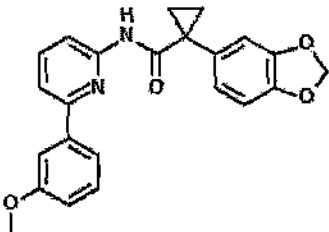
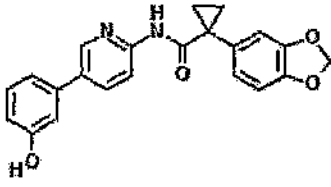
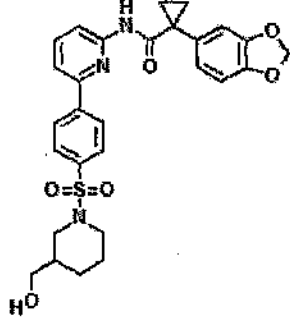
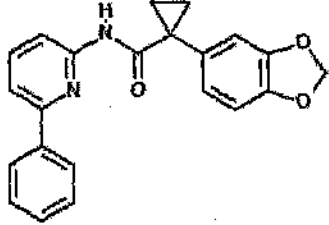
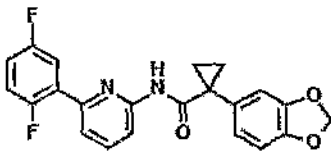
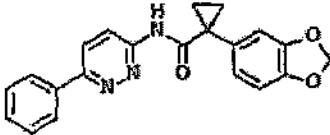
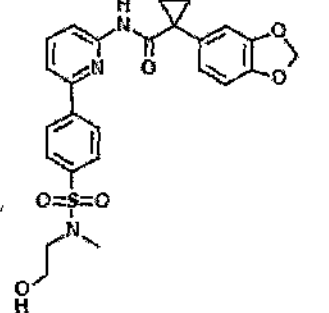
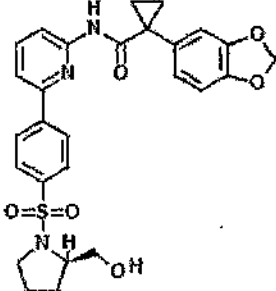
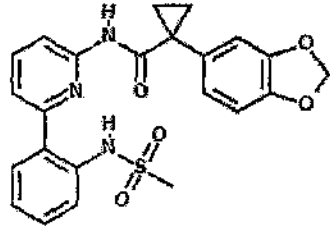
[00305] Alternative embodiments of R_1 , R_2 , R_3 , R'_3 , R_4 , and n in formula (I'-A) or formula (I'-B) are as defined for formula (I), formula (I'), and embodiments thereof.

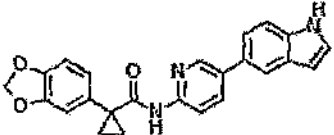
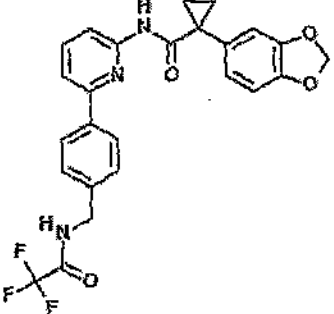
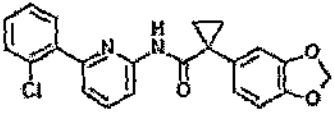
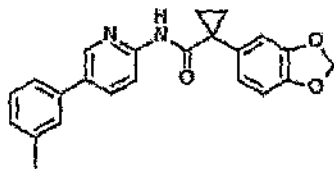
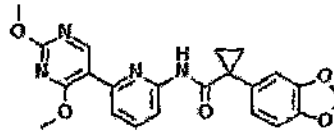
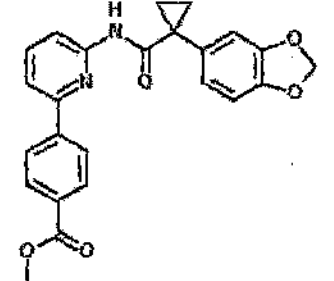
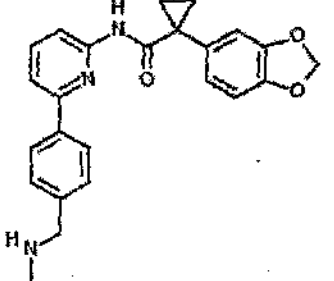
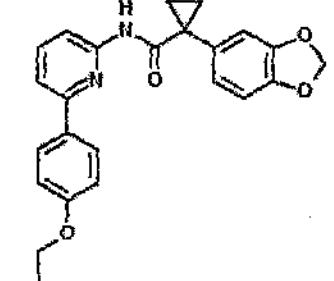
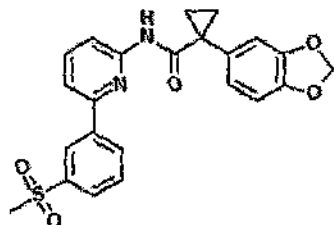
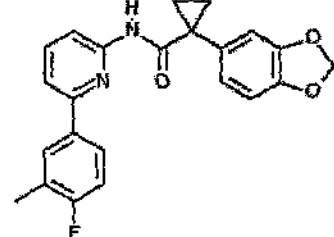
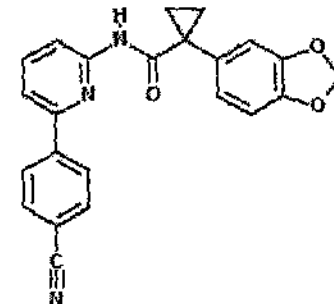
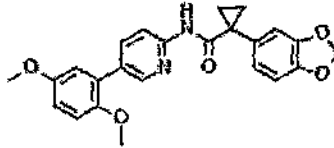
[00306] Exemplary compounds of the present invention include, but are not limited to, those illustrated in Table 1 below.

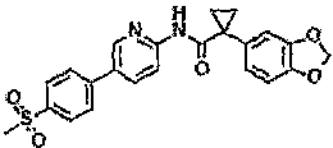
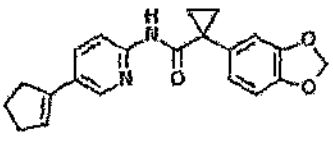
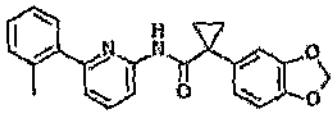
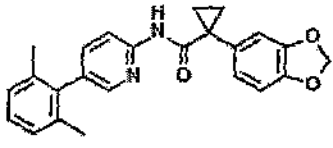
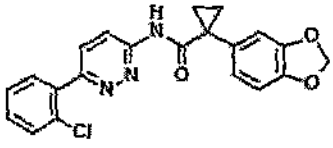
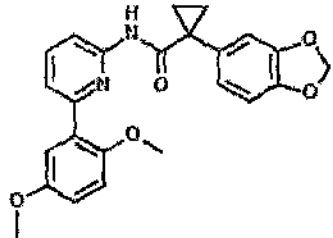
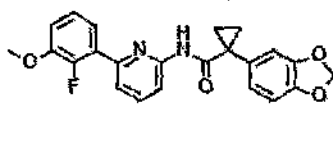
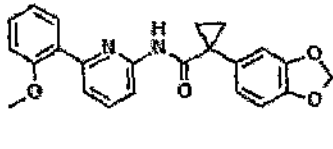
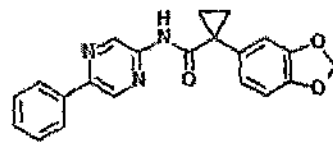
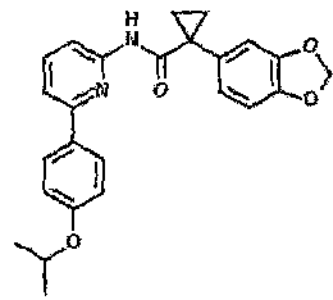
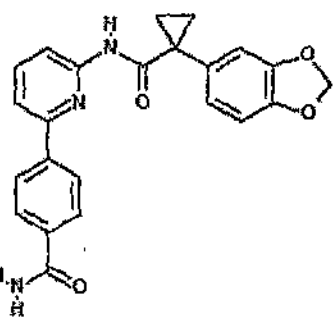
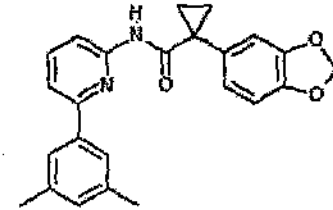
[00307] Table 1: Examples of compounds of the present invention

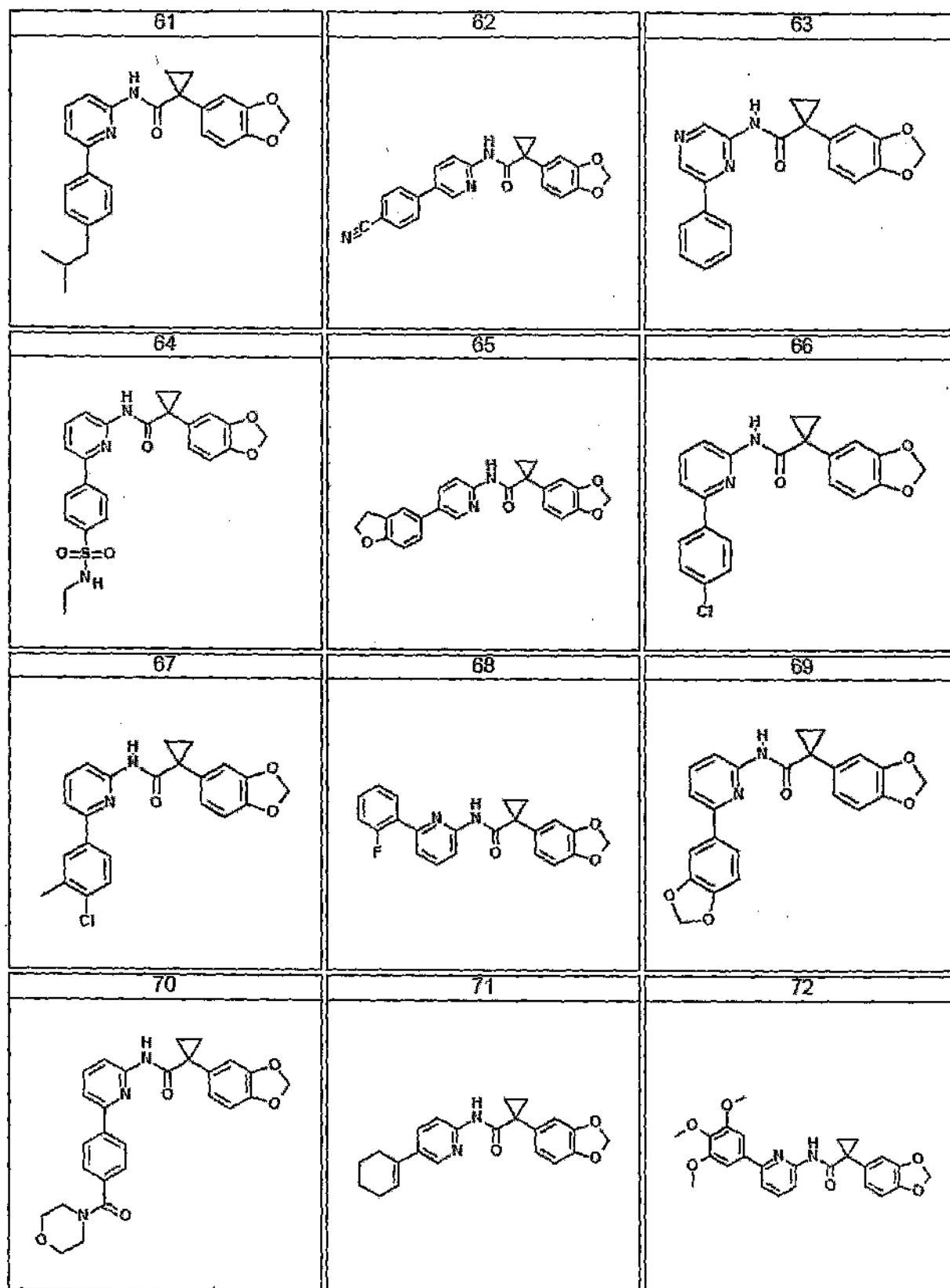
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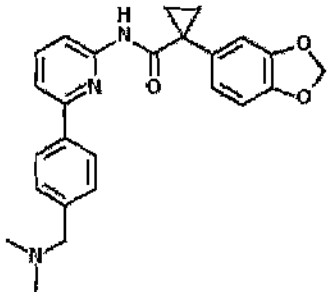
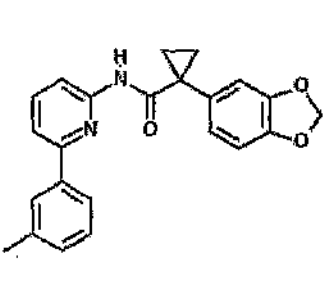
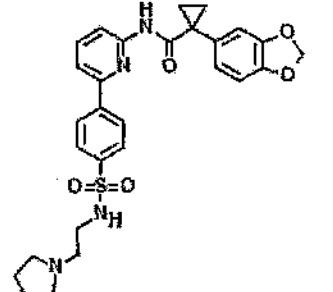
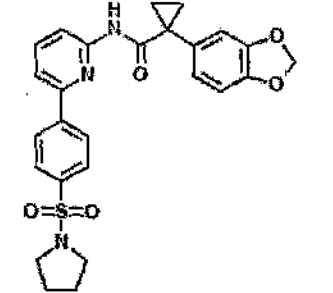
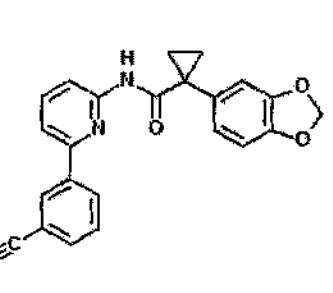
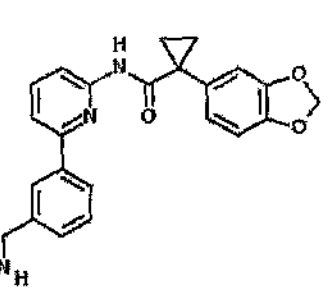
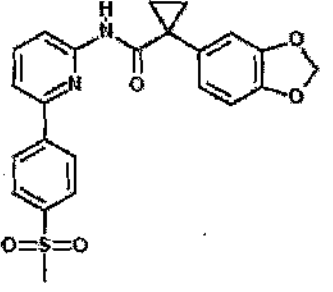
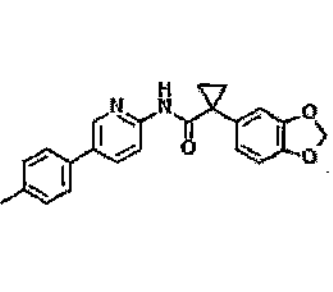
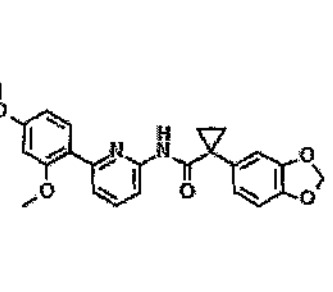
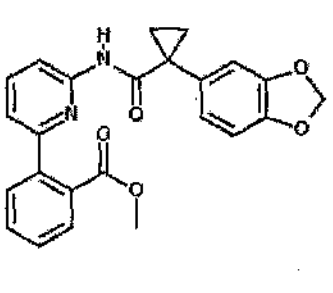
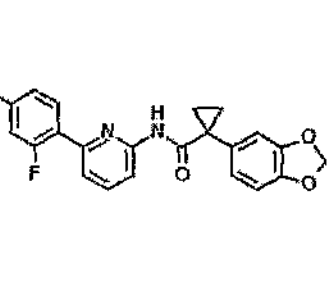
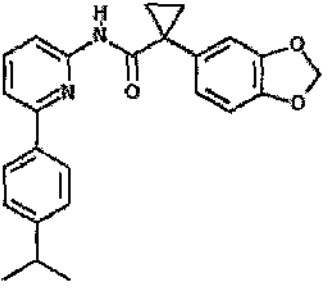


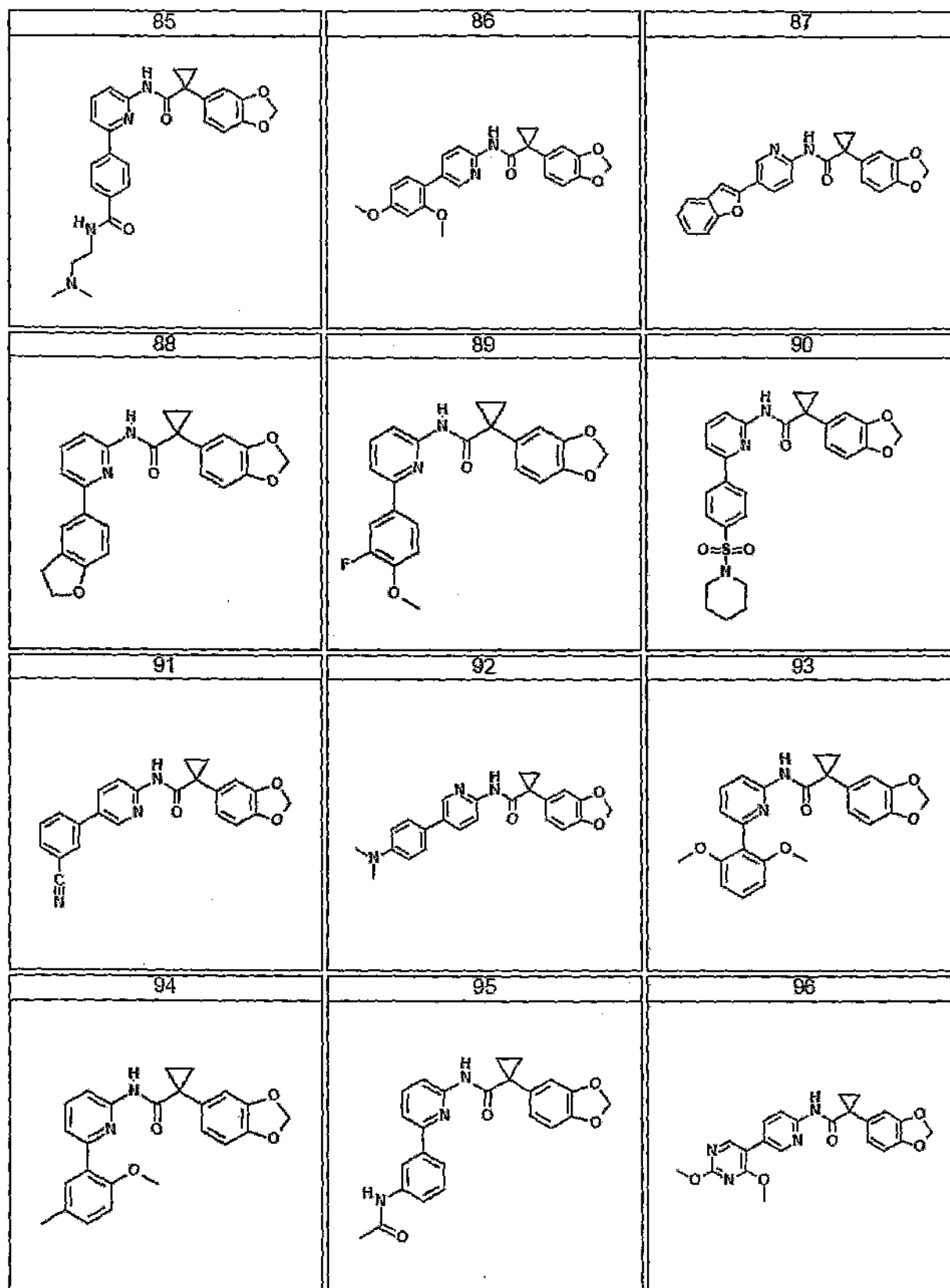
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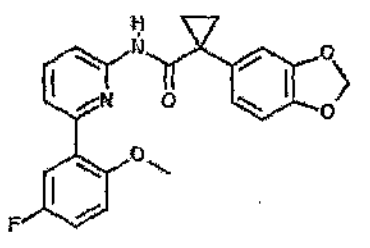
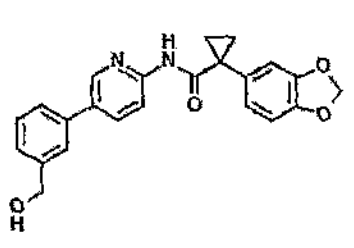
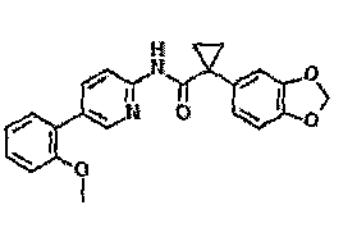
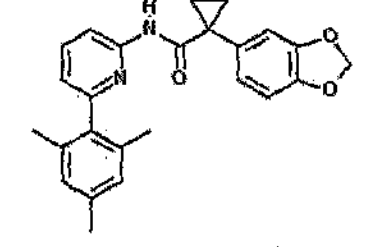
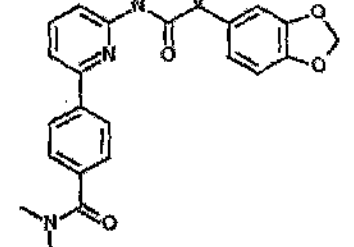
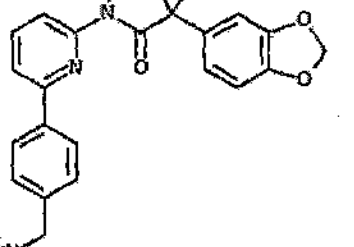
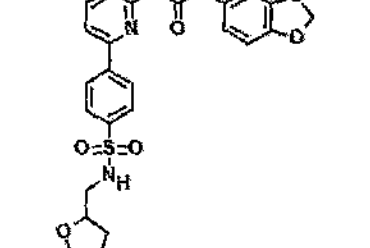
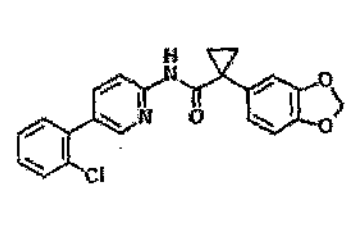
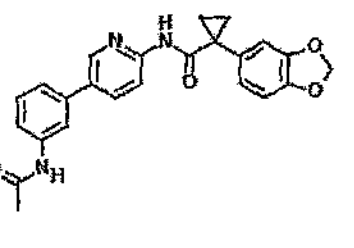
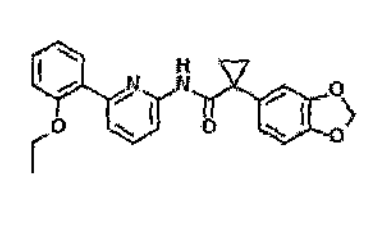
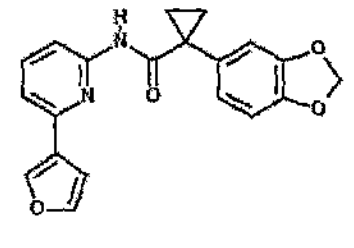
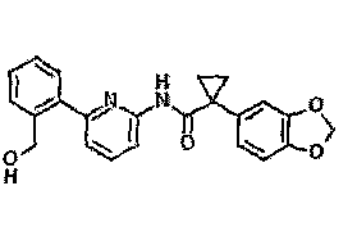
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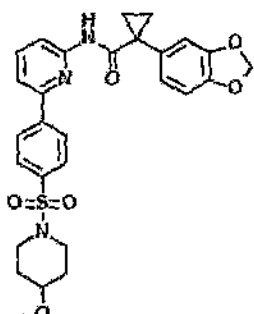
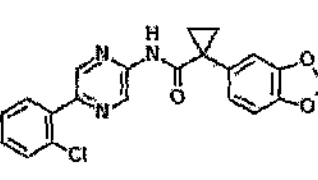
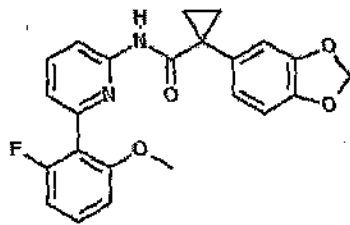
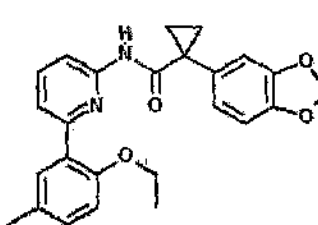
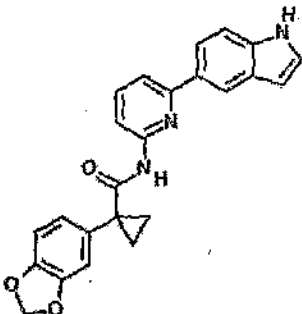
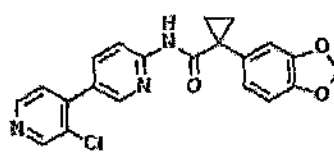
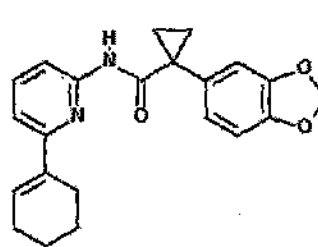
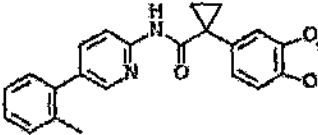
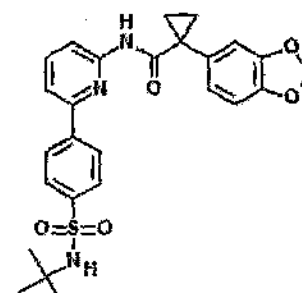
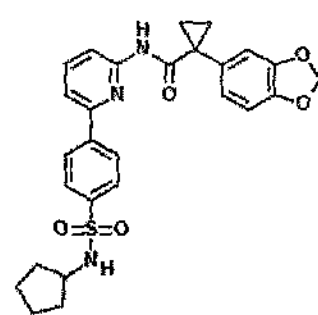
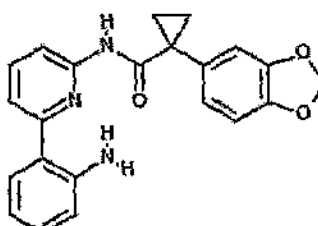
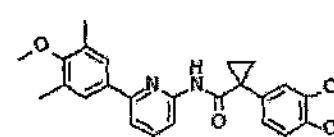
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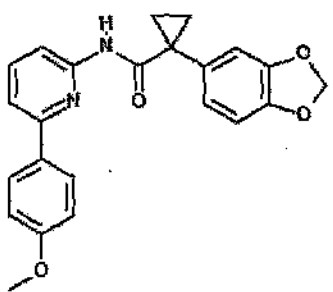
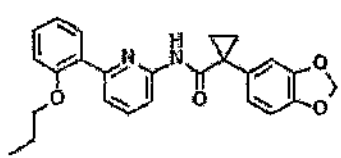
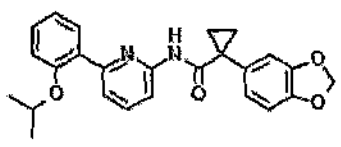
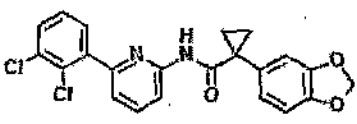
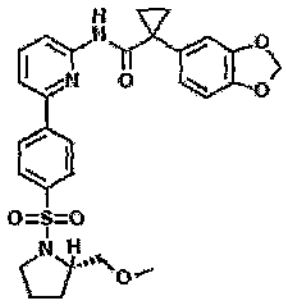
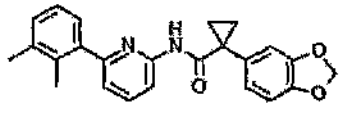
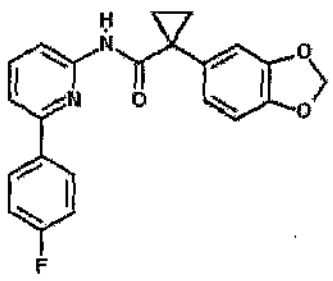
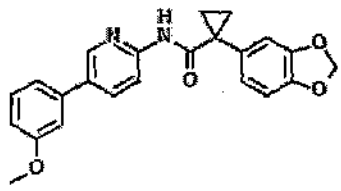
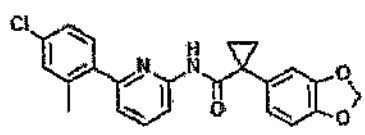
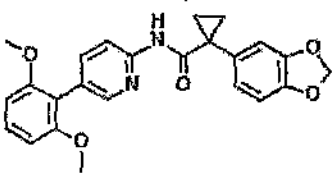
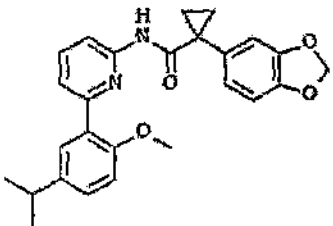
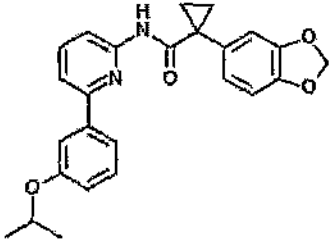


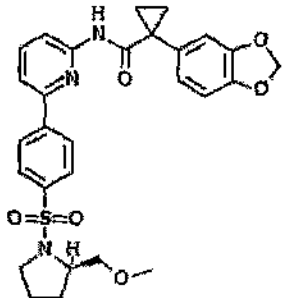
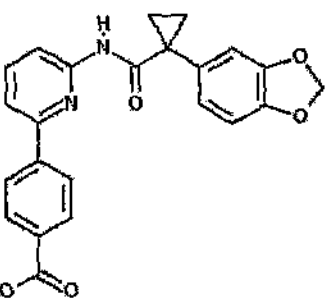
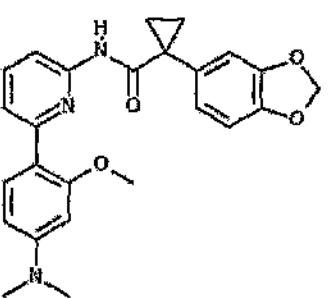
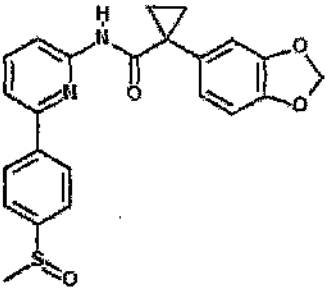
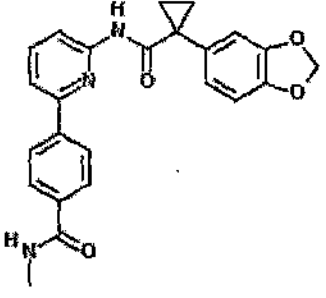
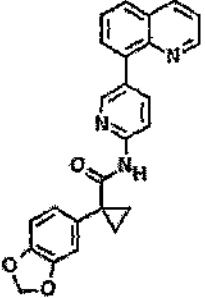
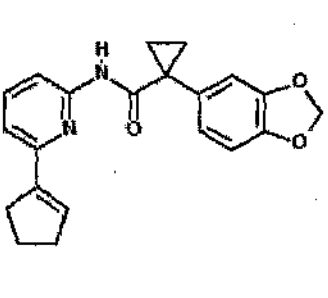
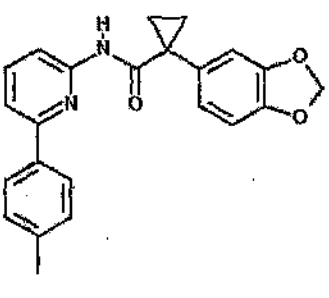
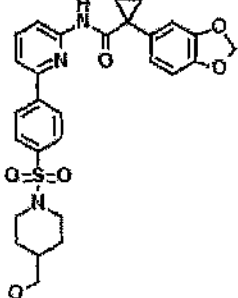
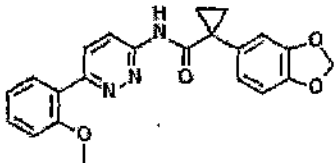
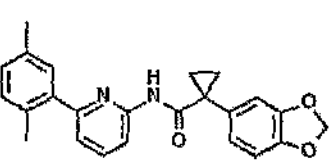
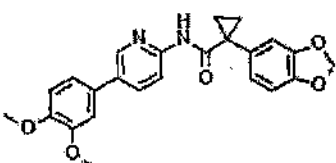
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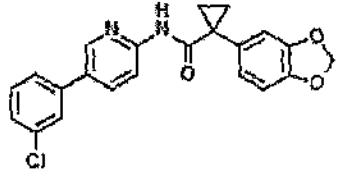
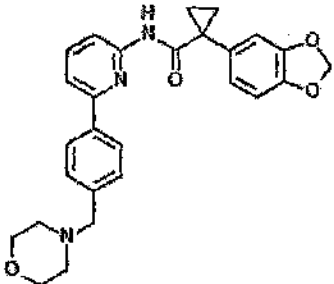
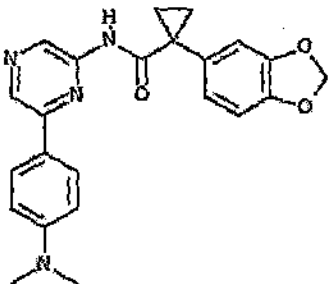
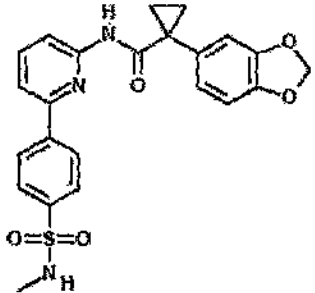
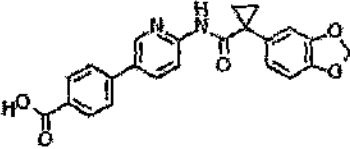
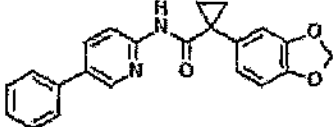
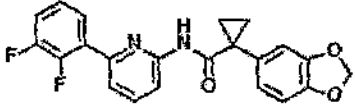
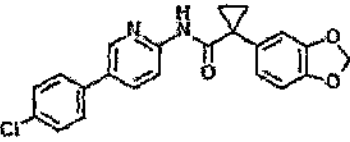
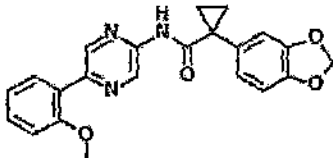
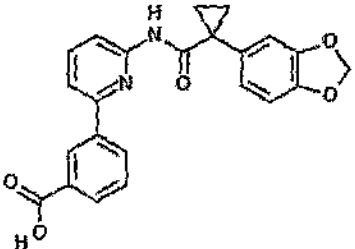
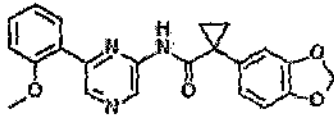
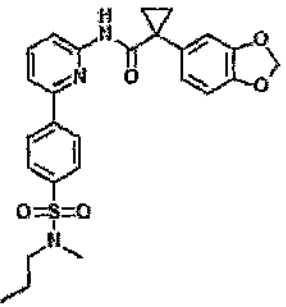


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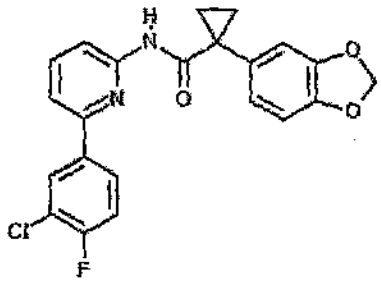
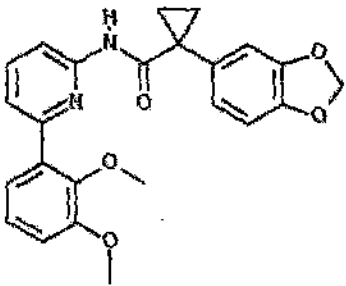
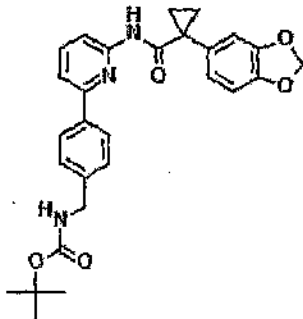
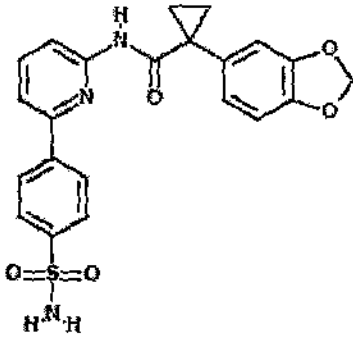
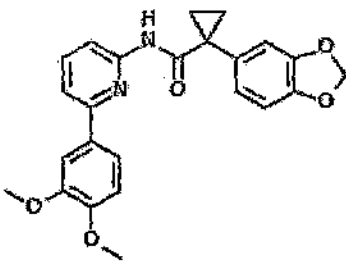
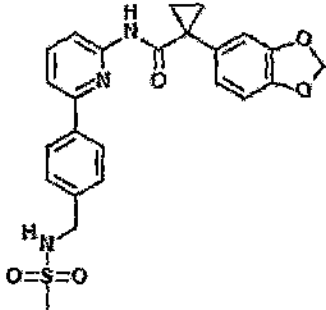
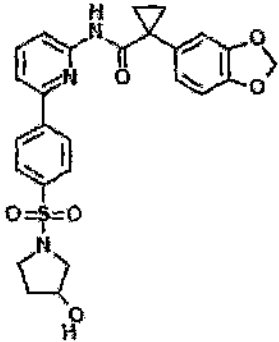
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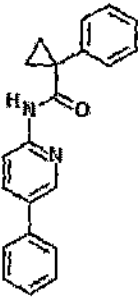
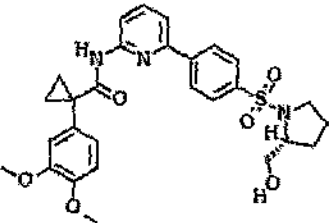
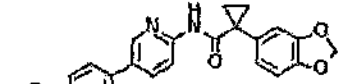
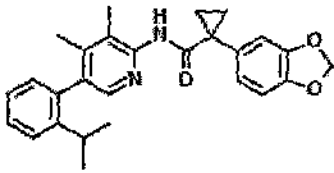
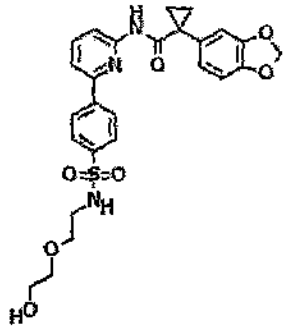
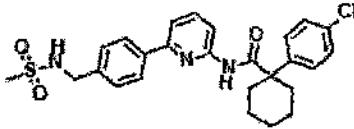
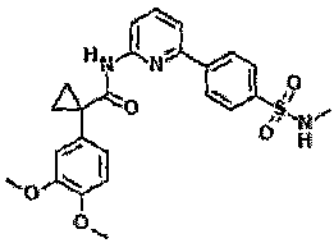
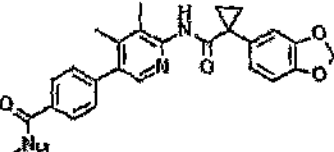
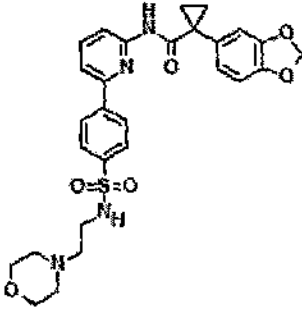
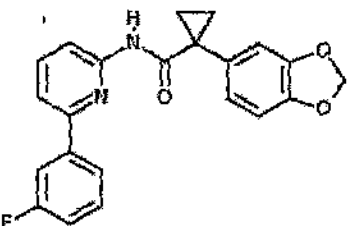
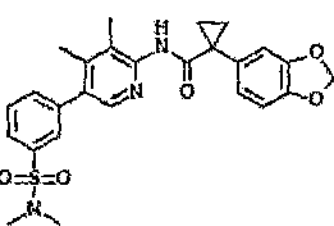
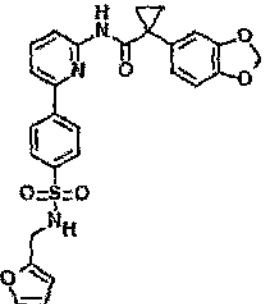
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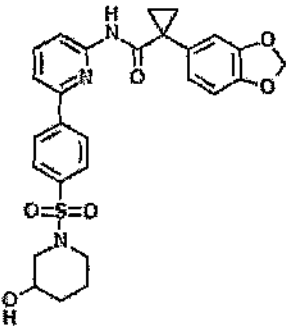
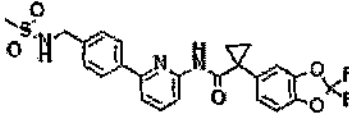
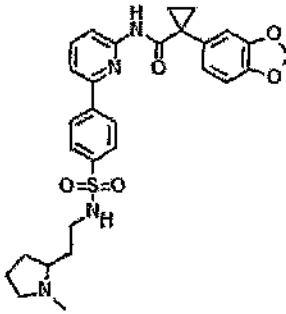
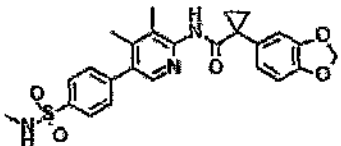
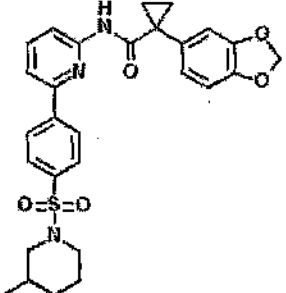
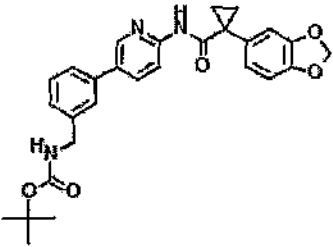
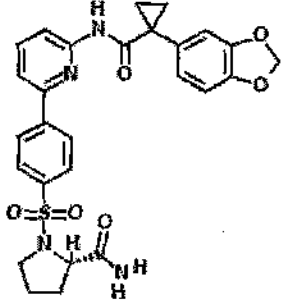
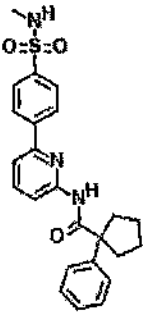
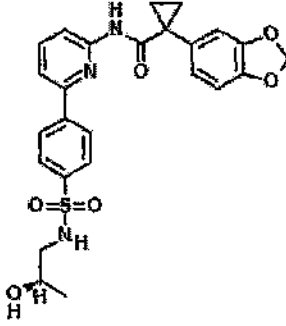
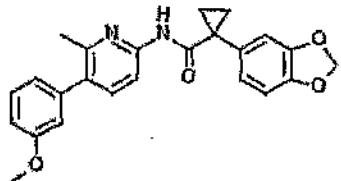
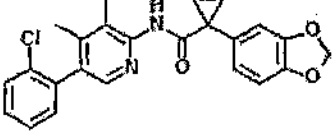
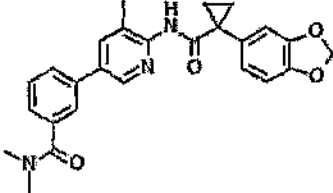
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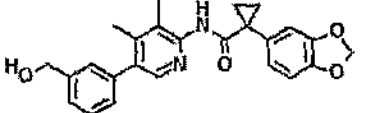
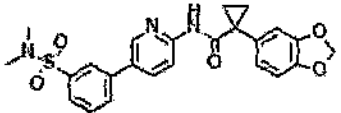
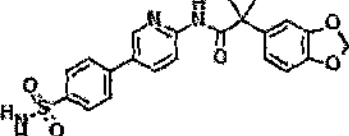
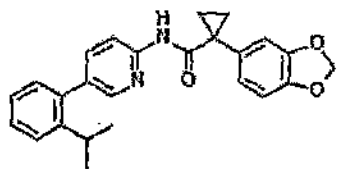
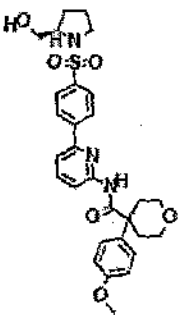
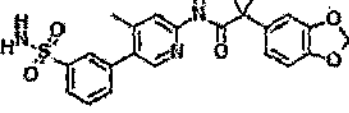
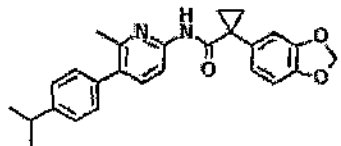
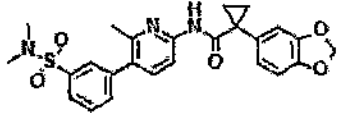
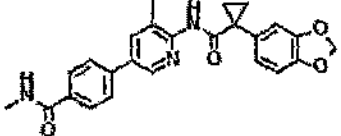
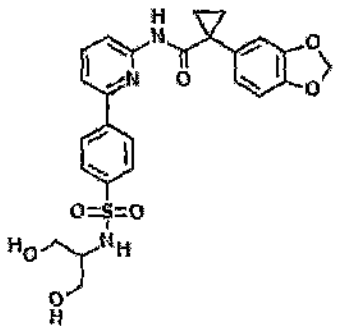
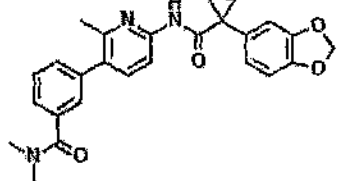
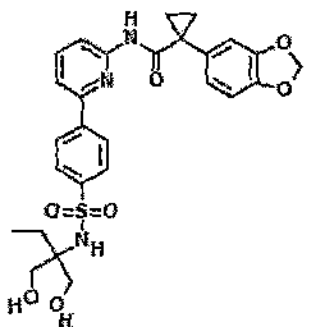
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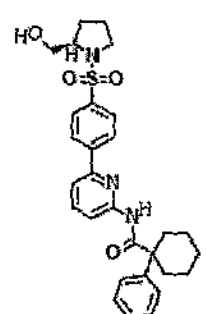
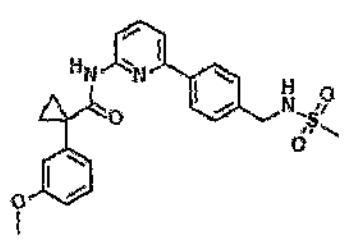
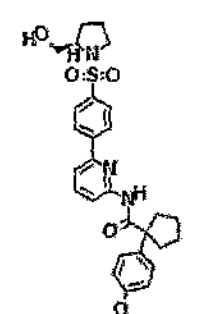
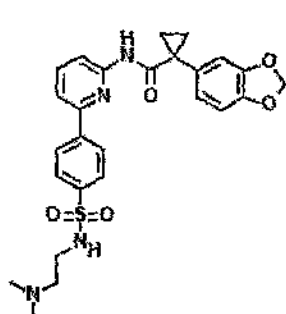
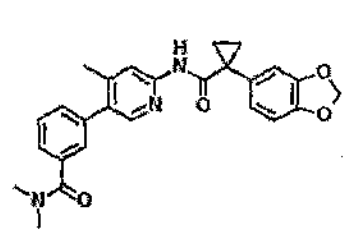
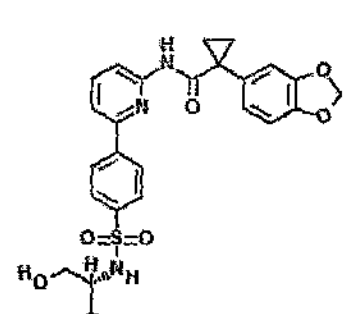
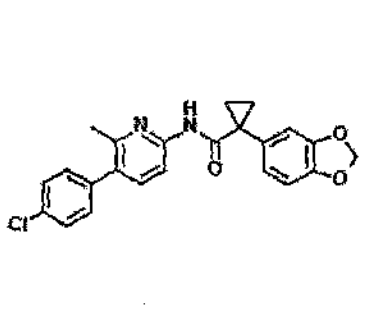
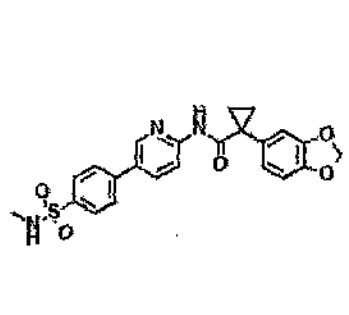
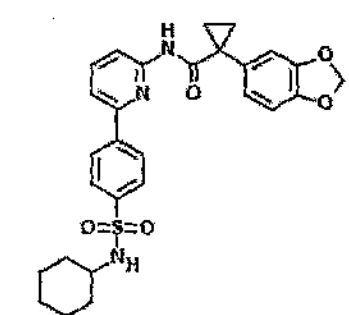
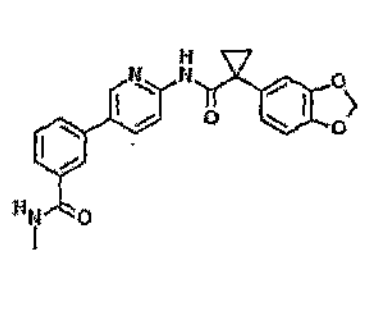
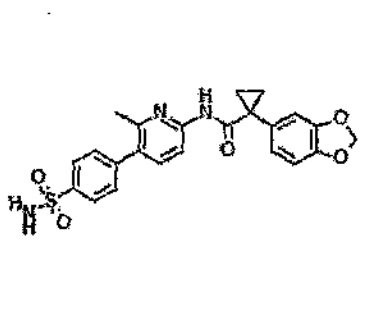
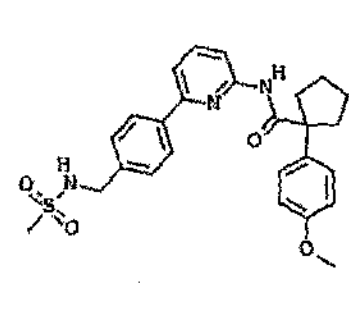
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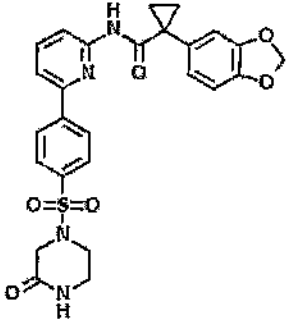
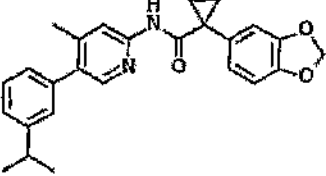
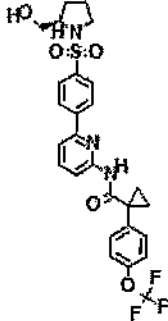
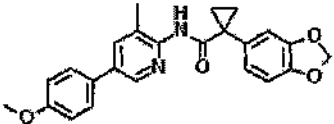
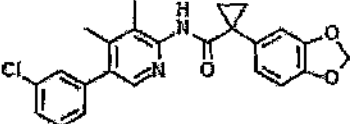
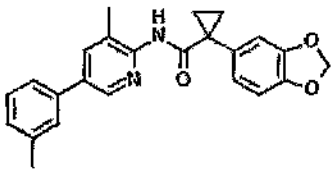
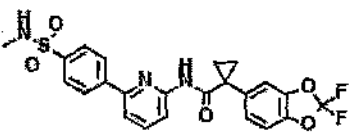
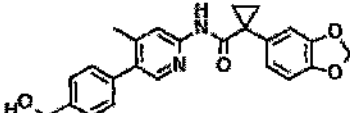
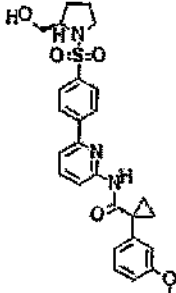
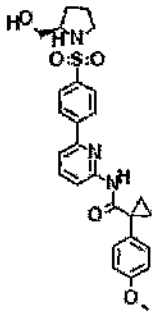
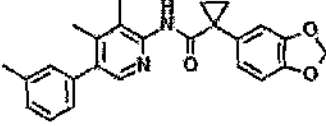
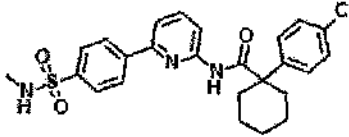
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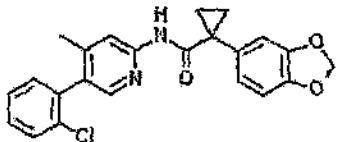
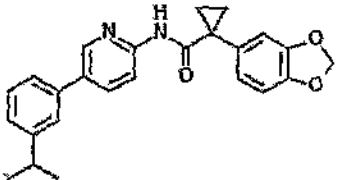
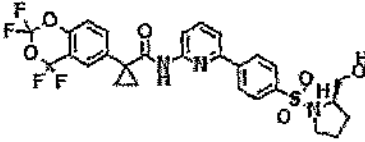
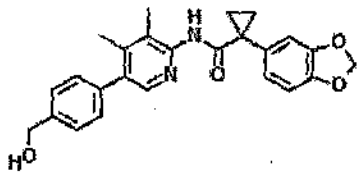
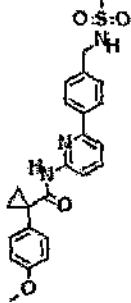
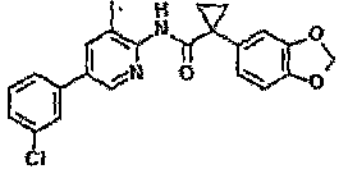
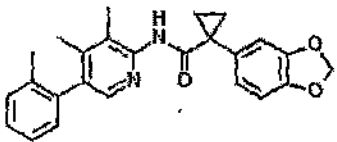
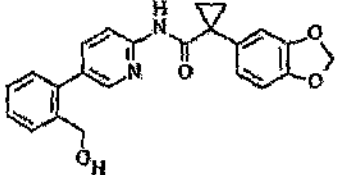
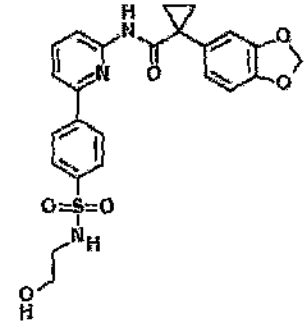
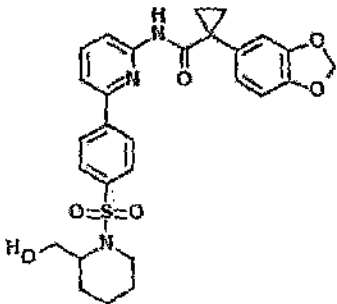
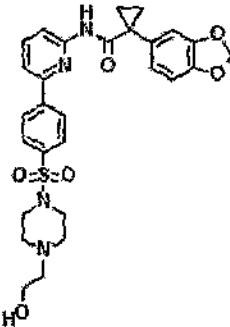
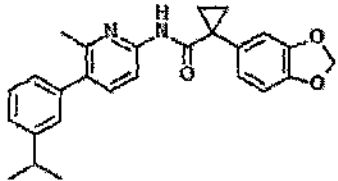
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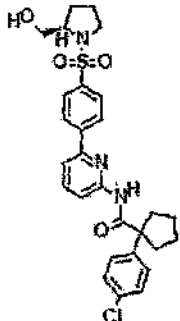
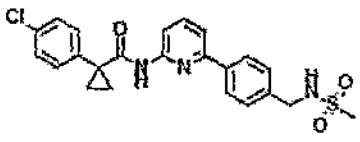
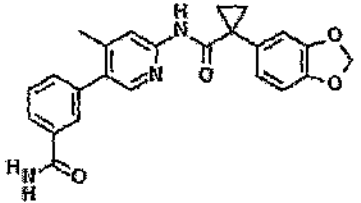
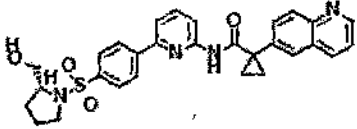
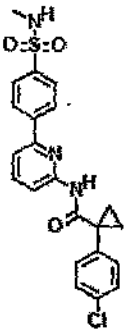
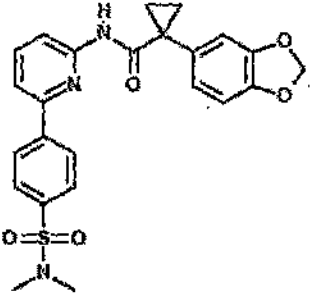
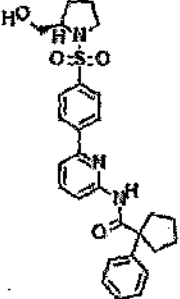
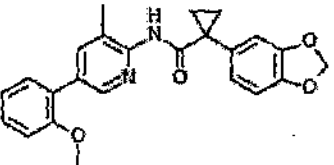
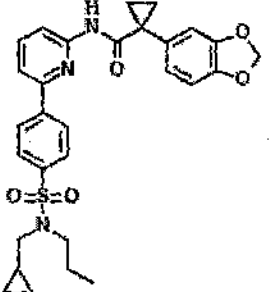
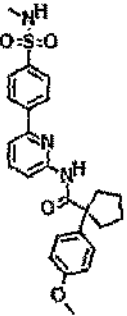
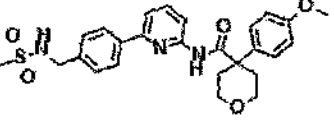
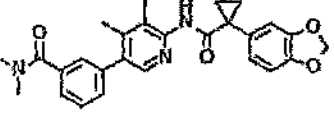
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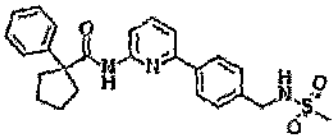
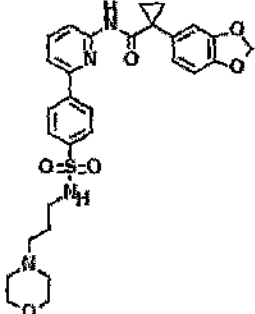
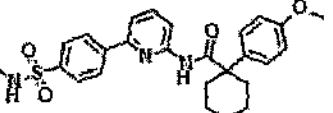
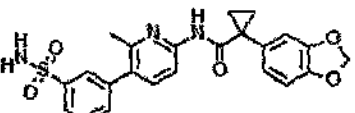
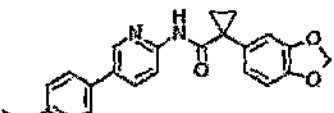
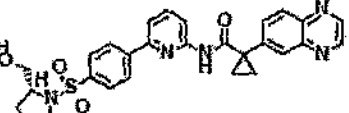
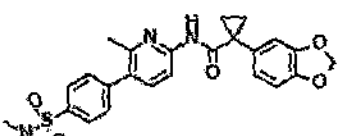
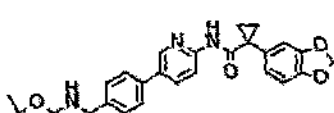
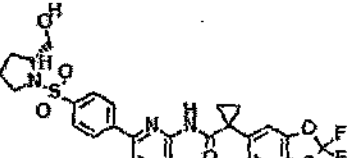
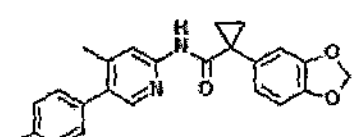
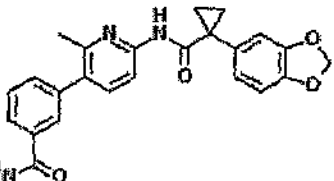
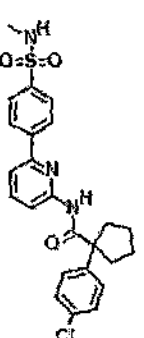
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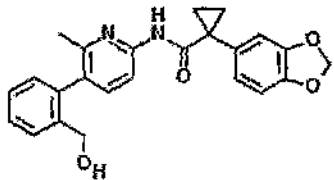
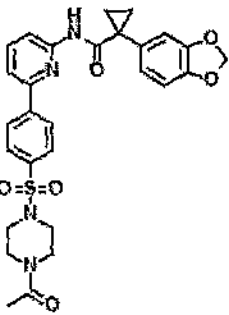
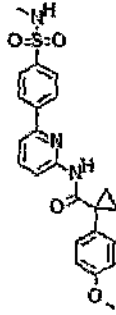
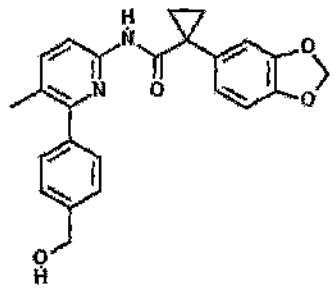
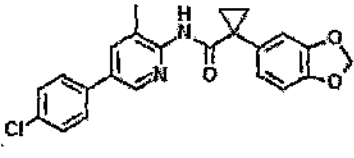
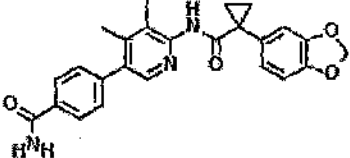
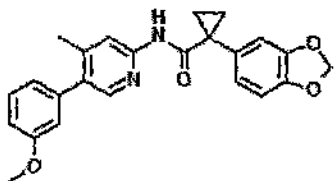
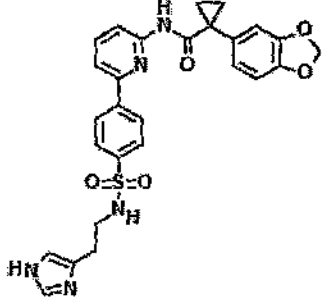
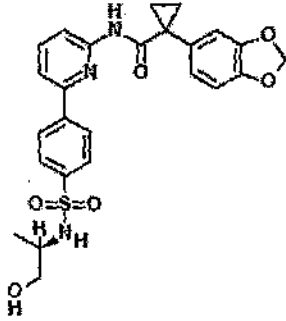
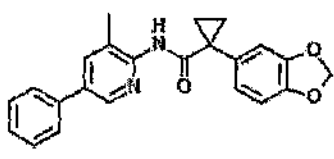
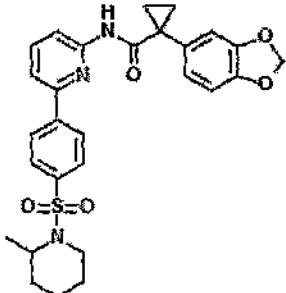
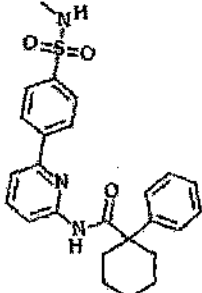
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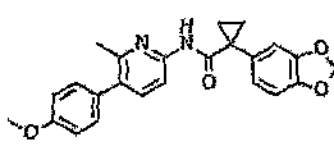
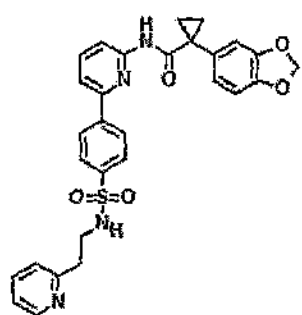
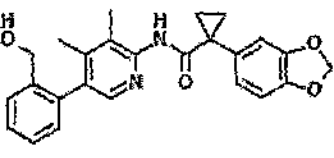
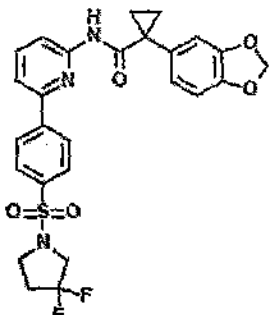
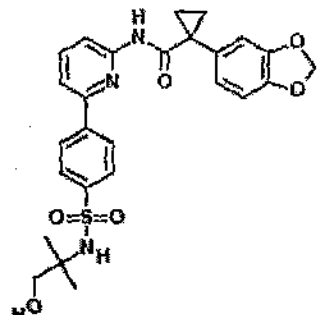
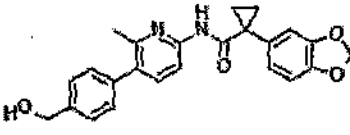
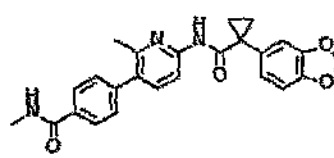
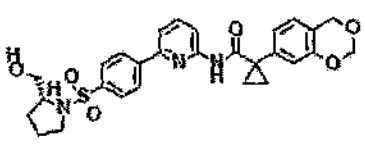
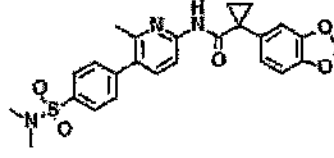
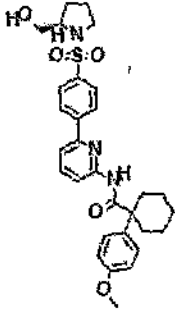
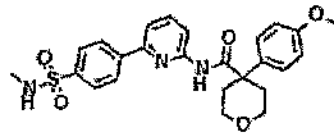
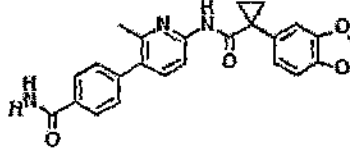
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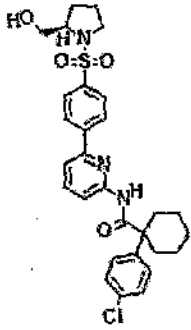
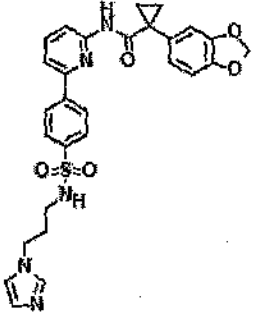
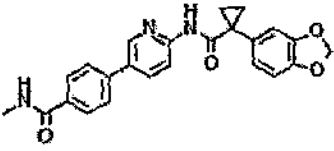
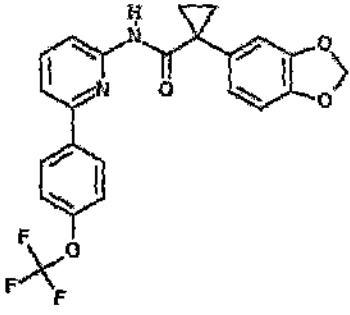
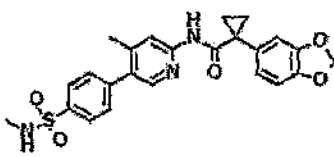
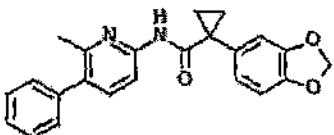
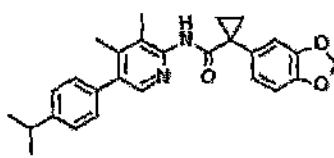
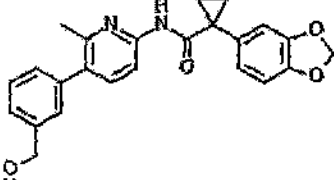
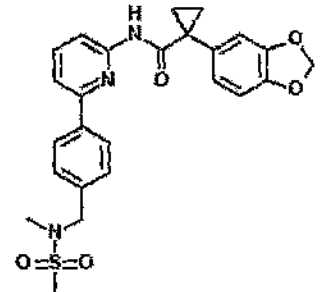
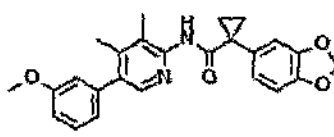
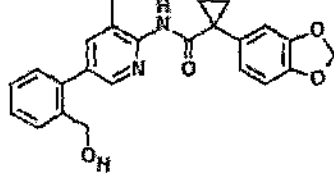
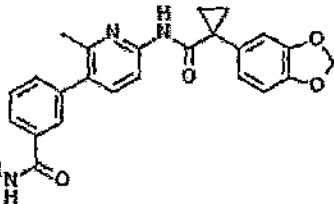
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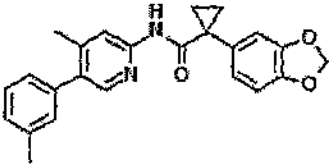
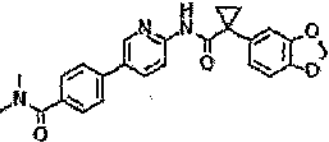
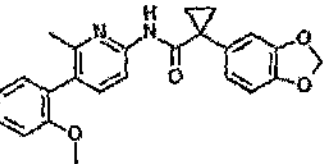
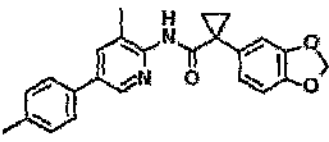
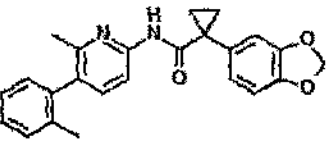
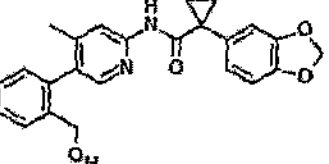
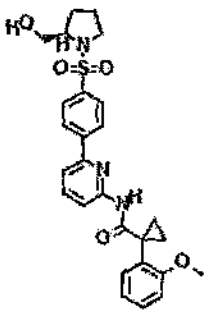
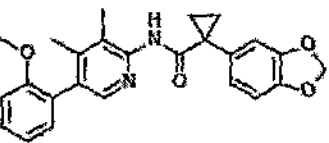
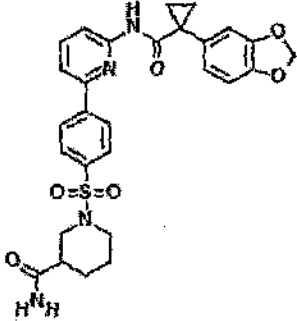
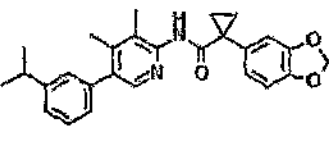
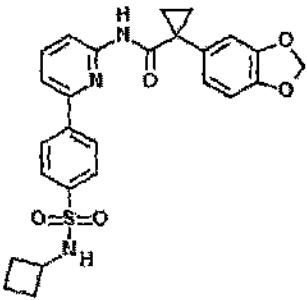
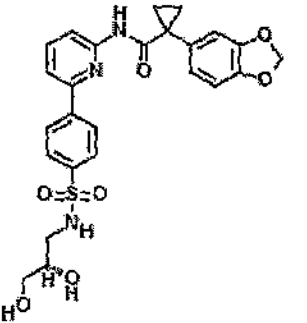
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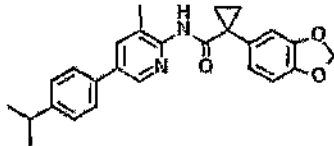
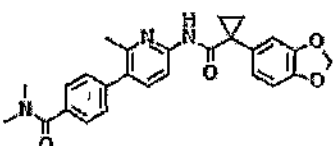
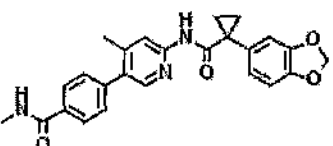
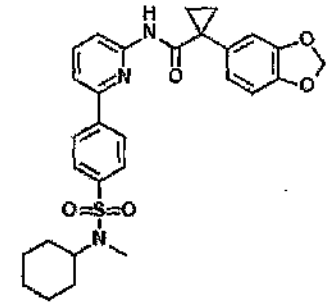
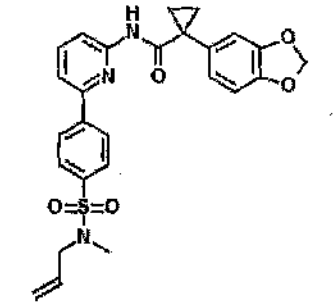
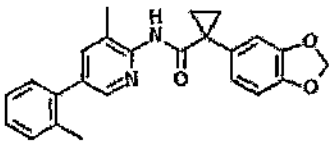
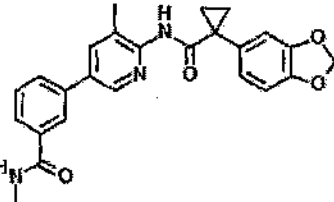
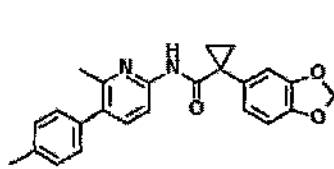
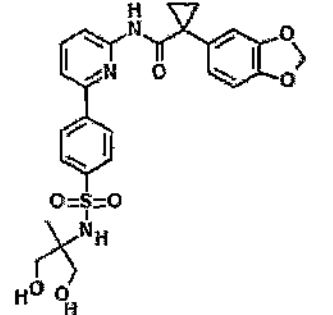
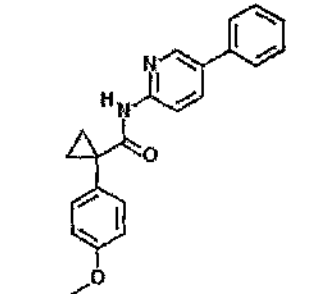
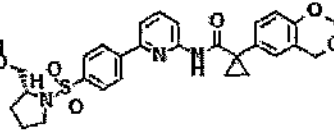
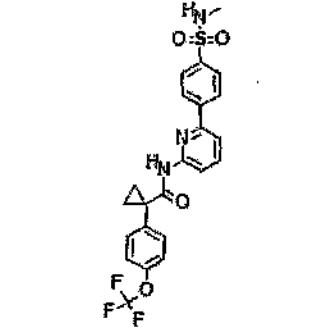
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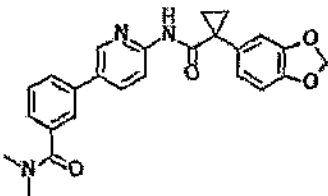
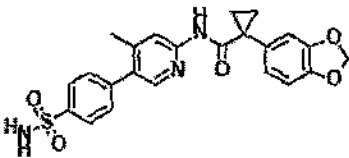
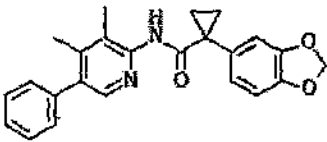
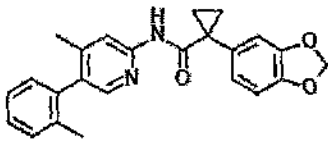
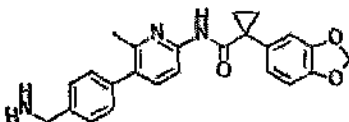
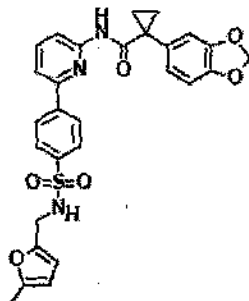
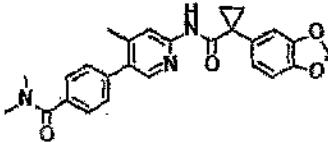
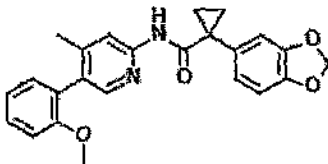
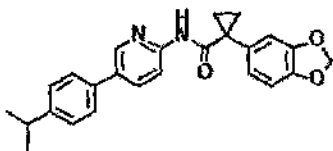
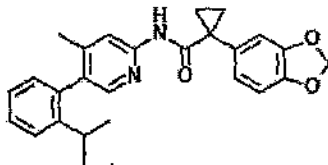
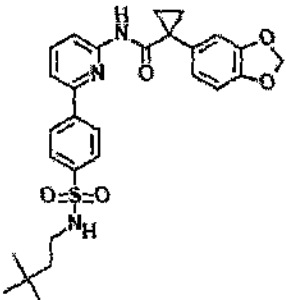
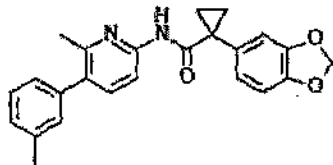
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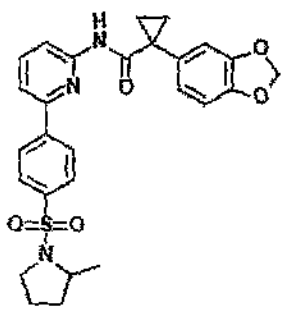
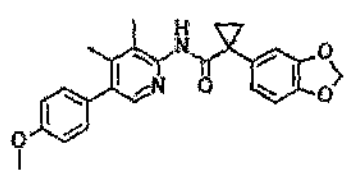
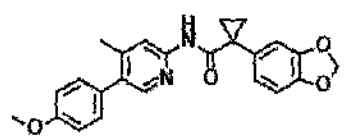
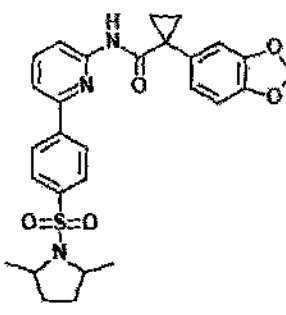
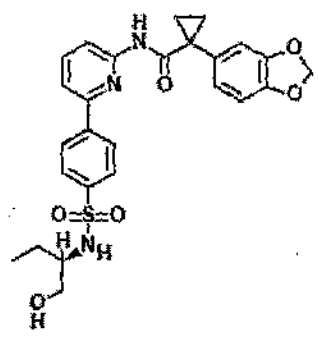
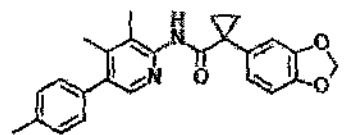
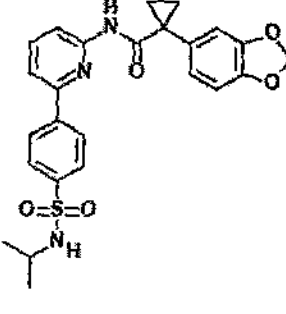
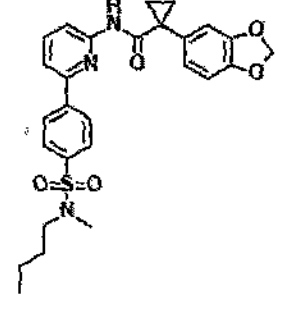
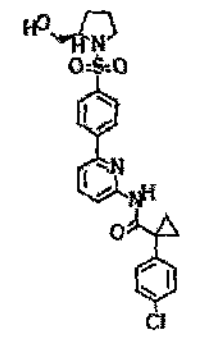
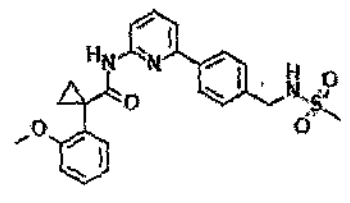
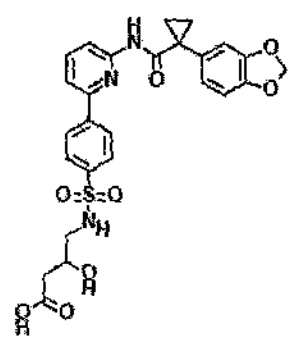
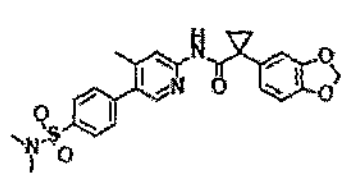
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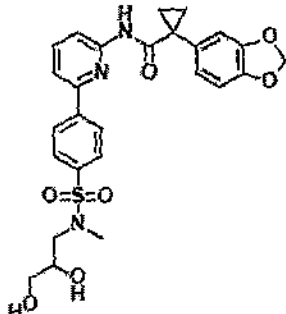
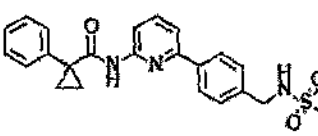
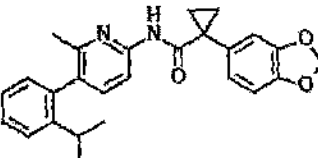
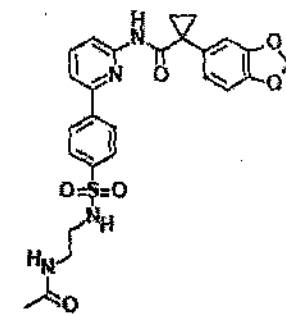
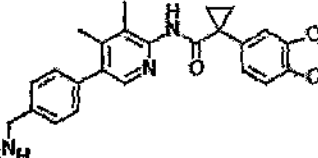
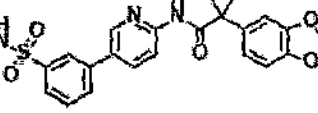
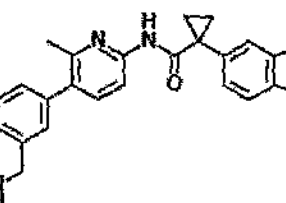
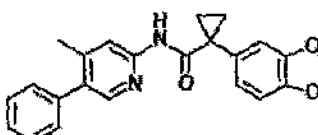
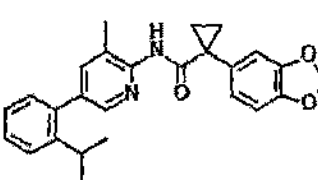
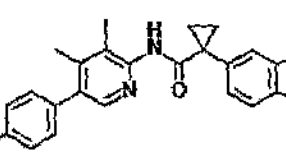
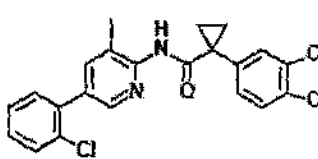
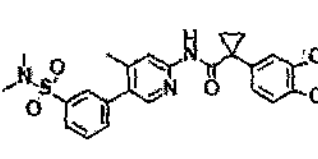
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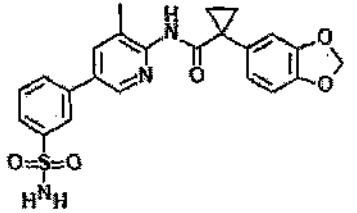
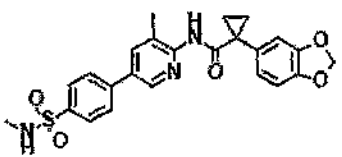
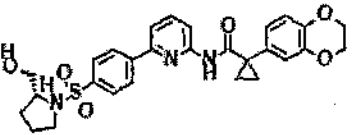
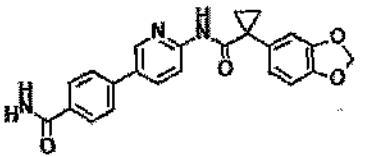
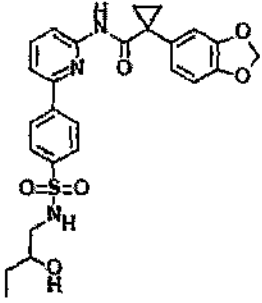
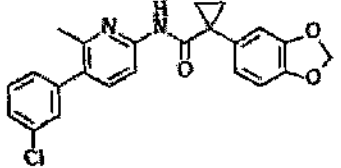
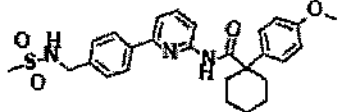
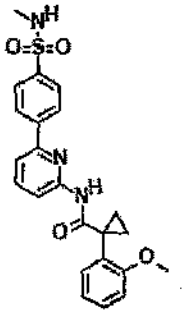
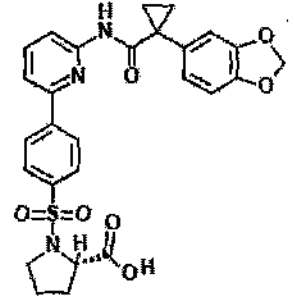
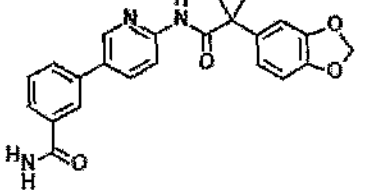
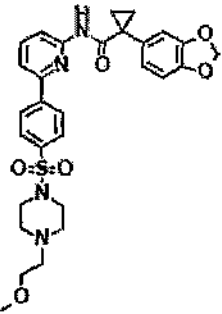
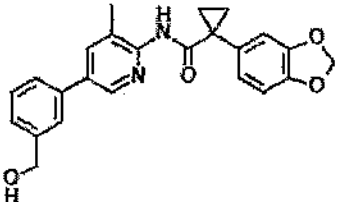
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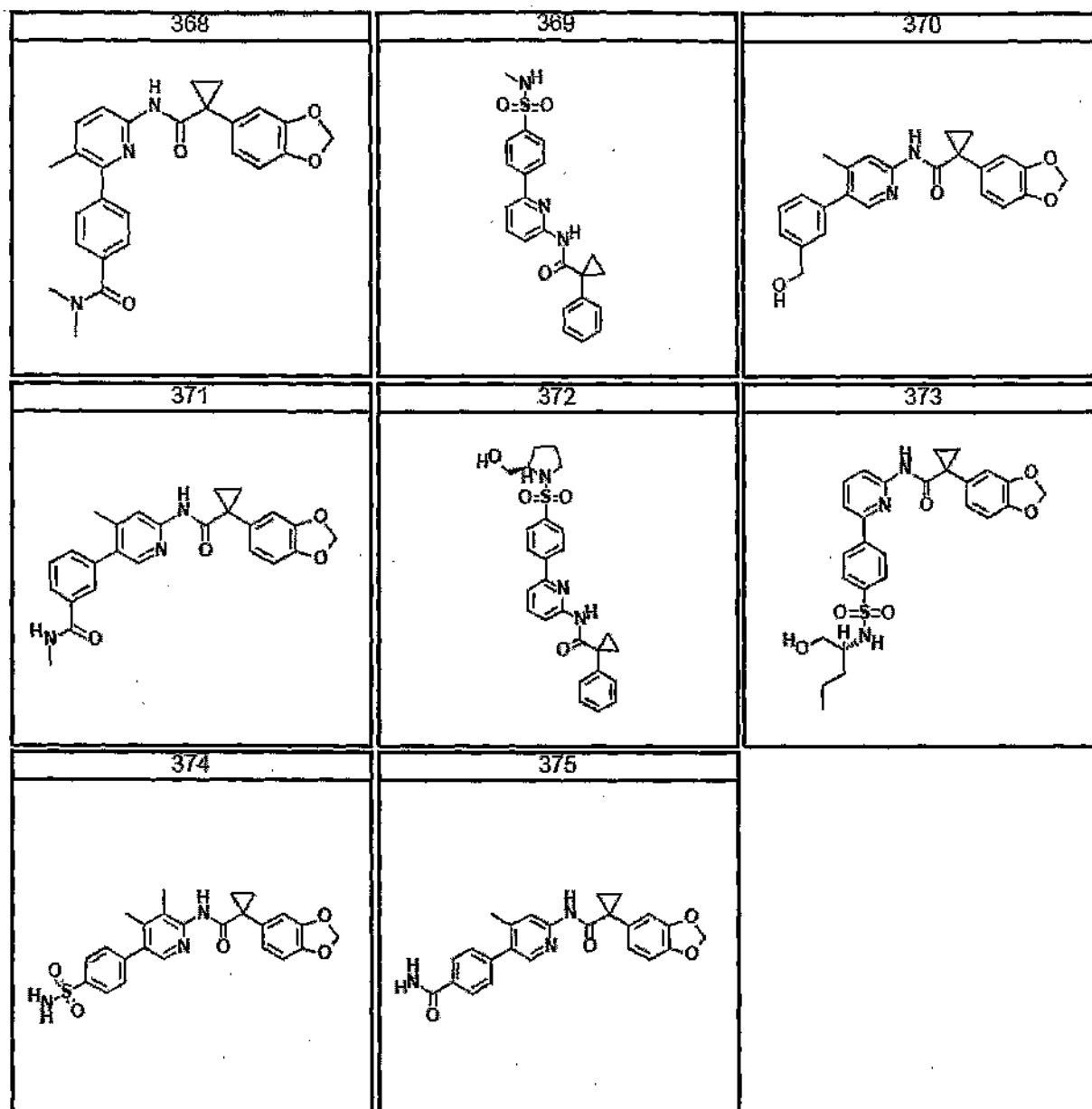
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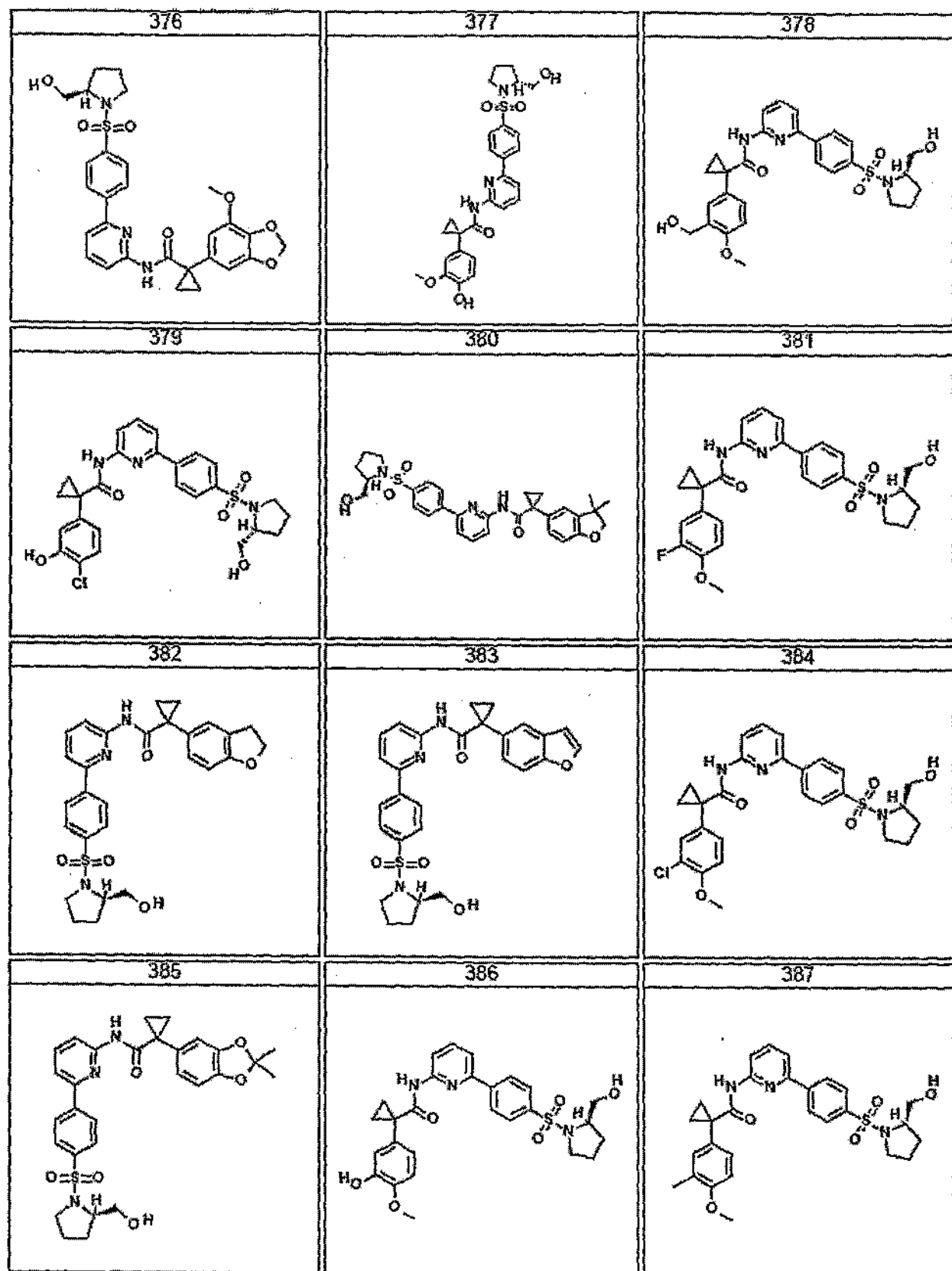
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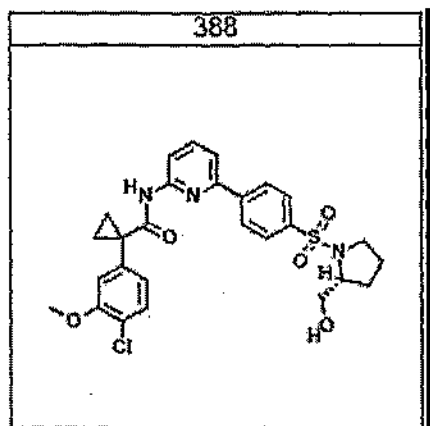
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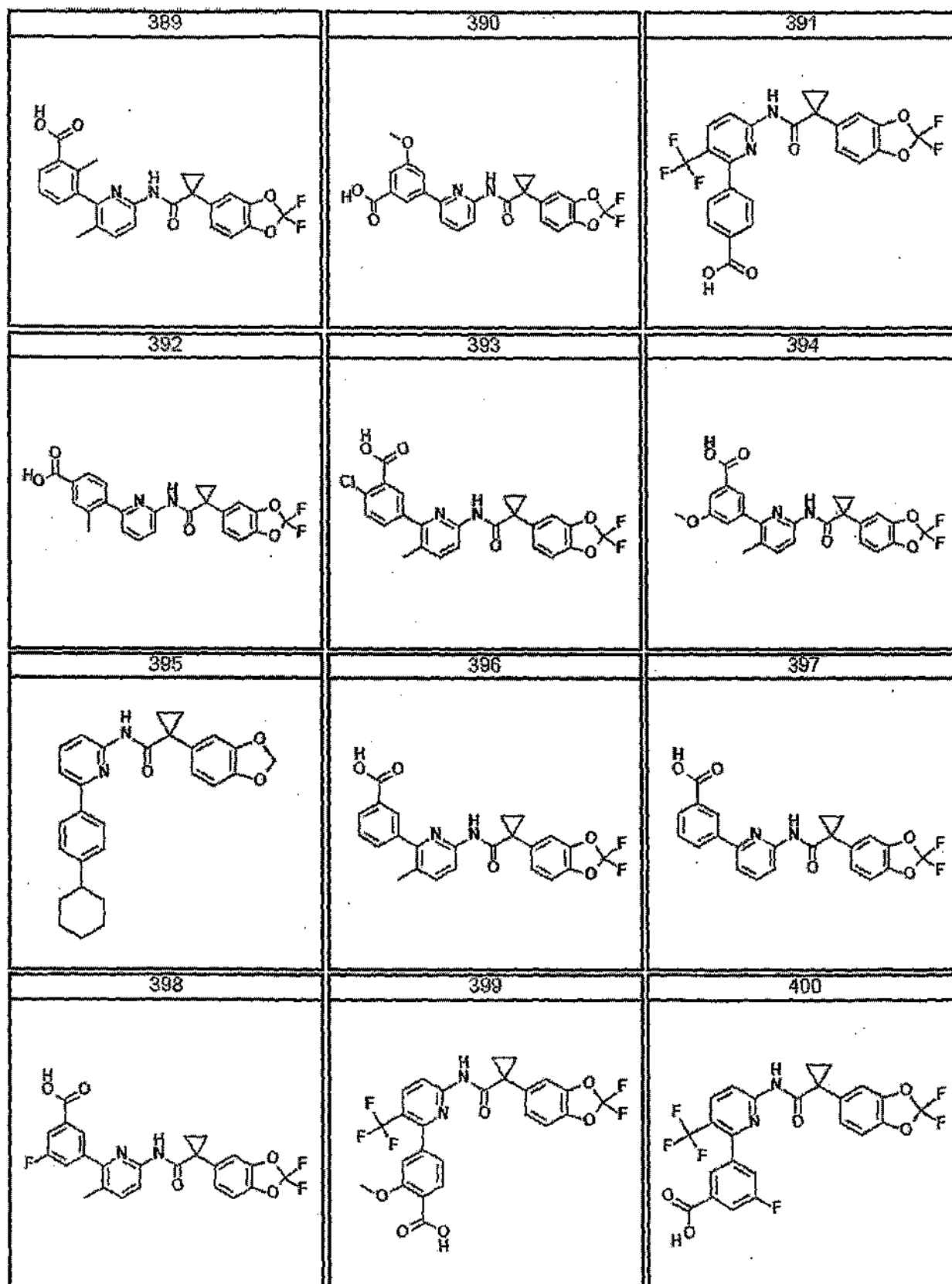




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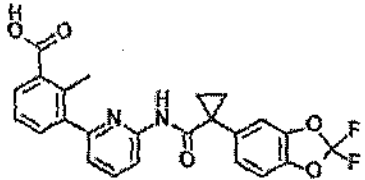
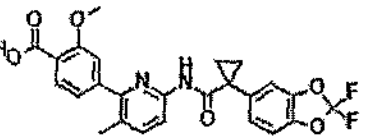
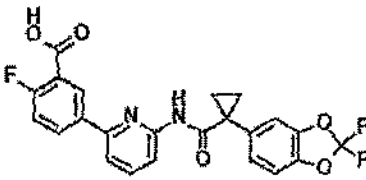
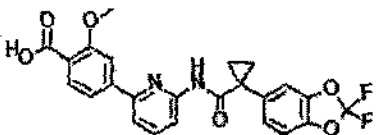
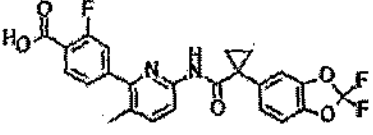
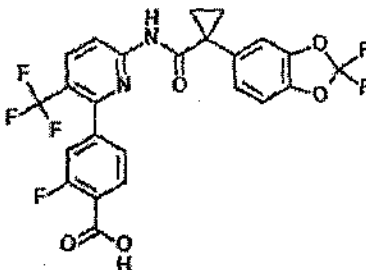
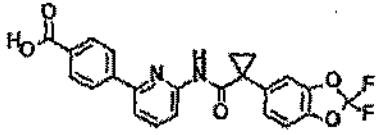
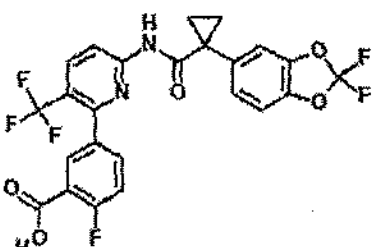
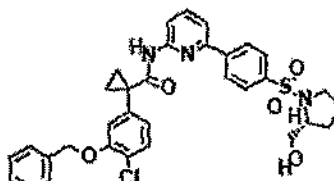
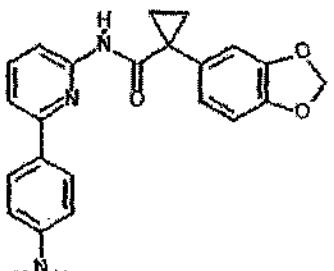
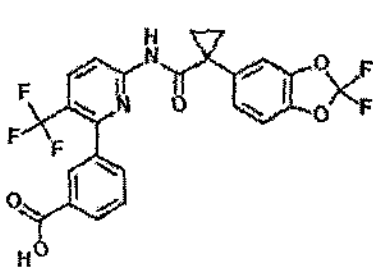
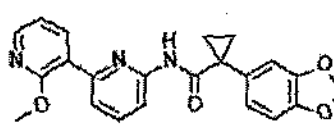
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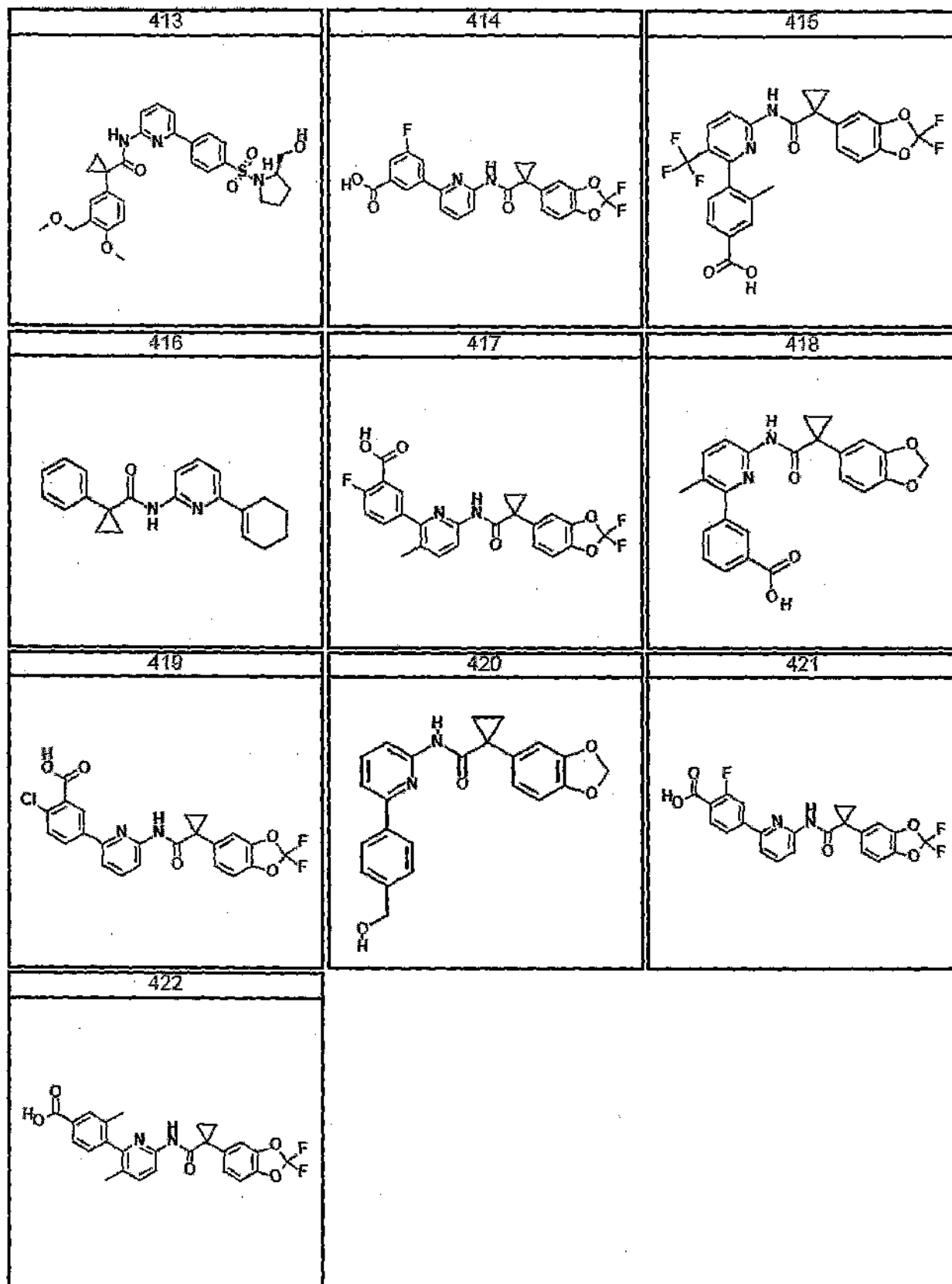
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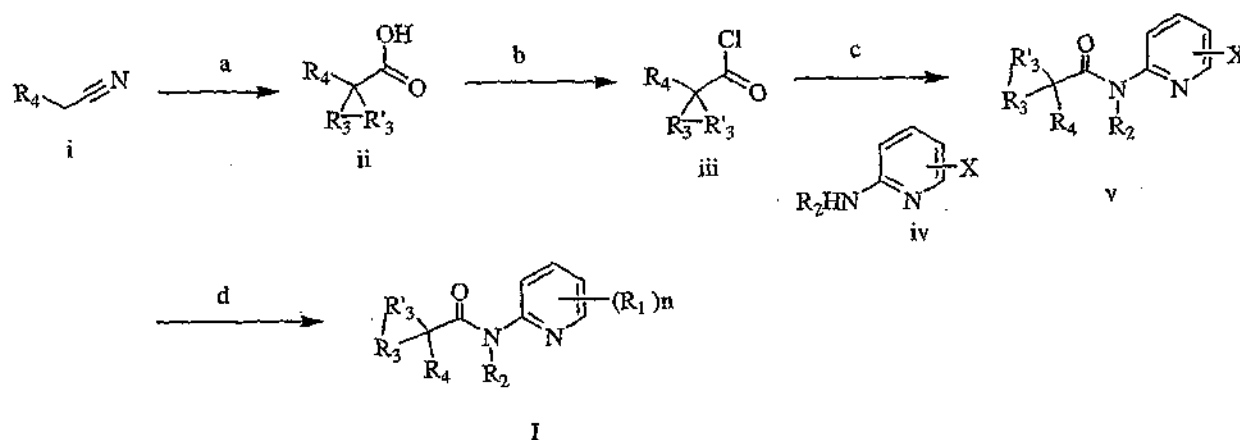


SYNTHETIC SCHEMES

[00308] Compounds of the invention may be prepared by known methods or as illustrated in the examples. In one instance wherein R_1 is aryl or heteroaryl, the compounds of

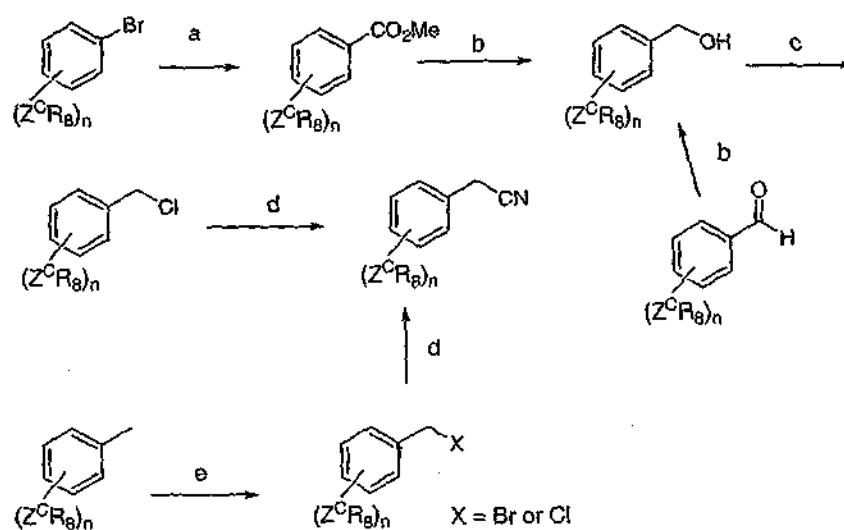
the invention may be prepared as illustrated in Scheme I.

[00309] Scheme I



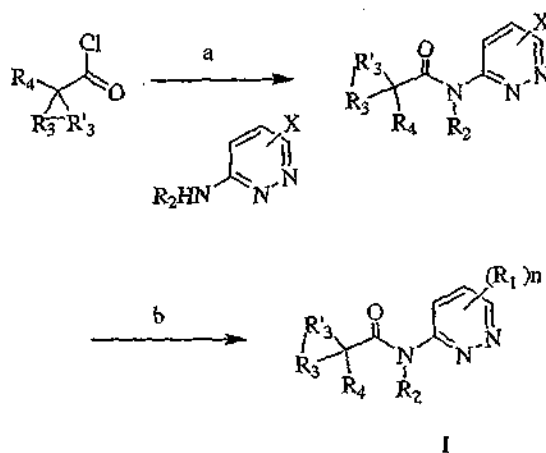
a) 50% NaOH, X-R₃-R'₃-Y, BTEAC; X, Y= leaving group; b) SOCl₂, DMF; c) pyridine; d) R₁-B(OR)₂, Pd(dppf)Cl₂, K₂CO₃, DMF, H₂O

[00310] Scheme II



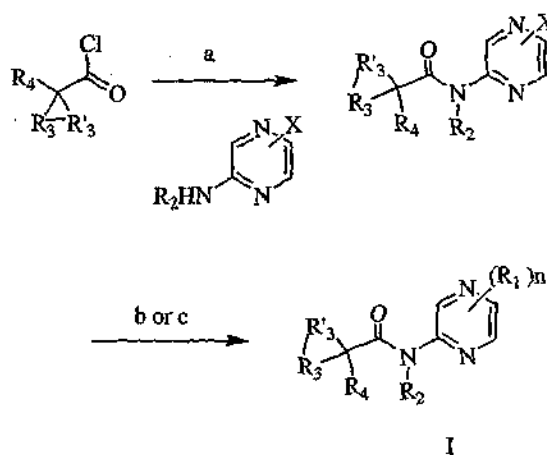
a) Pd(PPh₃)₄, CO, MeOH; b) LiAlH₄, THF; c) SOCl₂; d) NaCN; e) NBS or NCS, AIBN, CX₄ (X = Br or Cl)

[00311] Scheme III



a) pyridine, DCM; b) $R_1\text{-B(OR)}_2$, Pd(dppf)Cl_2 , K_2CO_3 , DMF, H_2O

[00312] Scheme IV

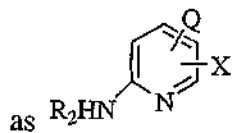


a) pyridine, DCM; b) $R_1\text{-B(OR)}_2$, Pd(dppf)Cl_2 , K_2CO_3 , DMF, H_2O

[00313] Referring to Scheme I, a nitrile of formula i is alkylated (step a) with a dihalo-aliphatic in the presence of a base such as, for example, 50% sodium hydroxide and, optionally, a phase transfer reagent such as, for example, benzyltriethylammonium chloride (BTEAC), to produce the corresponding alkylated nitrile (not shown) which on hydrolysis produces the acid ii. Compounds of formula ii are converted to the acid chloride iii with a suitable reagent such as, for example, thionyl chloride/DMF. Reaction of the acid chloride iii with an aminopyridine, wherein X is a halo, of formula iv (step c) produces the amide of formula v. Reaction of the amide v with an optionally substituted boronic acid derivative (step d) in the presence of a catalyst such as, for example, palladium acetate or dichloro-[1,1-bis(diphenylphosphino) ferrocene] palladium(II) (Pd(dppf)Cl_2), provides compounds of the invention wherein R_1 is aryl, heteroaryl, or cycloalkenyl. The boronic acid derivatives vi are commercially available or may be prepared by known methods such as reaction of an aryl bromide with a diborane ester in the presence of a coupling reagent such as, for example,

palladium acetate as described in the examples.

[00314] In another instance where one R_1 is aryl and another R_1 is an aliphatic, alkoxy, cycloaliphatic, or heterocycloaliphatic, compounds of the invention can be prepared as described in steps a, b, and c of Scheme I using an appropriately substituted aminopyridine such



as R_2HN , where X is halo and Q is C_{1-6} aliphatic, aryl, heteroaryl, or 3 to 10 membered cycloaliphatic or heterocycloaliphatic as a substitute for the aminopyridine of formula iv.

FORMULATIONS, ADMINISTRATIONS, AND USES

Pharmaceutically acceptable compositions

[00315] Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00316] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative or a prodrug thereof. According to the present invention, a pharmaceutically acceptable derivative or a prodrug includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00317] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[00318] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of

the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00319] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington: *The Science and Practice of Pharmacy*, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, the contents of each of which is incorporated by reference herein, disclose various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or

otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Uses of compounds and pharmaceutically acceptable compositions

[00320] In yet another aspect, the present invention provides a method of treating a condition, disease, or disorder implicated by ABC transporter activity. In certain embodiments, the present invention provides a method of treating a condition, disease, or disorder implicated by a deficiency of ABC transporter activity, the method comprising administering a composition comprising a compound of formulae (I, II, III, IV, V-A, V-B, I', I'-A, and I'-B) to a subject, preferably a mammal, in need thereof.

[00321] In certain preferred embodiments, the present invention provides a method of treating Cystic fibrosis, Hereditary emphysema, Hereditary hemochromatosis, Coagulation-Fibrinolysis deficiencies, such as Protein C deficiency, Type 1 hereditary angioedema, Lipid processing deficiencies, such as Familial hypercholesterolemia, Type 1 chylomicronemia, Abetalipoproteinemia, Lysosomal storage diseases, such as I-cell disease/Pseudo-Hurler, Mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II,

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Polyendocrinopathy/Hyperinsulemia, Diabetes mellitus, Laron dwarfism, Myeloperoxidase deficiency, Primary hypoparathyroidism, Melanoma, Glycanosis CDG type 1, Hereditary emphysema, Congenital hyperthyroidism, Osteogenesis imperfecta, Hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), Neurophyseal DI, Nephrogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders such as Huntington, Spinocerebellar ataxia type I, Spinal and bulbar muscular atrophy, Dentatorubal pallidoluyian, and Myotonic dystrophy, as well as Spongiform encephalopathies, such as Hereditary Creutzfeldt-Jakob disease (due to Prion protein processing defect), Fabry disease, Straussler-Scheinker disease, secretory diarrhea, polycystic kidney disease, chronic obstructive pulmonary disease (COPD), dry eye disease, and Sjögren's Syndrome, comprising the step of administering to said mammal an effective amount of a composition comprising a compound of formulae (I, II, III, IV, V-A, V-B, I', I'-A, and I'-B), or a preferred embodiment thereof as set forth above.

[00322] According to an alternative preferred embodiment, the present invention provides a method of treating cystic fibrosis comprising the step of administering to said mammal a composition comprising the step of administering to said mammal an effective amount of a composition comprising a compound of formulae (I, II, III, IV, V-A, V-B, I', I'-A, and I'-B), or a preferred embodiment thereof as set forth above.

[00323] According to the invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of Cystic fibrosis, Hereditary emphysema, Hereditary hemochromatosis, Coagulation-Fibrinolysis deficiencies, such as Protein C deficiency, Type 1 hereditary angioedema, Lipid processing deficiencies, such as Familial hypercholesterolemia, Type 1 chylomicronemia, Abetalipoproteinemia, Lysosomal storage diseases, such as I-cell disease/Pseudo-Hurler, Mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, Polyendocrinopathy/Hyperinsulemia, Diabetes mellitus, Laron dwarfism, Myeloperoxidase deficiency, Primary hypoparathyroidism, Melanoma, Glycanosis CDG type 1, Hereditary emphysema, Congenital hyperthyroidism, Osteogenesis imperfecta, Hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), Neurophyseal DI, Nephrogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders as such as

Huntington, Spinocerebellar ataxia type I, Spinal and bulbar muscular atrophy, Dentatorubal pallidoluisian, and Myotonic dystrophy, as well as Spongiform encephalopathies, such as Hereditary Creutzfeldt-Jakob disease, Fabry disease, Straussler-Scheinker disease, secretory diarrhea, polycystic kidney disease, chronic obstructive pulmonary disease (COPD), dry eye disease, and Sjögren's Syndrome.

[00324] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of Cystic fibrosis, Hereditary emphysema, Hereditary hemochromatosis, Coagulation-Fibrinolysis deficiencies, such as Protein C deficiency, Type 1 hereditary angioedema, Lipid processing deficiencies, such as Familial hypercholesterolemia, Type 1 chylomicronemia, Abetalipoproteinemia, Lysosomal storage diseases, such as I-cell disease/Pseudo-Hurler, Mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, Polyendocrinopathy/Hyperinsulemia, Diabetes mellitus, Laron dwarfism, Myeloperoxidase deficiency, Primary hypoparathyroidism, Melanoma, Glycanosis CDG type 1, Hereditary emphysema, Congenital hyperthyroidism, Osteogenesis imperfecta, Hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), Neurophyseal DI, Nephrogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders as such as Huntington, Spinocerebellar ataxia type I, Spinal and bulbar muscular atrophy, Dentatorubal pallidoluisian, and Myotonic dystrophy, as well as Spongiform encephalopathies, such as Hereditary Creutzfeldt-Jakob disease, Fabry disease, Straussler-Scheinker disease, secretory diarrhea, polycystic kidney disease, chronic obstructive pulmonary disease (COPD), dry eye disease, and Sjögren's Syndrome.

[00325] The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the

specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00326] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00327] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00328] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00329] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00330] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00331] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00332] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form

may also comprise buffering agents.

[00333] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00334] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00335] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across

the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00336] As described generally above, the compounds of the invention are useful as modulators of ABC transporters. Thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where hyperactivity or inactivity of ABC transporters is implicated in the disease, condition, or disorder. When hyperactivity or inactivity of an ABC transporter is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as an "ABC transporter-mediated disease, condition or disorder". Accordingly, in another aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where hyperactivity or inactivity of an ABC transporter is implicated in the disease state.

[00337] The activity of a compound utilized in this invention as a modulator of an ABC transporter may be assayed according to methods described generally in the art and in the Examples herein.

[00338] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[00339] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the

only therapeutically active agent.

[00340] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[00341] Another aspect of the invention relates to modulating ABC transporter activity in a biological sample or a patient (e.g., *in vitro* or *in vivo*), which method comprises administering to the patient, or contacting said biological sample with a compound of formula I or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00342] Modulation of ABC transporter activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of ABC transporters in biological and pathological phenomena; and the comparative evaluation of new modulators of ABC transporters.

[00343] In yet another embodiment, a method of modulating activity of an anion channel *in vitro* or *in vivo*, is provided comprising the step of contacting said channel with a compound of formulae (I, II, III, IV, V-A, V-B, I', I'-A, and I'-B). In preferred embodiments, the anion channel is a chloride channel or a bicarbonate channel. In other preferred embodiments, the anion channel is a chloride channel.

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[00344]

According to an alternative embodiment, the present invention provides a method of increasing the number of functional ABC transporters in a membrane of a cell, comprising the step of contacting said cell with a compound of formula (I, II, III, IV, V-A, V-B, I', I'-A, and I'-B). The term "functional ABC transporter" as used herein means an ABC transporter that is capable of transport activity. In preferred embodiments, said functional ABC transporter is CFTR.

[00345]

According to another preferred embodiment, the activity of the ABC transporter is measured by measuring the transmembrane voltage potential. Means for measuring the voltage potential across a membrane in the biological sample may employ any of the known methods in the art, such as optical membrane potential assay or other electrophysiological methods.

[00346]

The optical membrane potential assay utilizes voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" *Biophys J* 69(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" *Chem Biol* 4(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" *Drug Discov Today* 4(9): 431-439).

[00347]

These voltage sensitive assays are based on the change in fluorescence resonant energy transfer (FRET) between the membrane-soluble, voltage-sensitive dye, DiSBAC₂(3), and a fluorescent phospholipid, CC2-DMPE, which is attached to the outer leaflet of the plasma membrane and acts as a FRET donor. Changes in membrane potential (V_m) cause the negatively charged DiSBAC₂(3) to redistribute across the plasma membrane and the amount of energy transfer from CC2-DMPE changes accordingly. The changes in fluorescence emission can be monitored using VIPRTM II, which is an integrated liquid handler and fluorescent detector designed to conduct cell-based screens in 96- or 384-well microtiter plates.

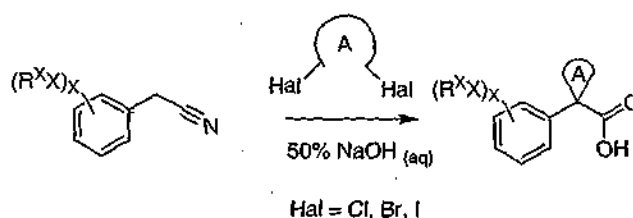
[00348]

In another aspect the present invention provides a kit for use in measuring the activity of a ABC transporter or a fragment thereof in a biological sample *in vitro* or *in vivo* comprising (i) a composition comprising a compound of formula (I, II, III, IV, V-A, V-B, I', I'-A, and I'-B) or any of the above embodiments; and (ii) instructions for a.) contacting the composition with the biological sample and b.) measuring activity of said ABC transporter or a fragment thereof. In one embodiment, the kit further comprises instructions for a.) contacting

an additional composition with the biological sample; b.) measuring the activity of said ABC transporter or a fragment thereof in the presence of said additional compound, and c.) comparing the activity of the ABC transporter in the presence of the additional compound with the density of the ABC transporter in the presence of a composition of formula (I, II, III, IV, V-A, V-B, I', I'-A, and I'-B). In preferred embodiments, the kit is used to measure the density of CFTR.

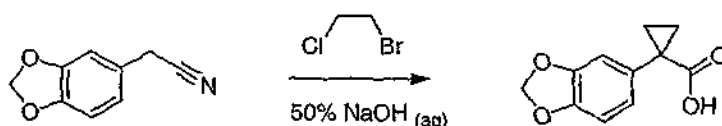
PREPARATIONS AND EXAMPLES

General Procedure I: Carboxylic Acid Building Block



[00349] Benzyltriethylammonium chloride (0.025 equivalents) and the appropriate dihalo compound (2.5 equivalents) were added to a substituted phenyl acetonitrile. The mixture was heated at 70 °C and then 50% sodium hydroxide (10 equivalents) was slowly added to the mixture. The reaction was stirred at 70 °C for 12-24 hours to ensure complete formation of the cycloalkyl moiety and then heated at 130 °C for 24-48 hours to ensure complete conversion from the nitrile to the carboxylic acid. The dark brown / black reaction mixture was diluted with water and extracted with ethyl acetate and then dichloromethane three times each to remove side products. The basic aqueous solution was acidified with concentrated hydrochloric acid to pH less than one and the precipitate which began to form at pH 4 was filtered and washed with 1 M hydrochloric acid two times. The solid material was dissolved in dichloromethane and extracted two times with 1 M hydrochloric acid and one time with a saturated aqueous solution of sodium chloride. The organic solution was dried over sodium sulfate and evaporated to dryness to give the cycloalkylcarboxylic acid.

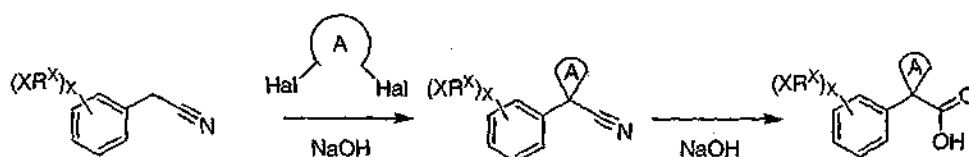
A. 1-Benzo[1,3]dioxol-5-yl-cyclopropanecarboxylic acid



[00350] A mixture of benzo[1,3]dioxole-5-acetonitrile (5.10 g, 31.7 mmol), 1-bromo-2-chloro-ethane (9.00 mL, 109 mmol), and benzyltriethylammonium chloride (0.181 g, 0.795 mmol) was heated at 70 °C and then 50% (wt./wt.) aqueous sodium hydroxide (26 mL) was slowly added to the mixture. The reaction was stirred at 70 °C for 18 hours and then heated

at 130 °C for 24 hours. The dark brown reaction mixture was diluted with water (400 mL) and extracted once with an equal volume of ethyl acetate and once with an equal volume of dichloromethane. The basic aqueous solution was acidified with concentrated hydrochloric acid to pH less than one and the precipitate filtered and washed with 1 M hydrochloric acid. The solid material was dissolved in dichloromethane (400 mL) and extracted twice with equal volumes of 1 M hydrochloric acid and once with a saturated aqueous solution of sodium chloride. The organic solution was dried over sodium sulfate and evaporated to dryness to give a white to slightly off-white solid (5.23 g, 80%) ESI-MS m/z calc. 206.1, found 207.1 ($M+1$)⁺. Retention time of 2.37 minutes. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.07-1.11 (m, 2H), 1.38-1.42 (m, 2H), 5.98 (s, 2H), 6.79 (m, 2H), 6.88 (m, 1H), 12.26 (s, 1H).

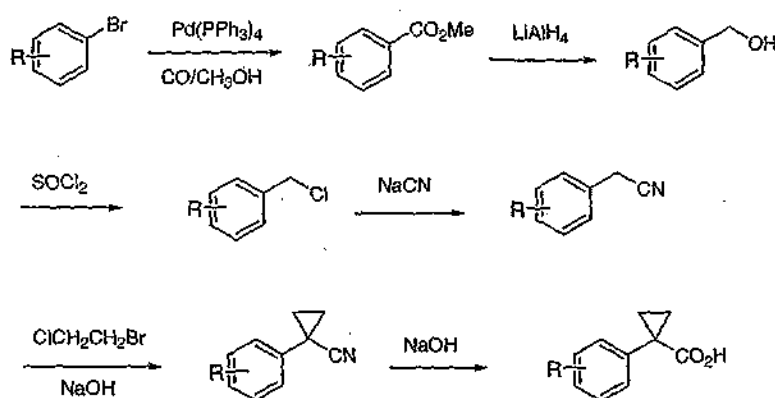
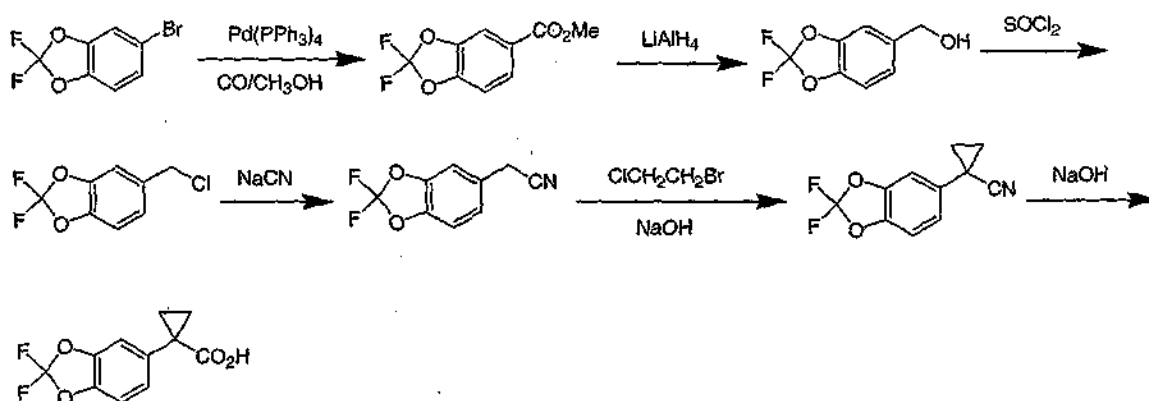
General Procedure II: Carboxylic Acid Building Block



Hal = Cl, Br, I, all other variables are as defined in the text.

[00351] Sodium hydroxide (50% aqueous solution, 7.4 equivalents) was slowly added to a mixture of the appropriate phenyl acetonitrile, benzyltriethylammonium chloride (1.1 equivalents), and the appropriate dihalo compound (2.3 equivalents) at 70 °C. The mixture was stirred overnight at 70 °C and the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated to dryness to give the crude cyclopropanecarbonitrile, which was used directly in the next step.

[00352] The crude cyclopropanecarbonitrile was heated at reflux in 10% aqueous sodium hydroxide (7.4 equivalents) for 2.5 hours. The cooled reaction mixture was washed with ether (100 mL) and the aqueous phase was acidified to pH 2 with 2M hydrochloric acid. The precipitated solid was filtered to give the cyclopropanecarboxylic acid as a white solid.

General Procedure III: Carboxylic Acid Building Block**B. 1-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-cyclopropanecarboxylic acid****[00353] Step a: 2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid methyl ester**

A solution of 5-bromo-2,2-difluoro-benzo[1,3]dioxole (11.8 g, 50.0 mmol) and tetrakis(triphenylphosphine)palladium (0) [Pd(PPh₃)₄, 5.78 g, 5.00 mmol] in methanol (20 mL) containing acetonitrile (30 mL) and triethylamine (10 mL) was stirred under a carbon monoxide atmosphere (55 PSI) at 75 °C (oil bath temperature) for 15 hours. The cooled reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by silica gel column chromatography to give crude 2,2-difluoro-benzo [1,3] dioxole-5-carboxylic acid methyl ester (11.5 g), which was used directly in the next step.

[00354] Step b: (2,2-Difluoro-benzo[1,3]dioxol-5-yl)-methanol

Crude 2,2-difluoro-benzo[1,3]dioxole-5-carboxylic acid methyl ester (11.5 g) dissolved in 20 mL of anhydrous tetrahydrofuran (THF) was slowly added to a suspension of lithium aluminum hydride (4.10 g, 106 mmol) in anhydrous THF (100 mL) at 0 °C. The mixture was then warmed to room temperature. After being stirred at room temperature for 1 hour, the reaction mixture was cooled to 0 °C and treated with water (4.1 g), followed by sodium hydroxide (10% aqueous solution, 4.1 mL). The resulting slurry was filtered and

washed with THF. The combined filtrate was evaporated to dryness and the residue was purified by silica gel column chromatography to give (2,2-difluoro-benzo[1,3]dioxol-5-yl)-methanol (7.2 g, 38 mmol, 76 % over two steps) as a colorless oil.

[00355] Step c: 5-Chloromethyl-2,2-difluoro-benzo[1,3]dioxole

Thionyl chloride (45 g, 38 mmol) was slowly added to a solution of (2,2-difluoro-benzo[1,3]dioxol-5-yl)-methanol (7.2 g, 38 mmol) in dichloromethane (200 mL) at 0 °C. The resulting mixture was stirred overnight at room temperature and then evaporated to dryness. The residue was partitioned between an aqueous solution of saturated sodium bicarbonate (100 mL) and dichloromethane (100 mL). The separated aqueous layer was extracted with dichloromethane (150 mL) and the organic layer was dried over sodium sulfate, filtered, and evaporated to dryness to give crude 5-chloromethyl-2,2-difluoro-benzo[1,3]dioxole (4.4 g) which was used directly in the next step.

[00356] Step d: (2,2-Difluoro-benzo[1,3]dioxol-5-yl)-acetonitrile

A mixture of crude 5-chloromethyl-2,2-difluoro-benzo[1,3]dioxole (4.4 g) and sodium cyanide (1.36 g, 27.8 mmol) in dimethylsulfoxide (50 mL) was stirred at room temperature overnight. The reaction mixture was poured into ice and extracted with ethyl acetate (300 mL). The organic layer was dried over sodium sulfate and evaporated to dryness to give crude (2,2-difluoro-benzo[1,3]dioxol-5-yl)-acetonitrile (3.3 g) which was used directly in the next step.

[00357] Step e: 1-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-cyclopropanecarbonitrile

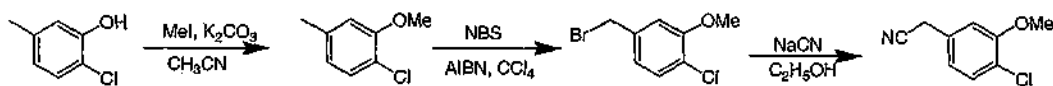
Sodium hydroxide (50% aqueous solution, 10 mL) was slowly added to a mixture of crude (2,2-difluoro-benzo[1,3]dioxol-5-yl)-acetonitrile, benzyltriethylammonium chloride (3.00 g, 15.3 mmol), and 1-bromo-2-chloroethane (4.9 g, 38 mmol) at 70 °C. The mixture was stirred overnight at 70 °C before the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated to dryness to give crude 1-(2,2-difluoro-benzo[1,3]dioxol-5-yl)-cyclopropanecarbonitrile, which was used directly in the next step.

[00358] Step f: 1-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-cyclopropanecarboxylic acid

1-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-cyclopropanecarbonitrile (crude from the last step) was refluxed in 10% aqueous sodium hydroxide (50 mL) for 2.5 hours. The cooled reaction mixture was washed with ether (100 mL) and the aqueous phase was acidified to pH 2

with 2M hydrochloric acid. The precipitated solid was filtered to give 1-(2,2-difluoro-benzo[1,3]dioxol-5-yl)-cyclopropanecarboxylic acid as a white solid (0.15 g, 1.6% over four steps). ESI-MS m/z calc. 242.2, found 243.3 ($M+1$)⁺; ¹H NMR (CDCl₃) δ 7.14-7.04 (m, 2H), 6.98-6.96 (m, 1H), 1.74-1.64 (m, 2H), 1.26-1.08 (m, 2H).

C. 2-(4-Chloro-3-methoxyphenyl)acetonitrile



[00359]

Step a: 1-Chloro-2-methoxy-4-methyl-benzene

To a solution of 2-chloro-5-methyl-phenol (93 g, 0.65 mol) in CH₃CN (700 mL) was added CH₃I (111 g, 0.78 mol) and K₂CO₃ (180 g, 1.3 mol). The mixture was stirred at 25 °C overnight. The solid was filtered off and the filtrate was evaporated under *vacuum* to give 1-chloro-2-methoxy-4-methyl-benzene (90 g, 89%). ¹H NMR (300 MHz, CDCl₃) δ 7.22 (d, J = 7.8 Hz, 1 H), 6.74-6.69 (m, 2 H), 3.88 (s, 3 H), 2.33 (s, 3 H).

[00360]

Step b: 4-Bromomethyl-1-chloro-2-methoxy-benzene

To a solution of 1-chloro-2-methoxy-4-methyl-benzene (50 g, 0.32 mol) in CCl₄ (350 mL) was added NBS (57.2 g, 0.32 mol) and AIBN (10 g, 60 mmol). The mixture was heated at reflux for 3 hours. The solvent was evaporated under *vacuum* and the residue was purified by column chromatography on silica gel (Petroleum Ether/EtOAc = 20:1) to give 4-bromomethyl-1-chloro-2-methoxy-benzene (69 g, 92%). ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.31 (m, 1 H), 6.95-6.91 (m, 2 H), 4.46 (s, 2 H), 3.92 (s, 3 H).

[00361]

Step c: 2-(4-Chloro-3-methoxyphenyl)acetonitrile

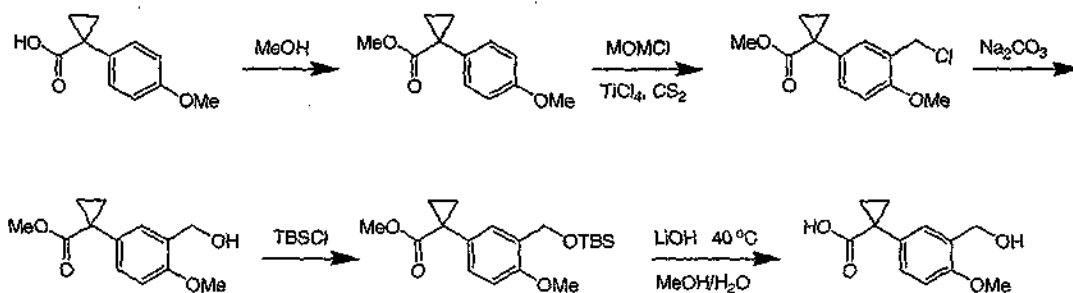
To a solution of 4-bromomethyl-1-chloro-2-methoxy-benzene (68.5 g, 0.29 mol) in C₂H₅OH (90%, 500 mL) was added NaCN (28.5 g, 0.58 mol). The mixture was stirred at 60 °C overnight. Ethanol was evaporated and the residue was dissolved in H₂O. The mixture was extracted with ethyl acetate (300 mL \times 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and purified by column chromatography on silica gel (Petroleum Ether/EtOAc 30:1) to give 2-(4-chloro-3-methoxyphenyl)acetonitrile (25 g, 48%). ¹H NMR (400 MHz, CDCl₃) δ 7.36 (d, J = 8 Hz, 1 H), 6.88-6.84 (m, 2 H), 3.92 (s, 3 H), 3.74 (s, 2 H). ¹³C NMR (100 MHz, CDCl₃) δ 155.4, 130.8, 129.7, 122.4, 120.7, 117.5, 111.5, 56.2, 23.5.

D. (4-Chloro-3-hydroxy-phenyl)-acetonitrile



[00362] BBr₃ (16.6 g, 66 mmol) was slowly added to a solution of 2-(4-chloro-3-methoxyphenyl)acetonitrile (12 g, 66 mmol) in DCM (120 mL) at -78 °C under N₂. The reaction temperature was slowly increased to room temperature. The reaction mixture was stirred overnight and then poured into ice-water. The organic layer was separated and the aqueous layer was extracted with DCM (40 mL × 3). The combined organic layers were washed with water, brine, dried over Na₂SO₄, and concentrated under *vacuum* to give (4-chloro-3-hydroxy-phenyl)-acetonitrile (9.3 g, 85%). ¹H NMR (300 MHz, CDCl₃) δ 7.34 (d, *J* = 8.4 Hz, 1 H), 7.02 (d, *J* = 2.1 Hz, 1 H), 6.87 (dd, *J* = 2.1, 8.4 Hz, 1 H), 5.15 (brs, 1H), 3.72 (s, 2 H).

E. 1-(3-(Hydroxymethyl)-4-methoxyphenyl)cyclopropanecarboxylic acid

**[00363]** Step a: 1-(4-Methoxy-phenyl)-cyclopropanecarboxylic acid methyl ester

To a solution of 1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid (50.0 g, 0.26 mol) in MeOH (500 mL) was added toluene-4-sulfonic acid monohydrate (2.5 g, 13 mmol) at room temperature. The reaction mixture was heated at reflux for 20 hours. MeOH was removed by evaporation under *vacuum* and EtOAc (200 mL) was added. The organic layer was washed with sat. aq. NaHCO₃ (100 mL) and brine, dried over anhydrous Na₂SO₄ and evaporated under *vacuum* to give 1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid methyl ester (53.5 g, 99%). ¹H NMR (CDCl₃, 400 MHz) δ 7.25-7.27 (m, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 3.80 (s, 3 H), 3.62 (s, 3 H), 1.58 (m, 2 H), 1.15 (m, 2 H).

[00364] Step b: 1-(3-Chloromethyl-4-methoxy-phenyl)-cyclopropanecarboxylic acid methyl ester

To a solution of 1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid methyl ester (30.0 g, 146 mmol) and MOMCl (29.1 g, 364 mmol) in CS₂ (300 mL) was added TiCl₄ (8.30 g, 43.5 mmol) at 5 °C. The reaction mixture was heated at 30 °C for 1 day and poured into ice-water. The mixture was extracted with CH₂Cl₂ (150 mL × 3). The combined organic extracts

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were evaporated under *vacuum* to give crude 1-(3-chloromethyl-4-methoxy-phenyl)-cyclopropanecarboxylic acid methyl ester (38.0 g), which was used in the next step without further purification.

[00365] Step c: 1-(3-Hydroxymethyl-4-methoxy-phenyl)-cyclopropanecarboxylic acid methyl ester

To a suspension of crude 1-(3-chloromethyl-4-methoxy-phenyl)-cyclopropanecarboxylic acid methyl ester (20.0 g) in water (350 mL) was added Bu₄NBr (4.0 g) and Na₂CO₃ (90.0 g, 0.85 mol) at room temperature. The reaction mixture was heated at 65 °C overnight. The resulting solution was acidified with aq. HCl (2 mol/L) and extracted with EtOAc (200 mL × 3). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and evaporated under *vacuum* to give crude product, which was purified by column (Petroleum Ether/EtOAc 15:1) to give 1-(3-hydroxymethyl-4-methoxy-phenyl)-cyclopropanecarboxylic acid methyl ester (8.0 g, 39%). ¹H NMR (CDCl₃, 400 MHz) δ 7.23-7.26 (m, 2 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 4.67 (s, 2 H), 3.86 (s, 3 H), 3.62 (s, 3 H), 1.58 (q, *J* = 3.6 Hz, 2 H), 1.14-1.17 (m, 2 H).

[00366] Step d: 1-[3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-methoxy-phenyl]cyclopropane-carboxylic acid methyl ester

To a solution of 1-(3-hydroxymethyl-4-methoxy-phenyl)-cyclopropanecarboxylic acid methyl ester (8.0 g, 34 mmol) in CH₂Cl₂ (100 mL) were added imidazole (5.8 g, 85 mmol) and TBSCl (7.6 g, 51 mmol) at room temperature. The mixture was stirred overnight at room temperature. The mixture was washed with brine, dried over anhydrous Na₂SO₄ and evaporated under *vacuum* to give crude product, which was purified by column (Petroleum Ether/EtOAc 30:1) to give 1-[3-(*tert*-butyl-dimethyl-silanyloxymethyl)-4-methoxy-phenyl]-cyclopropanecarboxylic acid methyl ester (6.7 g, 56%). ¹H NMR (CDCl₃, 400 MHz) δ 7.44-7.45 (m, 1 H), 7.19 (dd, *J* = 2.0, 8.4 Hz, 1 H), 6.76 (d, *J* = 8.4 Hz, 1 H), 4.75 (s, 2 H), 3.81 (s, 3 H), 3.62 (s, 3 H), 1.57-1.60 (m, 2 H), 1.15-1.18 (m, 2 H), 0.96 (s, 9 H), 0.11 (s, 6 H).

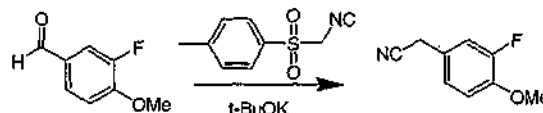
[00367] Step e: 1-(3-Hydroxymethyl-4-methoxy-phenyl)-cyclopropanecarboxylic acid

To a solution of 1-[3-(*tert*-butyl-dimethyl-silanyloxymethyl)-4-methoxy-phenyl]-cyclopropanecarboxylic acid methyl ester (6.2 g, 18 mmol) in MeOH (75 mL) was added a solution of LiOH·H₂O (1.50 g, 35.7 mmol) in water (10 mL) at 0 °C. The reaction mixture was stirred overnight at 40 °C. MeOH was removed by evaporation under *vacuum*. AcOH (1 mol/L, 40 mL) and EtOAc (200 mL) were added. The organic layer was separated, washed

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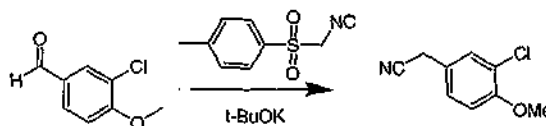
with brine, dried over anhydrous Na_2SO_4 and evaporated under *vacuum* to provide 1-(3-hydroxymethyl-4-methoxy-phenyl)-cyclopropanecarboxylic acid (5.3 g).

F. 2-(3-Fluoro-4-methoxyphenyl)acetonitrile



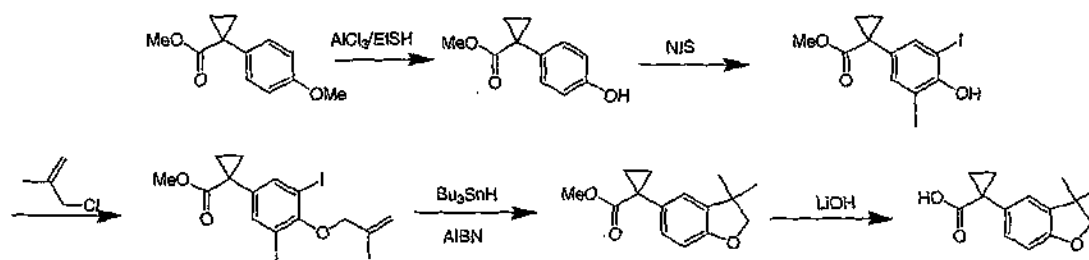
[00368] To a suspension of t-BuOK (25.3 g, 0.207 mol) in THF (150 mL) was added a solution of TosMIC (20.3 g, 0.104 mol) in THF (50 mL) at -78°C . The mixture was stirred for 15 minutes, treated with a solution of 3-fluoro-4-methoxy-benzaldehyde (8.00 g, 51.9 mmol) in THF (50 mL) dropwise, and continued to stir for 1.5 hours at -78°C . To the cooled reaction mixture was added methanol (50 mL). The mixture was heated at reflux for 30 minutes. Solvent of the reaction mixture was removed to give a crude product, which was dissolved in water (200 mL). The aqueous phase was extracted with EtOAc (100 mL \times 3). The combined organic layers were dried and evaporated under reduced pressure to give crude product, which was purified by column chromatography (Petroleum Ether/EtOAc 10:1) to afford 2-(3-fluoro-4-methoxyphenyl)acetonitrile (5.0 g, 58%). ^1H NMR (400 MHz, CDCl_3) δ 7.02-7.05 (m, 2 H), 6.94 (t, $J = 8.4$ Hz, 1 H), 3.88 (s, 3 H), 3.67 (s, 2 H). ^{13}C NMR (100 MHz, CDCl_3) δ 152.3, 147.5, 123.7, 122.5, 117.7, 115.8, 113.8, 56.3, 22.6.

G. 2-(3-Chloro-4-methoxyphenyl)acetonitrile



[00369] To a suspension of t-BuOK (4.8 g, 40 mmol) in THF (30 mL) was added a solution of TosMIC (3.9 g, 20 mmol) in THF (10 mL) at -78°C . The mixture was stirred for 10 minutes, treated with a solution of 3-chloro-4-methoxy-benzaldehyde (1.65 g, 10 mmol) in THF (10 mL) dropwise, and continued to stir for 1.5 hours at -78°C . To the cooled reaction mixture was added methanol (10 mL). The mixture was heated at reflux for 30 minutes. Solvent of the reaction mixture was removed to give a crude product, which was dissolved in water (20 mL). The aqueous phase was extracted with EtOAc (20 mL \times 3). The combined organic layers were dried and evaporated under reduced pressure to give crude product, which was purified by column chromatography (Petroleum Ether/EtOAc 10:1) to afford 2-(3-chloro-4-methoxyphenyl)acetonitrile (1.5 g, 83%). ^1H NMR (400 MHz, CDCl_3) δ 7.33 (d, $J = 2.4$ Hz, 1 H), 7.20 (dd, $J = 2.4, 8.4$ Hz, 1 H), 6.92 (d, $J = 8.4$ Hz, 1 H), 3.91 (s, 3 H), 3.68 (s, 2 H). ^{13}C

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NMR (100 MHz, CDCl₃) δ 154.8, 129.8, 127.3, 123.0, 122.7, 117.60, 112.4, 56.2, 22.4.H. 1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)cyclopropanecarboxylic acid**[00370]** Step a: 1-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid methyl ester

To a solution of methyl 1-(4-methoxyphenyl)cyclopropanecarboxylate (10.0 g, 48.5 mmol) in DCM (80 mL) was added EtSH (16 mL) under ice-water bath. The mixture was stirred at 0 °C for 20 min before AlCl₃ (19.5 g, 0.15 mmol) was added slowly at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction mixture was poured into ice-water, the organic layer was separated, and the aqueous phase was extracted with DCM (50 mL \times 3). The combined organic layers were washed with H₂O, brine, dried over Na₂SO₄ and evaporated under vacuum to give 1-(4-hydroxy-phenyl)-cyclopropanecarboxylic acid methyl ester (8.9 g, 95%). ¹H NMR (400 MHz, CDCl₃) δ 7.20-7.17 (m, 2 H), 6.75-6.72 (m, 2 H), 5.56 (s, 1 H), 3.63 (s, 3 H), 1.60-1.57 (m, 2 H), 1.17-1.15 (m, 2 H).

[00371] Step b: 1-(4-Hydroxy-3,5-diiodo-phenyl)-cyclopropanecarboxylic acid methyl ester

To a solution of 1-(4-hydroxy-phenyl)-cyclopropanecarboxylic acid methyl ester (8.9 g, 46 mmol) in CH₃CN (80 mL) was added NIS (15.6 g, 69 mmol). The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (Petroleum Ether/EtOAc 10:1) to give 1-(4-hydroxy-3,5-diiodo-phenyl)-cyclopropanecarboxylic acid methyl ester (3.5 g, 18%). ¹H NMR (400 MHz, CDCl₃) δ 7.65 (s, 2 H), 5.71 (s, 1 H), 3.63 (s, 3 H), 1.59-1.56 (m, 2 H), 1.15-1.12 (m, 2 H).

[00372] Step c: 1-[3,5-Diiodo-4-(2-methyl-allyloxy)-phenyl]-cyclopropanecarboxylic acid methyl ester

A mixture of 1-(4-hydroxy-3,5-diiodo-phenyl)-cyclopropanecarboxylic acid methyl ester (3.2 g, 7.2 mmol), 3-chloro-2-methyl-propene (1.0 g, 11 mmol), K₂CO₃ (1.2 g, 8.6 mmol), NaI (0.1 g, 0.7 mmol) in acetone (20 mL) was stirred at 20 °C overnight. The solid was filtered

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off and the filtrate was concentrated under *vacuum* to give 1-[3,5-diiodo-4-(2-methyl-allyloxy)-phenyl]-cyclopropane-carboxylic acid methyl ester (3.5 g, 97%). ^1H NMR (300 MHz, CDCl_3) δ 7.75 (s, 2 H), 5.26 (s, 1 H), 5.06 (s, 1 H), 4.38 (s, 2 H), 3.65 (s, 3 H), 1.98 (s, 3H), 1.62-1.58 (m, 2 H), 1.18-1.15 (m, 2 H).

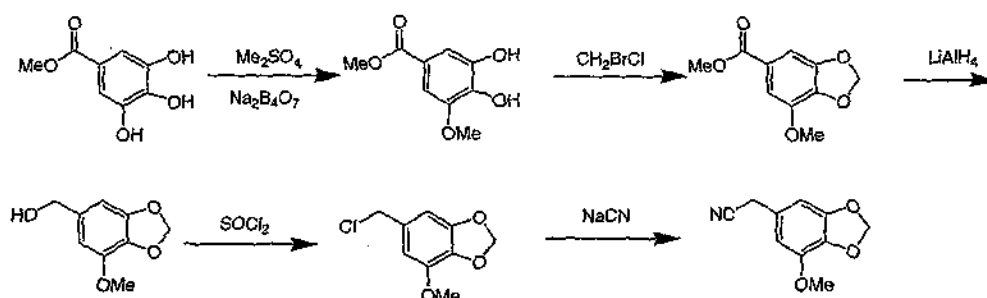
[00373] Step d: 1-(3,3-Dimethyl-2,3-dihydro-benzofuran-5-yl)-cyclopropanecarboxylic acid methyl ester

To a solution of 1-[3,5-diiodo-4-(2-methyl-allyloxy)-phenyl]-cyclopropane-carboxylic acid methyl ester (3.5 g, 7.0 mmol) in toluene (15 mL) was added Bu_3SnH (2.4 g, 8.4 mmol) and AIBN (0.1 g, 0.7 mmol). The mixture was heated at reflux overnight. The reaction mixture was concentrated under *vacuum* and the residue was purified by column chromatography on silica gel (Petroleum Ether/EtOAc 20:1) to give 1-(3,3-dimethyl-2,3-dihydro-benzofuran-5-yl)-cyclopropanecarboxylic acid methyl ester (1.05 g, 62%). ^1H NMR (400 MHz, CDCl_3) δ 7.10-7.07 (m, 2 H), 6.71 (d, $J = 8$ Hz, 1 H), 4.23 (s, 2 H), 3.62 (s, 3 H), 1.58-1.54 (m, 2 H), 1.34 (s, 6 H), 1.17-1.12 (m, 2 H).

[00374] Step e: 1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)cyclopropanecarboxylic acid

To a solution of 1-(3,3-dimethyl-2,3-dihydro-benzofuran-5-yl)-cyclopropanecarboxylic acid methyl ester (1 g, 4 mmol) in MeOH (10 mL) was added LiOH (0.40 g, 9.5 mmol). The mixture was stirred at 40 °C overnight. HCl (10%) was added slowly to adjust the pH to 5. The resulting mixture was extracted with ethyl acetate (10 mL \times 3). The extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed under *vacuum* and the crude product was purified by preparative HPLC to give 1-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)cyclopropanecarboxylic acid (0.37 g, 41%). ^1H NMR (400 MHz, CDCl_3) δ 7.11-7.07 (m, 2 H), 6.71 (d, $J = 8$ Hz, 1 H), 4.23 (s, 2 H), 1.66-1.63 (m, 2 H), 1.32 (s, 6 H), 1.26-1.23 (m, 2 H).

I. 2-(7-Methoxybenzo[d][1,3]dioxol-5-yl)acetonitrile



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[00375]

Step a: 3,4-Dihydroxy-5-methoxybenzoate

To a solution of 3,4,5-trihydroxy-benzoic acid methyl ester (50 g, 0.27 mol) and $\text{Na}_2\text{B}_4\text{O}_7$ (50 g) in water (1000 mL) was added Me_2SO_4 (120 mL) and aqueous NaOH solution (25%, 200 mL) successively at room temperature. The mixture was stirred at room temperature for 6 h before it was cooled to 0 °C. The mixture was acidified to pH ~ 2 by adding conc. H_2SO_4 and then filtered. The filtrate was extracted with EtOAc (500 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give methyl 3,4-dihydroxy-5-methoxybenzoate (15.3 g 47%), which was used in the next step without further purification.

[00376] Step b: Methyl 7-methoxybenzo[d][1,3]dioxole-5-carboxylate

To a solution of methyl 3,4-dihydroxy-5-methoxybenzoate (15.3 g, 0.078 mol) in acetone (500 mL) was added CH_2BrCl (34.4 g, 0.27 mol) and K_2CO_3 (75 g, 0.54 mol) at 80 °C. The resulting mixture was heated at reflux for 4 h. The mixture was cooled to room temperature and solid K_2CO_3 was filtered off. The filtrate was concentrated under reduced pressure, and the residue was dissolved in EtOAc (100 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4 , and evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (Petroleum Ether/Ethyl Acetate = 10:1) to afford methyl 7-methoxybenzo[d][1,3]dioxole-5-carboxylate (12.6 g, 80%). ^1H NMR (400 MHz, CDCl_3) δ 7.32 (s, 1 H), 7.21 (s, 1 H), 6.05 (s, 2 H), 3.93 (s, 3 H), 3.88 (s, 3 H).

[00377] Step c: (7-Methoxybenzo[d][1,3]dioxol-5-yl)methanol

To a solution of methyl 7-methoxybenzo[d][1,3]dioxole-5-carboxylate (13.9 g, 0.040 mol) in THF (100 mL) was added LiAlH_4 (3.1 g, 0.080 mol) in portions at room temperature. The mixture was stirred for 3 h at room temperature. The reaction mixture was cooled to 0 °C and treated with water (3.1 g) and NaOH (10%, 3.1 mL) successively. The slurry was filtered off and washed with THF. The combined filtrates were evaporated under reduced pressure to give (7-methoxy-benzo[d][1,3]dioxol-5-yl)methanol (7.2 g, 52%). ^1H NMR (400 MHz, CDCl_3) δ 6.55 (s, 1H), 6.54 (s, 1H), 5.96 (s, 2 H), 4.57 (s, 2 H), 3.90 (s, 3 H).

[00378] Step d: 6-(Chloromethyl)-4-methoxybenzo[d][1,3]dioxole

To a solution of SOCl_2 (150 mL) was added (7-methoxybenzo[d][1,3]dioxol-5-yl)methanol (9.0 g, 54 mmol) in portions at 0 °C. The mixture was stirred for 0.5 h. The excess SOCl_2 was evaporated under reduced pressure to give the crude product, which was basified with sat. aq. NaHCO_3 to pH ~ 7. The aqueous phase was extracted with EtOAc (100 mL \times 3).

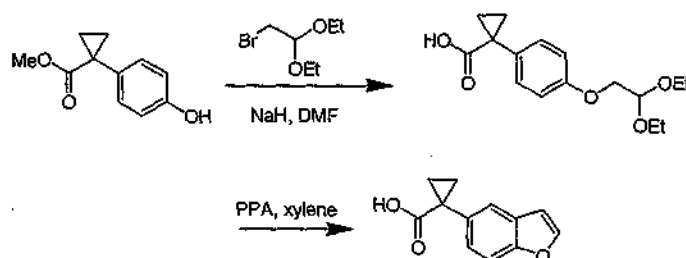
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The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to give 6-(chloromethyl)-4-methoxybenzo[d][1,3]dioxole (10.2 g 94%), which was used in the next step without further purification. ^1H NMR (400 MHz, CDCl_3) δ 6.58 (s, 1 H), 6.57 (s, 1 H), 5.98 (s, 2 H), 4.51 (s, 2 H), 3.90 (s, 3 H).

[00379] Step e: 2-(7-Methoxybenzo[d][1,3]dioxol-5-yl)acetonitrile

To a solution of 6-(chloromethyl)-4-methoxybenzo[d][1,3]dioxole (10.2 g, 40 mmol) in DMSO (100 mL) was added NaCN (2.43 g, 50 mmol) at room temperature. The mixture was stirred for 3 h and poured into water (500 mL). The aqueous phase was extracted with EtOAc (100 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to give the crude product, which was washed with ether to afford 2-(7-methoxybenzo[d][1,3]dioxol-5-yl)acetonitrile (4.6 g, 45%). ^1H NMR (400 MHz, CDCl_3) δ 6.49 (s, 2 H), 5.98 (s, 2 H), 3.91 (s, 3 H), 3.65 (s, 2 H). ^{13}C NMR (400 MHz, CDCl_3) δ 148.9, 143.4, 134.6, 123.4, 117.3, 107.2, 101.8, 101.3, 56.3, 23.1.

J. 1-(Benzofuran-5-yl)cyclopropanecarboxylic acid



[00380] Step a: 1-[4-(2,2-Diethoxy-ethoxy)-phenyl]-cyclopropanecarboxylic acid

To a stirred solution of 1-(4-hydroxy-phenyl)-cyclopropanecarboxylic acid methyl ester (15.0 g, 84.3 mmol) in DMF (50 mL) was added sodium hydride (6.7 g, 170 mmol, 60% in mineral oil) at 0 °C. After hydrogen evolution ceased, 2-bromo-1,1-diethoxy-ethane (16.5 g, 84.3 mmol) was added dropwise to the reaction mixture. The reaction was stirred at 160 °C for 15 hours. The reaction mixture was poured onto ice (100 g) and extracted with CH_2Cl_2 . The combined organics were dried over Na_2SO_4 . The solvent was evaporated under *vacuum* to give crude 1-[4-(2,2-diethoxy-ethoxy)-phenyl]-cyclopropanecarboxylic acid (10 g), which was used directly in the next step without purification.

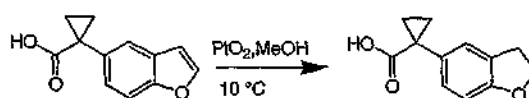
[00381] Step b: 1-Benzofuran-5-yl-cyclopropanecarboxylic acid

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To a suspension of crude 1-[4-(2,2-diethoxy-ethoxy)-phenyl]-

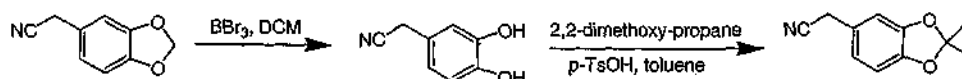
cyclopropanecarboxylic acid (20 g, ~65 mmol) in xylene (100 mL) was added PPA (22.2 g, 64.9 mmol) at room temperature. The mixture was heated at reflux (140 °C) for 1 hour before it was cooled to room temperature and decanted from the PPA. The solvent was evaporated under *vacuum* to obtain the crude product, which was purified by preparative HPLC to provide 1-(benzofuran-5-yl)cyclopropanecarboxylic acid (1.5 g, 5%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.25 (br s, 1 H), 7.95 (d, *J* = 2.8 Hz, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H), 7.47 (d, *J* = 11.6 Hz, 1 H), 7.25 (dd, *J* = 2.4, 11.2 Hz, 1 H), 6.89 (d, *J* = 1.6 Hz, 1 H), 1.47-1.44 (m, 2 H), 1.17-1.14 (m, 2 H).

K. 1-(2,3-Dihydrobenzofuran-5-yl)cyclopropanecarboxylic acid



[00382] To a solution of 1-(benzofuran-5-yl)cyclopropanecarboxylic acid (700 mg, 3.47 mmol) in MeOH (10 mL) was added PtO₂ (140 mg, 20%) at room temperature. The stirred reaction mixture was hydrogenated under hydrogen (1 atm) at 10 °C for 3 days. The reaction mixture was filtered. The solvent was evaporated under *vacuum* to afford the crude product, which was purified by preparative HPLC to give 1-(2,3-dihydrobenzofuran-5-yl)cyclopropanecarboxylic acid (330 mg, 47%). ¹H NMR (400 MHz, CDCl₃) δ 7.20 (s, 1 H), 7.10 (d, *J* = 10.8 Hz, 1 H), 6.73 (d, *J* = 11.2 Hz, 1 H), 4.57 (t, *J* = 11.6 Hz, 2 H), 3.20 (t, *J* = 11.6 Hz, 2 H), 1.67-1.63 (m, 2 H), 1.25-1.21 (m, 2 H).

L. 2-(2,2-Dimethylbenzo[d][1,3]dioxol-5-yl)acetonitrile



[00383] Step a: (3,4-Dihydroxy-phenyl)-acetonitrile

To a solution of benzo[1,3]dioxol-5-yl-acetonitrile (0.50 g, 3.1 mmol) in CH₂Cl₂ (15 mL) was added dropwise BBr₃ (0.78 g, 3.1 mmol) at -78 °C under N₂. The mixture was slowly warmed to room temperature and stirred overnight. H₂O (10 mL) was added to quench the reaction and the CH₂Cl₂ layer was separated. The aqueous phase was extracted with CH₂Cl₂ (2 × 7 mL). The combined organics were washed with brine, dried over Na₂SO₄ and purified by column chromatography on silica gel (Petroleum Ether/EtOAc 5:1) to give (3,4-dihydroxy-

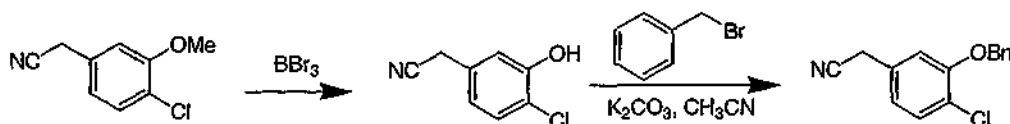
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phenyl)-acetonitrile (0.25 g, 54%) as a white solid. ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.07 (s, 1 H), 8.95 (s, 1 H), 6.68-6.70 (m, 2 H), 6.55 (dd, $J = 8.0, 2.0$ Hz, 1 H), 3.32 (s, 2 H).

[00384] Step b: 2-(2,2-Dimethylbenzo[d][1,3]dioxol-5-yl)acetonitrile

To a solution of (3,4-dihydroxy-phenyl)-acetonitrile (0.2 g, 1.3 mmol) in toluene (4 mL) was added 2,2-dimethoxy-propane (0.28 g, 2.6 mmol) and TsOH (0.010 g, 0.065 mmol). The mixture was heated at reflux overnight. The reaction mixture was evaporated to remove the solvent and the residue was dissolved in ethyl acetate. The organic layer was washed with NaHCO_3 solution, H_2O , brine, and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure to give a residue, which was purified by column chromatography on silica gel (Petroleum Ether/EtOAc 10:1) to give 2-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)acetonitrile (40 mg, 20%). ^1H NMR (CDCl_3 , 400 MHz) δ 6.68-6.71 (m, 3 H), 3.64 (s, 2 H), 1.67 (s, 6 H).

M. 2-(3-(Benzyloxy)-4-chlorophenyl)acetonitrile



[00385] Step a: (4-Chloro-3-hydroxy-phenyl)acetonitrile

BBr_3 (16.6 g, 66 mmol) was slowly added to a solution of 2-(4-chloro-3-methoxyphenyl)acetonitrile (12 g, 66 mmol) in DCM (120 mL) at -78°C under N_2 . The reaction temperature was slowly increased to room temperature. The reaction mixture was stirred overnight and then poured into ice and water. The organic layer was separated, and the aqueous layer was extracted with DCM (40 mL \times 3). The combined organic layers were washed with water, brine, dried over Na_2SO_4 , and concentrated under vacuum to give (4-chloro-3-hydroxy-phenyl)-acetonitrile (9.3 g, 85%). ^1H NMR (300 MHz, CDCl_3) δ 7.34 (d, $J = 8.4$ Hz, 1 H), 7.02 (d, $J = 2.1$ Hz, 1 H), 6.87 (dd, $J = 2.1, 8.4$ Hz, 1 H), 5.15 (brs, 1H), 3.72 (s, 2 H).

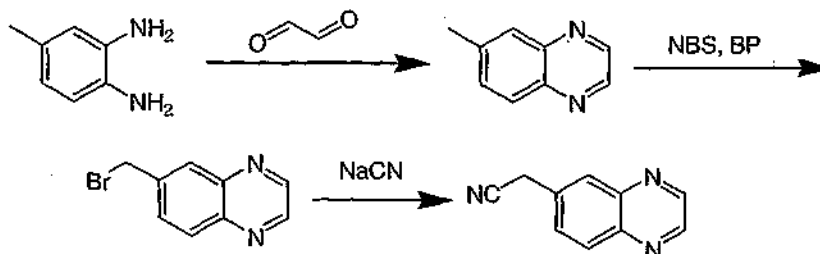
[00386] Step b: 2-(3-(Benzyloxy)-4-chlorophenyl)acetonitrile

To a solution of (4-chloro-3-hydroxy-phenyl)acetonitrile (6.2 g, 37 mmol) in CH_3CN (80 mL) was added K_2CO_3 (10.2 g, 74 mmol) and BnBr (7.6 g, 44 mmol). The mixture was stirred at room temperature overnight. The solids were filtered off and the filtrate was evaporated under vacuum. The residue was purified by column chromatography on silica gel (Petroleum Ether/Ethyl Acetate 50:1) to give 2-(3-(benzyloxy)-4-chlorophenyl)acetonitrile (5.6

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g, 60%). ^1H NMR (400 MHz, CDCl_3) δ 7.48-7.32 (m, 6 H), 6.94 (d, $J = 2$ Hz, 2 H), 6.86 (dd, $J = 2.0, 8.4$ Hz, 1 H), 5.18 (s, 2 H), 3.71 (s, 2 H).

N. 2-(Quinoxalin-6-yl)acetonitrile



[00387] Step a: 6-Methylquinoxaline

To a solution of 4-methylbenzene-1,2-diamine (50.0 g, 0.41 mol) in isopropanol (300 mL) was added a solution of glyoxal (40% in water, 65.3 g, 0.45 mol) at room temperature. The reaction mixture was heated at 80 °C for 2 hours and evaporated under vacuum to give 6-methylquinoxaline (55 g, 93%), which was used directly in the next step. ^1H NMR (300 MHz, CDCl_3) δ 8.77 (dd, $J = 1.5, 7.2$ Hz, 2 H), 7.99 (d, $J = 8.7$ Hz, 1 H), 7.87 (s, 1 H), 7.60 (dd, $J = 1.5, 8.4$ Hz, 1 H), 2.59 (s, 3 H).

[00388] Step b: 6-Bromomethylquinoxaline

To a solution of 6-methylquinoxaline (10.0 g, 69.4 mmol) in CCl_4 (80 mL) was added NBS (13.5 g, 76.3 mmol) and benzoyl peroxide (BP, 1.7 g, 6.9 mmol) at room temperature. The mixture was heated at reflux for 2 hours. After cooling, the mixture was evaporated under vacuum to give a yellow solid, which was extracted with Petroleum Ether (50 mL \times 5). The extracts were concentrated under vacuum. The organics were combined and concentrated to give crude 6-bromomethylquinoxaline (12.0 g), which was used directly in the next step. ^1H NMR (300 MHz, CDCl_3) δ 8.85-8.87 (m, 2 H), 8.10-8.13 (m, 2 H), 7.82 (dd, $J = 2.1, 8.7$ Hz, 1 H), 4.70 (s, 2 H).

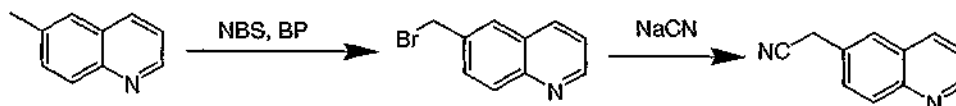
[00389] Step c: 2-(Quinoxalin-6-yl)acetonitrile

To a solution of crude 6-bromomethylquinoxaline (36.0 g) in 95% ethanol (200 mL) was added NaCN (30.9 g, 0.63 mol) at room temperature. The mixture was heated at 50 °C for 3 hours and then concentrated under vacuum. Water (100 mL) and ethyl acetate (100 mL) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column (Petroleum Ether/EtOAc 10:1) to give

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2-(quinoxalin-6-yl)acetonitrile (7.9 g, 23% over two steps). ^1H NMR (300 MHz, CDCl_3) δ 8.88-8.90 (m, 2 H), 8.12-8.18 (m, 2 H), 7.74 (dd, $J = 2.1, 8.7$ Hz, 1 H), 4.02 (s, 2 H). MS (ESI) m/z ($\text{M}+\text{H}$) $^+$ 170.0.

O. 2-(Quinolin-6-yl)acetonitrile



[00390] Step a: 6-Bromomethylquinoline

To a solution of 6-methylquinoline (2.15 g, 15.0 mmol) in CCl_4 (30 mL) was added NBS (2.92 g, 16.5 mmol) and benzoyl peroxide (BP, 0.36 g, 1.5 mmol) at room temperature. The mixture was heated at reflux for 2 hours. After cooling, the mixture was evaporated under vacuum to give a yellow solid, which was extracted with Petroleum Ether (30 mL \times 5). The extracts were concentrated under vacuum to give crude 6-bromomethylquinoline (1.8 g), which was used directly in the next step.

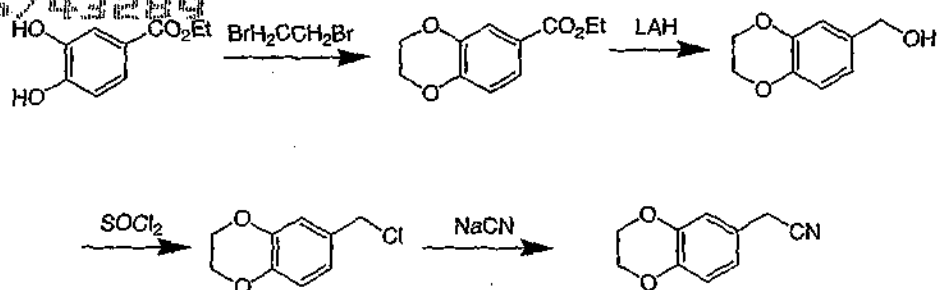
[00391] Step b: 2-(Quinolin-6-yl)acetonitrile

To a solution of crude 6-bromomethylquinoline (1.8 g) in 95% ethanol (30 mL) was added NaCN (2.0 g, 40.8 mmol) at room temperature. The mixture was heated at 50 $^\circ\text{C}$ for 3 hours and then concentrated under vacuum. Water (50 mL) and ethyl acetate (50 mL) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The combined crude product was purified by column (Petroleum Ether /EtOAc 5:1) to give 2-(quinolin-6-yl)acetonitrile (0.25 g, 8% over two steps). ^1H NMR (300 MHz, CDCl_3) δ 8.95 (dd, $J = 1.5, 4.2$ Hz, 1 H), 8.12-8.19 (m, 2 H), 7.85 (s, 1 H), 7.62 (dd, $J = 2.1, 8.7$ Hz, 1 H), 7.46 (q, $J = 4.2$ Hz, 1 H), 3.96 (s, 2 H). MS (ESI) m/e ($\text{M}+\text{H}$) $^+$ 169.0.

P. 2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)acetonitrile

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[00392] Step a: 2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester

To a suspension of Cs_2CO_3 (270 g, 1.49 mol) in DMF (1000 mL) were added 3,4-dihydroxybenzoic acid ethyl ester (54.6 g, 0.3 mol) and 1,2-dibromoethane (54.3 g, 0.29 mol) at room temperature. The resulting mixture was stirred at 80 °C overnight and then poured into ice-water. The mixture was extracted with EtOAc (200 mL \times 3). The combined organic layers were washed with water (200 mL \times 3) and brine (100 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column (Petroleum Ether /Ethyl Acetate 50:1) on silica gel to obtain 2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester (18 g, 29%). ^1H NMR (300 MHz, CDCl_3) δ 7.53 (dd, J = 1.8, 7.2 Hz, 2 H), 6.84-6.87 (m, 1 H), 4.22-4.34 (m, 6 H), 1.35 (t, J = 7.2 Hz, 3 H).

[00393] Step b: (2,3-Dihydro-benzo[1,4]dioxin-6-yl)-methanol

To a suspension of LAH (2.8 g, 74 mmol) in THF (20 mL) was added dropwise a solution of 2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester (15 g, 72 mmol) in THF (10 mL) at 0 °C under N_2 . The mixture was stirred at room temperature for 1 h and then quenched carefully with addition of water (2.8 mL) and NaOH (10%, 28 mL) with cooling. The precipitated solid was filtered off and the filtrate was evaporated to dryness to obtain (2,3-dihydro-benzo[1,4]dioxin-6-yl)-methanol (10.6 g). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 6.73-6.78 (m, 3 H), 5.02 (t, J = 5.7 Hz, 1 H), 4.34 (d, J = 6.0 Hz, 2 H), 4.17-4.20 (m, 4 H).

[00394] Step c: 6-Chloromethyl-2,3-dihydro-benzo[1,4]dioxine

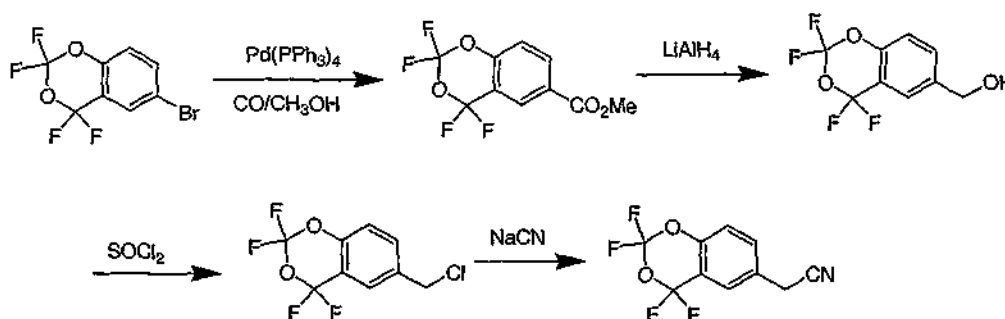
A mixture of (2,3-dihydro-benzo[1,4]dioxin-6-yl)methanol (10.6 g) in SOCl_2 (10 mL) was stirred at room temperature for 10 min and then poured into ice-water. The organic layer was separated and the aqueous phase was extracted with dichloromethane (50 mL \times 3). The combined organic layers were washed with NaHCO_3 (sat solution), water and brine, dried over Na_2SO_4 and concentrated to dryness to obtain 6-chloromethyl-2,3-dihydro-benzo[1,4]dioxine (12 g, 88% over two steps), which was used directly in next step.

[00395] Step d: 2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)acetonitrile

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A mixture of 6-chloromethyl-2,3-dihydro-benzo[1,4]dioxine (12.5 g, 67.7 mmol) and NaCN (4.30 g, 87.8 mmol) in DMSO (50 mL) was stirred at rt for 1 h. The mixture was poured into water (150 mL) and then extracted with dichloromethane (50 mL \times 4). The combined organic layers were washed with water (50 mL \times 2) and brine (50 mL), dried over Na₂SO₄ and concentrated to dryness. The residue was purified by column (Petroleum Ether/Ethyl Acetate 50:1) on silica gel to obtain 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)acetonitrile as a yellow oil (10.2 g, 86%). ¹H-NMR (300 MHz, CDCl₃) δ 6.78-6.86 (m, 3 H), 4.25 (s, 4 H), 3.63 (s, 2 H).

Q. 2-(2,2,4,4-Tetrafluoro-4H-benzo[d][1,3]dioxin-6-yl)acetonitrile



[00396] Step a: 2,2,4,4-Tetrafluoro-4H-benzo[1,3]dioxine-6-carboxylic acid methyl ester

A suspension of 6-bromo-2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxine (4.75 g, 16.6 mmol) and Pd(PPh₃)₄ (950 mg, 8.23 mmol) in MeOH (20 mL), MeCN (30 mL) and Et₃N (10 mL) was stirred under carbon monoxide atmosphere (55 psi) at 75 °C (oil bath temperature) overnight. The cooled reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel column (Petroleum Ether) to give 2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxine-6-carboxylic acid methyl ester (3.75 g, 85%). ¹H NMR (CDCl₃, 300 MHz) δ 8.34 (s, 1 H), 8.26 (dd, J = 2.1, 8.7 Hz, 1 H), 7.22 (d, J = 8.7 Hz, 1 H), 3.96 (s, 3 H).

[00397] Step b: (2,2,4,4-Tetrafluoro-4H-benzo[1,3]dioxin-6-yl)methanol

To a suspension of LAH (2.14 g, 56.4 mmol) in dry THF (200 mL) was added dropwise a solution of 2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxine-6-carboxylic acid methyl ester (7.50 g, 28.2 mmol) in dry THF (50 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was treated with water (2.14 g) and 10% NaOH (2.14 mL). The slurry was filtered and washed with THF. The combined filtrates were evaporated to dryness to give the crude (2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxin-6-yl)-methanol (6.5 g), which was used directly in the

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next step. $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.64 (s, 1 H), 7.57-7.60 (m, 1 H), 7.58 (d, $J = 8.7$ Hz, 1 H), 4.75 (s, 2 H).

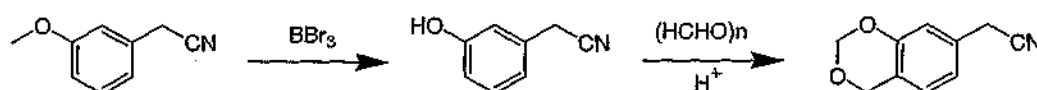
[00398] Step c: 6-Chloromethyl-2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxine

A mixture of (2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxin-6-yl)-methanol (6.5 g) in thionyl chloride (75 mL) was heated at reflux overnight. The resulting mixture was concentrated under vacuum. The residue was basified with aqueous saturated NaHCO_3 . The aqueous layer was extracted with dichloromethane (50 mL \times 3). The combined organic layers were dried over Na_2SO_4 , filtrated, and concentrated under reduced pressure to give 6-chloromethyl-2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxine (6.2 g), which was used directly in the next step. $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.65 (s, 1 H), 7.61 (dd, $J = 2.1, 8.7$ Hz, 1 H), 7.15 (d, $J = 8.4$ Hz, 1 H), 4.60 (s, 2 H).

[00399] Step d: (2,2,4,4-Tetrafluoro-4H-benzo[1,3]dioxin-6-yl)-acetonitrile

A mixture of 6-chloromethyl-2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxine (6.2 g) and NaCN (2.07 g, 42.3 mmol) in DMSO (50 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into ice and extracted with EtOAc (50 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 , and evaporated to give a crude product, which was purified by silica gel column (Petroleum Ether/EtOAc 10:1) to give (2,2-difluoro-benzo[1,3]dioxol-5-yl)-acetonitrile (4.5 g, 68% over 3 steps). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.57-7.60 (m, 2 H), 7.20 (d, $J = 8.7$ Hz, 1 H), 3.82 (s, 2 H).

R. 2-(4H-Benzo[d][1,3]dioxin-7-yl)acetonitrile



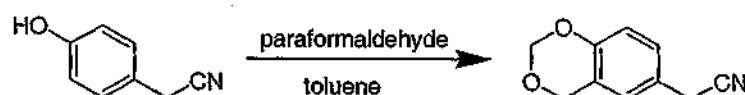
[00400] Step a: (3-Hydroxyphenyl)acetonitrile

To a solution of (3-methoxyphenyl)acetonitrile (150 g, 1.03 mol) in CH_2Cl_2 (1000 mL) was added BBr_3 (774 g, 3.09 mol) dropwise at -70°C . The mixture was stirred and warmed to room temperature slowly. Water (300 mL) was added at 0°C . The resulting mixture was extracted with CH_2Cl_2 . The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated under vacuum. The crude residue was purified by column (Petroleum Ether /EtOAc 10:1) to give (3-hydroxyphenyl)acetonitrile (75.0 g, 55%). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.18-7.24 (m, 1 H), 6.79-6.84 (m, 3 H), 3.69 (s, 2 H).

[00401] Step b: 2-(4H-Benzo[d][1,3]dioxin-7-yl)acetonitrile

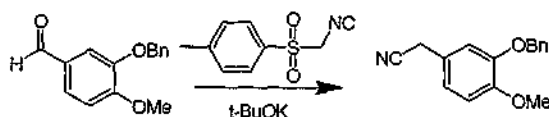
To a solution of (3-hydroxyphenyl)acetonitrile (75.0 g, 0.56 mol) in toluene (750 mL) was added paraformaldehyde (84.0 g, 2.80 mol) and toluene-4-sulfonic acid monohydrate (10.7 g, 56.0 mmol) at room temperature. The reaction mixture was heated at reflux for 40 minutes. Toluene was removed by evaporation. Water (150 mL) and ethyl acetate (150 mL) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was separated by preparative HPLC to give 2-(4H-benzo[d][1,3]dioxin-7-yl)acetonitrile (4.7 g, 5%). ^1H NMR (300 MHz, CDCl_3) δ 6.85-6.98 (m, 3 H), 5.25 (d, $J = 3.0$ Hz, 2 H), 4.89 (s, 2 H), 3.69 (s, 2 H).

S. 2-(4H-Benzo[d][1,3]dioxin-6-yl)acetonitrile



[00402] To a solution of (4-hydroxyphenyl)acetonitrile (17.3 g, 0.13 mol) in toluene (350 mL) were added paraformaldehyde (39.0 g, 0.43 mmol) and toluene-4-sulfonic acid monohydrate (2.5 g, 13 mmol) at room temperature. The reaction mixture was heated at reflux for 1 hour. Toluene was removed by evaporation. Water (150 mL) and ethyl acetate (150 mL) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The residue was separated by preparative HPLC to give 2-(4H-benzo[d][1,3]dioxin-6-yl)acetonitrile (7.35 g, 32%). ^1H NMR (400 MHz, CDCl_3) δ 7.07-7.11 (m, 1 H), 6.95-6.95 (m, 1 H), 6.88 (d, $J = 11.6$ Hz, 1 H), 5.24 (s, 2 H), 4.89 (s, 2 H), 3.67 (s, 2 H).

T. 2-(3-(Benzyloxy)-4-methoxyphenyl)acetonitrile



[00403] To a suspension of $t\text{-BuOK}$ (20.15 g, 0.165 mol) in THF (250 mL) was added a solution of TosMIC (16.1 g, 82.6 mmol) in THF (100 mL) at -78°C . The mixture was stirred for 15 minutes, treated with a solution of 3-benzyloxy-4-methoxy-benzaldehyde (10.0 g,

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51.9 mmol) in THF (50 mL) dropwise, and continued to stir for 1.5 hours at -78°C . To the cooled reaction mixture was added methanol (50 mL). The mixture was heated at reflux for 30 minutes. Solvent of the reaction mixture was removed to give a crude product, which was dissolved in water (300 mL). The aqueous phase was extracted with EtOAc (100 mL \times 3). The combined organic layers were dried and evaporated under reduced pressure to give crude product, which was purified by column chromatography (Petroleum Ether/EtOAc 10:1) to afford 2-(3-(Benzyloxy)-4-methoxyphenyl)acetonitril (5.0 g, 48%). ^1H NMR (300 MHz, CDCl_3) δ 7.48-7.33 (m, 5 H), 6.89-6.86 (m, 3 H), 5.17 (s, 2 H), 3.90 (s, 3 H), 3.66 (s, 2 H). ^{13}C NMR (75 MHz, CDCl_3) δ 149.6, 148.6, 136.8, 128.8, 128.8, 128.2, 127.5, 127.5, 122.1, 120.9, 118.2, 113.8, 112.2, 71.2, 56.2, 23.3.

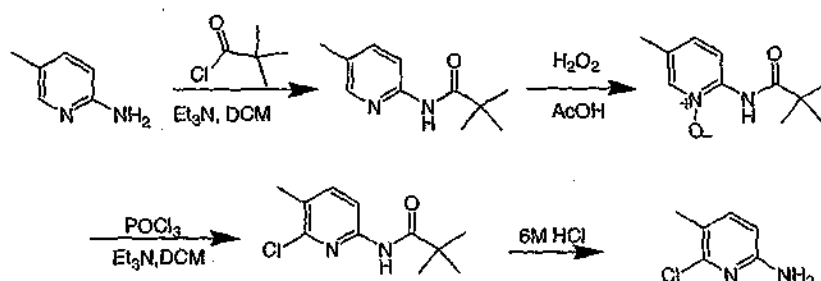
[00404] The following Table 2 contains a list of carboxylic acid building blocks that were commercially available, or prepared by one of the methods described above:

[00405] Table 2: Carboxylic acid building blocks.

Compound	Name
A-1	1-benzo[1,3]dioxol-5-ylcyclopropane-1-carboxylic acid
A-2	1-(2,2-difluorobenzo[1,3]dioxol-5-yl)cyclopropane-1-carboxylic acid
A-3	1-(3,4-dimethoxyphenyl)cyclopropane-1-carboxylic acid
A-4	1-(3-methoxyphenyl)cyclopropane-1-carboxylic acid
A-5	1-(2-methoxyphenyl)cyclopropane-1-carboxylic acid
A-6	1-[4-(trifluoromethoxy)phenyl]cyclopropane-1-carboxylic acid
A-8	tetrahydro-4-(4-methoxyphenyl)-2H-pyran-4-carboxylic acid
A-9	1-phenylcyclopropane-1-carboxylic acid
A-10	1-(4-methoxyphenyl)cyclopropane-1-carboxylic acid
A-11	1-(4-chlorophenyl)cyclopropane-1-carboxylic acid
A-13	1-phenylcyclopentanecarboxylic acid
A-14	1-phenylcyclohexanecarboxylic acid
A-15	1-(4-methoxyphenyl)cyclopentanecarboxylic acid
A-16	1-(4-methoxyphenyl)cyclohexanecarboxylic acid
A-17	1-(4-chlorophenyl)cyclohexanecarboxylic acid
A-18	1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)cyclopropanecarboxylic acid
A-19	1-(4H-benzo[d][1,3]dioxin-7-yl)cyclopropanecarboxylic acid
A-20	1-(2,2,4,4-tetrafluoro-4H-benzo[d][1,3]dioxin-6-yl)cyclopropanecarboxylic acid
A-21	1-(4H-benzo[d][1,3]dioxin-6-yl)cyclopropanecarboxylic acid
A-22	1-(quinoxalin-6-yl)cyclopropanecarboxylic acid
A-23	1-(quinolin-6-yl)cyclopropanecarboxylic acid
A-24	1-(4-chlorophenyl)cyclopentanecarboxylic acid
A-25	1-(benzofuran-5-yl)cyclopropanecarboxylic acid
A-26	1-(4-chloro-3-methoxyphenyl)cyclopropanecarboxylic acid
A-27	1-(3-(hydroxymethyl)-4-methoxyphenyl)cyclopropanecarboxylic acid

A-28	1-(2,3-dihydrobenzofuran-5-yl)cyclopropanecarboxylic acid
A-29	1-(3-fluoro-4-methoxyphenyl)cyclopropanecarboxylic acid
A-30	1-(3-chloro-4-methoxyphenyl)cyclopropanecarboxylic acid
A-31	1-(3-hydroxy-4-methoxyphenyl)cyclopropanecarboxylic acid
A-32	1-(4-hydroxy-3-methoxyphenyl)cyclopropanecarboxylic acid
A-33	1-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxylic acid
A-34	1-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)cyclopropanecarboxylic acid
A-35	1-(7-methoxybenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxylic acid
A-36	1-(4-chloro-3-hydroxyphenyl)cyclopropanecarboxylic acid
A-37	1-(4-methoxy-3-methylphenyl)cyclopropanecarboxylic acid
A-38	1-(3-(benzyloxy)-4-chlorophenyl)cyclopropanecarboxylic acid
A-45	1-(4-methoxy-3-(methoxymethyl)phenyl)cyclopropanecarboxylic acid

U. 6-Chloro-5-methylpyridin-2-amine



[00406] Step a: 2,2-Dimethyl-N-(5-methyl-pyridin-2-yl)-propionamide

To a stirred solution of 5-methylpyridin-2-amine (200 g, 1.85 mol) in anhydrous CH_2Cl_2 (1000 mL) was added dropwise a solution of Et_3N (513 mL, 3.70 mol) and 2,2-dimethyl-propionyl chloride (274 mL, 2.22 mol) at 0 °C under N_2 . The ice bath was removed and stirring was continued at room temperature for 2 hours. The reaction was poured into ice (2000 g). The organic layer was separated and the remaining aqueous layer was extracted with CH_2Cl_2 (3x). The combined organics were dried over Na_2SO_4 and evaporated to afford 2,2-dimethyl-N-(5-methyl-pyridin-2-yl)-propionamide (350 g), which was used in the next step without further purification. ^1H NMR (400 MHz, CDCl_3) δ 8.12 (d, $J = 8.4$ Hz, 1 H), 8.06 (d, $J = 1.2$ Hz, 1 H), 7.96 (s, 1 H), 7.49 (dd, $J = 1.6, 8.4$ Hz, 1 H), 2.27 (s, 1 H), 1.30 (s, 9 H).

[00407] Step b: 2,2-Dimethyl-N-(5-methyl-1-oxy-pyridin-2-yl)-propionamide

To a stirred solution of 2,2-dimethyl-N-(5-methyl-pyridin-2-yl)-propionamide (100 g, 0.52 mol) in AcOH (500 mL) was added drop-wise 30% H_2O_2 (80 mL, 2.6 mol) at room temperature. The mixture was stirred at 80 °C for 12 hours. The reaction mixture was evaporated under *vacuum* to obtain 2,2-dimethyl-N-(5-methyl-1-oxy-pyridin-2-yl)-

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propionamide (80 g, 85% purity). ^1H NMR (400 MHz, CDCl_3) δ 10.26 (br s, 1 H), 8.33 (d, $J = 8.4$ Hz, 1 H), 8.12 (s, 1 H), 7.17 (dd, $J = 0.8, 8.8$ Hz, 1 H), 2.28 (s, 1 H), 1.34 (s, 9 H).

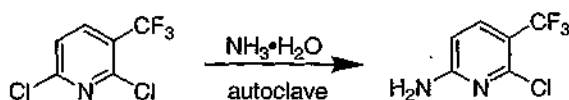
[00408] Step c: *N*-(6-Chloro-5-methyl-pyridin-2-yl)-2,2-dimethyl-propionamide

To a stirred solution of 2,2-dimethyl-*N*-(5-methyl-1-oxy-pyridin-2-yl)-propionamide (10 g, 48 mmol) in anhydrous CH_2Cl_2 (50 mL) was added Et_3N (60 mL, 240 mmol) at room temperature. After being stirred for 30 min, POCl_3 (20 mL) was added drop-wise to the reaction mixture. The reaction was stirred at 50 °C for 15 hours. The reaction mixture was poured into ice (200 g). The organic layer was separated and the remaining aqueous layer was extracted with CH_2Cl_2 (3x). The combined organics were dried over Na_2SO_4 . The solvent was evaporated under *vacuum* to obtain the crude product, which was purified by chromatography (Petroleum Ether/EtOAc 100:1) to provide *N*-(6-chloro-5-methyl-pyridin-2-yl)-2,2-dimethyl-propionamide (0.5 g, 5%). ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, $J = 8.0$ Hz, 1 H), 7.94 (br s, 1 H), 7.55 (d, $J = 8.4$ Hz, 1 H), 2.33 (s, 1 H), 1.30 (s, 9 H).

[00409] Step d: 6-Chloro-5-methyl-pyridin-2-ylamine

To *N*-(6-chloro-5-methyl-pyridin-2-yl)-2,2-dimethyl-propionamide (4.00 g, 17.7 mmol) was added 6 N HCl (20 mL) at room temperature. The mixture was stirred at 80 °C for 12 hours. The reaction mixture was basified with drop-wise addition of sat. NaHCO_3 to pH 8-9, and then the mixture was extracted with CH_2Cl_2 (3x). The organic phases were dried over Na_2SO_4 and evaporated under *vacuum* to obtain the 6-chloro-5-methyl-pyridin-2-ylamine (900 mg, 36%). ^1H NMR (400 MHz, CDCl_3) δ 7.28 (d, $J = 8.0$ Hz, 1 H), 6.35 (d, $J = 8.0$ Hz, 1 H), 4.39 (br s, 2 H), 2.22 (s, 3 H). MS (ESI) m/z : 143 ($\text{M}+\text{H}^+$).

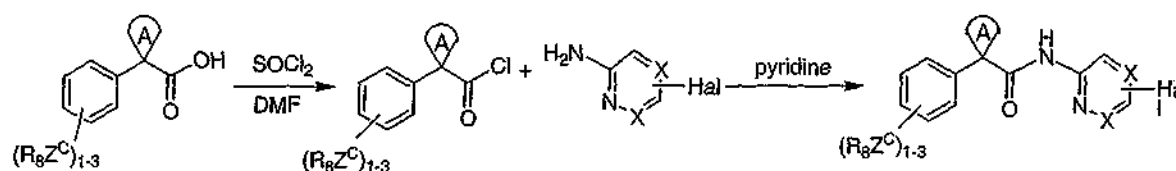
V. 6-Chloro-5-(trifluoromethyl)pyridin-2-amine



[00410] 2,6-Dichloro-3-(trifluoromethyl)pyridine (5.00 g, 23.2 mmol) and 28% aqueous ammonia (150 mL) were placed in a 250 mL autoclave. The mixture was heated at 93 °C for 21h. The reaction was cooled to rt and extracted with EtOAc (100 mL \times 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under vacuum to give the crude product, which was purified by column chromatography on silica gel (2–20% EtOAc in petroleum ether as eluant) to give 6-chloro-5-(trifluoromethyl)pyridin-2-amine (2.1 g,

46% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.69 (d, $J = 8.4$ Hz, 1 H), 7.13 (br s, 2 H), 6.43 (d, $J = 8.4$ Hz, 1 H). MS (ESI) m/z ($M + H$) $^+$ 197.2

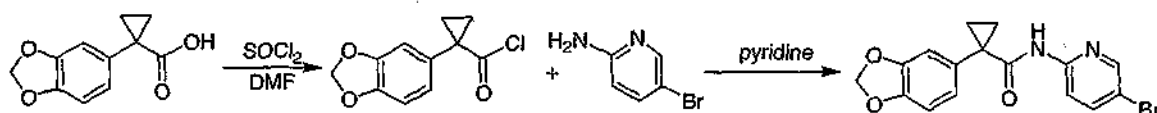
General Procedure IV: Coupling Reactions



Hal = Cl, Br, I, all other variables. Ring A is the ring formed by R_3 and R'_3 . X = C or N

[00411] One equivalent of the appropriate carboxylic acid was placed in an oven-dried flask under nitrogen. Thionyl chloride (3 equivalents) and a catalytic amount of *N,N*-dimethylformamide was added and the solution was allowed to stir at 60 °C for 30 minutes. The excess thionyl chloride was removed under vacuum and the resulting solid was suspended in a minimum of anhydrous pyridine. This solution was slowly added to a stirred solution of one equivalent the appropriate aminoheterocycle dissolved in a minimum of anhydrous pyridine. The resulting mixture was allowed to stir for 15 hours at 110 °C. The mixture was evaporated to dryness, suspended in dichloromethane, and then extracted three times with 1N NaOH. The organic layer was then dried over sodium sulfate, evaporated to dryness, and then purified by column chromatography.

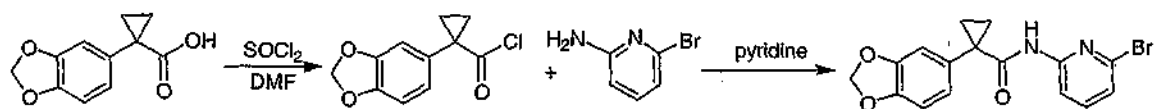
W. 1-(Benzo[d][1,3]dioxol-5-yl)-*N*-(5-bromopyridin-2-yl)cyclopropane-carboxamide (B-1)



[00412] 1-Benzo[1,3]dioxol-5-yl-cyclopropanecarboxylic acid (2.38 g, 11.5 mmol) was placed in an oven-dried flask under nitrogen. Thionyl chloride (2.5 mL) and *N,N*-dimethylformamide (0.3 mL) were added and the solution was allowed to stir for 30 minutes at 60 °C. The excess thionyl chloride was removed under vacuum and the resulting solid was suspended in 7 mL of anhydrous pyridine. This solution was then slowly added to a solution of 5-bromo-pyridin-2-ylamine (2.00 g, 11.6 mmol) suspended in 10 mL of anhydrous pyridine. The resulting mixture was allowed to stir for 15 hours at 110 °C. The mixture was then evaporated to dryness, suspended in 100 mL of dichloromethane, and washed with three 25 mL portions of 1N NaOH. The organic layer was dried over sodium sulfate, evaporated to near dryness, and then purified by silica gel column chromatography utilizing dichloromethane as the eluent to yield the pure product (3.46 g, 83%) ESI-MS m/z calc. 361.2, found 362.1 ($M+1$) $^+$;

Retention time 3.40 minutes. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.06-1.21 (m, 2H), 1.44-1.51 (m, 2H), 6.07 (s, 2H), 6.93-7.02 (m, 2H), 7.10 (d, $J = 1.6$ Hz, 1H), 8.02 (d, $J = 1.6$ Hz, 2H), 8.34 (s, 1H), 8.45 (s, 1H).

X. 1-(Benzo[d][1,3]dioxol-6-yl)-N-(6-bromopyridin-2-yl)cyclopropane-carboxamide (B-2)



[00413] (1-Benzo[1,3]dioxol-5-yl-cyclopropanecarboxylic acid (1.2 g, 5.8 mmol) was placed in an oven-dried flask under nitrogen. Thionyl chloride (2.5 mL) and *N,N*-dimethylformamide (0.3 mL) were added and the solution was allowed to stir at 60 °C for 30 minutes. The excess thionyl chloride was removed under vacuum and the resulting solid was suspended in 5 mL of anhydrous pyridine. This solution was then slowly added to a solution of 6-bromopyridin-2-amine (1.0 g, 5.8 mmol) suspended in 10 mL of anhydrous pyridine. The resulting mixture was allowed to stir for 15 hours at 110 °C. The mixture was then evaporated to dryness, suspended in 50 mL of dichloromethane, and washed with three 20 mL portions of 1N NaOH. The organic layer was dried over sodium sulfate, evaporated to near dryness, and then purified by silica gel column chromatography utilizing dichloromethane containing 2.5 % triethylamine as the eluent to yield the pure product. ESI-MS m/z calc. 361.2, found 362.1 ($M+1$) $^+$; Retention time 3.43 minutes. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.10-1.17 (m, 2H), 1.42-1.55 (m, 2H), 6.06 (s, 2H), 6.92-7.02 (m, 2H), 7.09 (d, $J = 1.6$ Hz, 1H), 7.33 (d, $J = 7.6$ Hz, 1H), 7.73 (t, $J = 8.0$ Hz, 1H), 8.04 (d, $J = 8.2$ Hz, 1H), 8.78 (s, 1H).

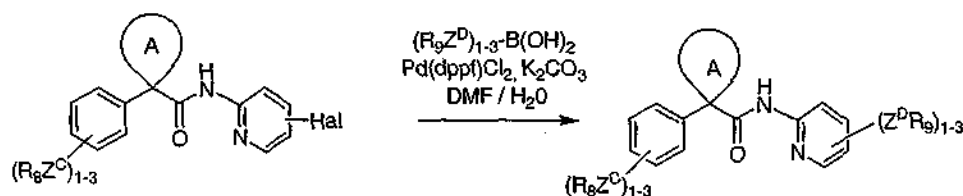
[00414] The compounds in the following Table 3 were prepared in a manner analogous to that described above:

[00415] Table 3: Exemplary compounds synthesized according to Preparations W and X.

Compound	Name	Retention Time (min)	($M+1$) $^+$	^1H NMR (400 MHz, $\text{DMSO}-d_6$)
B-3	1-(Benzo[d][1,3]dioxol-5-yl)-N-(5-bromo-6-methylpyridin-2-yl)cyclopropanecarboxamide	3.58	375.3	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.39 (s, 1H), 7.95 (d, $J = 8.7$ Hz, 1H), 7.83 (d, $J = 8.8$ Hz, 1H), 7.10 (d, $J = 1.6$ Hz, 1H), 7.01 - 6.94 (m, 2H), 6.06 (s, 2H), 2.41 (s,

				3H), 1.48 - 1.46 (m, 2H), 1.14 - 1.10 (m, 2H)
B-4	1-(Benzo[d][1,3]dioxol-5-yl)-N-(6-chloro-5-methylpyridin-2-yl)cyclopropanecarboxamide	2.90	331.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.64 (s, 1H), 7.94-7.91 (m, 1H), 7.79-7.77 (m, 1H), 7.09 (m, 1H), 7.00-6.88 (m, 2H), 6.06 (s, 2H), 2.25 (s, 3H), 1.47-1.44 (m, 2H), 1.13-1.10 (m, 2H)
B-5	1-(Benzo[d][1,3]dioxol-5-yl)-N-(5-bromo-4-methylpyridin-2-yl)cyclopropanecarboxamide	3.85	375.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.36 (s, 1H), 8.30 (s, 1H), 8.05 (s, 1H), 7.09 (d, J = 1.6 Hz, 1H), 7.01 - 6.95 (m, 2H), 6.07 (s, 2H), 2.35 (s, 3H), 1.49 - 1.45 (m, 2H), 1.16 - 1.13 (m, 2H)
B-6	1-(Benzo[d][1,3]dioxol-5-yl)-N-(5-bromo-3,4-dimethylpyridin-2-yl)cyclopropanecarboxamide	3.25	389.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.82 (s, 1H), 8.35 (s, 1H), 7.01 (m, 1H), 6.96-6.89 (m, 2H), 6.02 (s, 2H), 2.35 (s, 3H), 2.05 (s, 3H), 1.40-1.38 (m, 2H), 1.08-1.05 (m, 2H)
B-7	1-(Benzo[d][1,3]dioxol-5-yl)-N-(5-bromo-3-methylpyridin-2-yl)cyclopropanecarboxamide	2.91	375.1	
B-8	1-(Benzo[d][1,3]dioxol-5-yl)-N-(6-chloropyridazin-3-yl)cyclopropanecarboxamide	2.88	318.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 1.15-1.19 (m, 2H), 1.48-1.52 (m, 2H), 6.05 (s, 2H), 6.93-7.01 (m, 2H), 7.09 (d, J = 1.7 Hz, 1H), 7.88 (d, J = 9.4 Hz, 1H), 8.31 (d, J = 9.4 Hz, 1H), 9.46 (s, 1H)
B-9	1-(Benzo[d][1,3]dioxol-5-	3.20	318.3	¹ H NMR (400

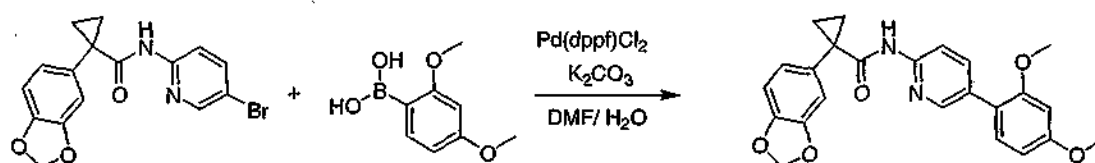
	yl)- <i>N</i> -(5-bromopyrazin-2-yl)cyclopropanecarboxamide			MHz, DMSO- <i>d</i> ₆) δ 1.13-1.18 (m, 2H), 1.47-1.51 (m, 2H), 6.04 (s, 2H), 6.90- 6.99 (m, 2H), 7.06 (d, <i>J</i> = 1.6 Hz, 1H), , 8.47 (s, 1H), 9.21 (s, 1H), 9.45 (s, 1H)
B-10	1-(Benzo[d][1,3]dioxol-5-yl)- <i>N</i> -(6-chloropyrazin-2-yl)cyclopropanecarboxamide	3.45	362.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 1.12-1.23 (m, 2H), 1.41-1.58 (m, 2H), 6.04 (s, 2H), 6.90- 7.00 (m, 2H), 7.07 (d, <i>J</i> = 1.6 Hz, 1H), 8.55 (s, 1H), 8.99- 9.21 (m, 2H)
B-11	<i>N</i> -(6-bromopyridin-2-yl)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamide	2.12	397.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.46 (s, 1H), 8.01- 7.99 (m, 1H), 7.75- 7.71 (m, 1H), 7.54 (m, 1H), 7.41-7.39 (m, 1H), 7.36-7.30 (m, 2H), 1.52-1.49 (m, 2H), 1.20-1.17 (m, 2H)
B-12	<i>N</i> -(6-chloro-5-methylpyridin-2-yl)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamide	2.18	367.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.30 (s, 1H), 7.89- 7.87 (m, 1H), 7.78- 7.76 (m, 1H), 7.53 (m, 1H), 7.41-7.39 (m, 1H), 7.33-7.30 (m, 1H), 2.26 (s, 3H), 1.51-1.49 (m, 2H), 1.18-1.16 (m, 2H)
B-13	<i>N</i> -(6-chloro-5-(trifluoromethyl)pyridin-2-yl)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamide	1.98	421.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.09 (s, 1H), 8.29 (m, 1H), 8.16 (m, 1H), 7.53 (m, 1H), 7.41-7.38 (m, 1H), 7.34-7.29 (m, 1H), 1.56-1.53 (m, 2H), 1.24-1.22 (m, 2H)

General Procedure V: Compounds of Formula I

Hal = Cl, Br, I. Ring A is the ring formed by R_9 and R'_3 .

[00416] The appropriate aryl halide (1 equivalent) was dissolved in 1 mL of *N,N*-dimethylformamide (DMF) in a reaction tube. The appropriate boronic acid (1.3 equivalents), 0.1 mL of an aqueous 2 M potassium carbonate solution (2 equivalents), and a catalytic amount of $Pd(dppf)Cl_2$ (0.09 equivalents) were added and the reaction mixture was heated at 80 °C for three hours or at 150 °C for 5 min in the microwave. The resulting material was cooled to room temperature, filtered, and purified by reverse-phase preparative liquid chromatography.

Y. 1-Benzo[1,3]dioxol-5-yl-cyclopropanecarboxylic acid [5-(2,4-dimethoxy-phenyl)-pyridin-2-yl]-amide

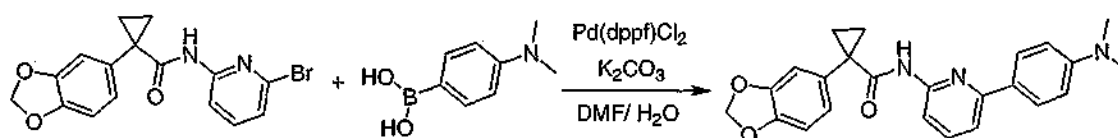


[00417] 1-Benzo[1,3]dioxol-5-yl-cyclopropanecarboxylic acid (5-bromo-pyridin-2-yl)-amide (36.1 mg, 0.10 mmol) was dissolved in 1 mL of *N,N*-dimethylformamide in a reaction tube. 2,4-Dimethoxybenzeneboronic acid (24 mg, 0.13 mmol), 0.1 mL of an aqueous 2 M potassium carbonate solution, and a catalytic amount of $Pd(dppf)Cl_2$ (6.6 mg, 0.0090 mmol) were added and the reaction mixture was heated at 80 °C for three hours. The resulting material was cooled to room temperature, filtered, and purified by reverse-phase preparative liquid chromatography to yield the pure product as a trifluoroacetic acid salt. ESI-MS m/z calc. 418.2, found 419.0 ($M+1$)⁺. Retention time 3.18 minutes. ¹H NMR (400 MHz, CD₃CN) δ 1.25-1.29 (m, 2H), 1.63-1.67 (m, 2H), 3.83 (s, 3H), 3.86 (s, 3H), 6.04 (s, 2H), 6.64-6.68 (m, 2H), 6.92 (d, J = 8.4 Hz, 1H), 7.03-7.06 (m, 2H), 7.30 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 8.9 Hz, 1H), 8.14 (dd, J = 8.9, 2.3 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 8.65 (s, 1H).

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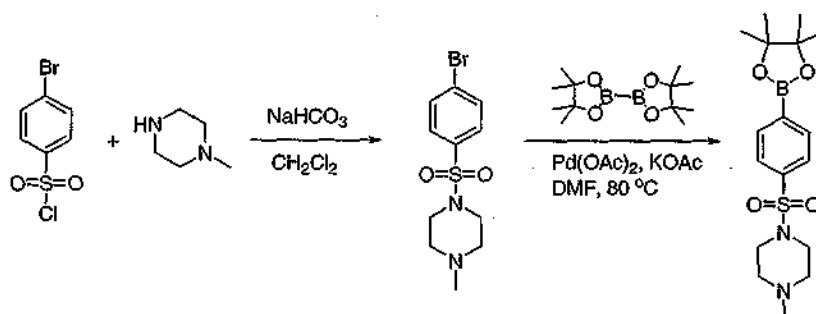
Z. 1-Benzo[1,3]dioxol-5-yl-cyclopropanecarboxylic acid [6-(4-dimethylamino-phenyl)-pyridin-2-yl]-amide



[00418] 1-Benzo[1,3]dioxol-5-yl-cyclopropanecarboxylic acid (6-bromo-pyridin-2-yl)-amide (36 mg, 0.10 mmol) was dissolved in 1 mL of *N,N*-dimethylformamide in a reaction tube. 4-(Dimethylamino)phenylboronic acid (21 mg, 0.13 mmol), 0.1 mL of an aqueous 2 M potassium carbonate solution, and Pd(dppf)Cl_2 (6.6 mg, 0.0090 mmol) were added and the reaction mixture was heated at 80 °C for three hours. The resulting material was cooled to room temperature, filtered, and purified by reverse-phase preparative liquid chromatography to yield the pure product as a trifluoroacetic acid salt. ESI-MS m/z calc. 401.2, found 402.5 ($M+1$)⁺. Retention time 2.96 minutes. ¹H NMR (400 MHz, CD₃CN) δ 1.23-1.27 (m, 2H), 1.62-1.66 (m, 2H), 3.04 (s, 6H), 6.06 (s, 2H), 6.88-6.90 (m, 2H), 6.93-6.96 (m, 1H), 7.05-7.07 (m, 2H), 7.53-7.56 (m, 1H), 7.77-7.81 (m, 3H), 7.84-7.89 (m, 1H), 8.34 (s, 1H).

[00419] The following schemes were utilized to prepare additional boronic esters which were not commercially available:

AA. 1-Methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-sulfonylpiperazine



[00420] Step a: 1-(4-Bromophenylsulfonyl)-4-methylpiperazine

A solution of 4-bromobenzoyl chloride (256 mg, 1.00 mmol) in 1 mL of dichloromethane was slowly added to a vial (40 mL) containing 5 mL of a saturated aqueous solution of sodium bicarbonate, dichloromethane (5 mL) and 1-methylpiperazine (100 mg, 1.00 mmol). The reaction was stirred at room temperature overnight. The phases were separated and the organic layer was dried over magnesium sulfate. Evaporation of the solvent under reduced pressure provided the required product, which was used in the next step without further purification. ESI-MS m/z calc. 318.0, found 318.9 ($M+1$)⁺. Retention time of 1.30 minutes. ¹H

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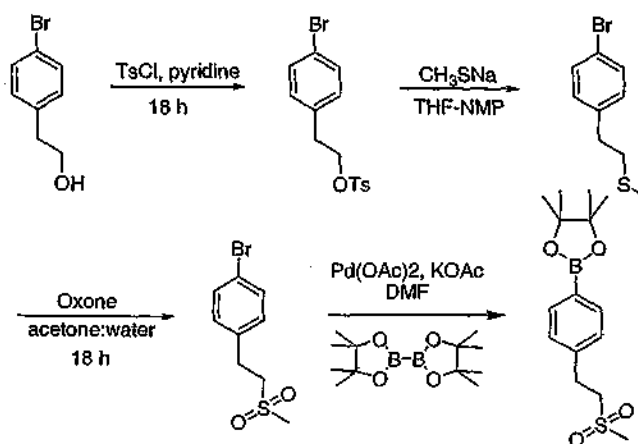
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NMR (300 MHz, CDCl_3) δ 7.65 (d, $J = 8.7$ Hz, 2H), 7.58 (d, $J = 8.7$ Hz, 2H), 3.03 (t, $J = 4.2$ Hz, 4H), 2.48 (t, $J = 4.2$ Hz, 4H), 2.26 (s, 3H).

[00421] Step b: 1-Methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfonyl-piperazine

A 50 mL round bottom flask was charged with 1-(4-bromophenyl-sulfonyl)-4-methylpiperazine (110 mg, 0.350 mmol), *bis*-(pinacolato)-diboron (93 mg, 0.37 mmol), palladium acetate (6 mg, 0.02 mmol), and potassium acetate (103 mg, 1.05 mmol) in *N,N*-dimethylformamide (6 mL). The mixture was degassed by gently bubbling argon through the solution for 30 minutes at room temperature. The mixture was then heated at 80 °C under argon until the reaction was complete (4 hours). The desired product, 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-sulfonyl-piperazine, and the bi-aryl product, 4-(4-methylpiperazin-1-ylsulfonyl)-phenyl-phenylsulfonyl-4-methylpiperazine, were obtained in a ratio of 1:2 as indicated by LC/MS analysis. The mixture was used without further purification.

BB. 4,4,5,5-Tetramethyl-2-(4-(2-(methylsulfonyl)ethyl)phenyl)-1,3,2-dioxaborolane



[00422] Step a: 4-Bromophenethyl-4-methylbenzenesulfonate

To a 50 mL round-bottom flask was added *p*-bromophenethyl alcohol (1.0 g, 4.9 mmol), followed by the addition of pyridine (15 mL). To this clear solution was added, under argon, *p*-toluenesulfonyl chloride (TsCl) (1.4 g, 7.5 mmol) as a solid. The reaction mixture was purged with Argon and stirred at room temperature for 18 hours. The crude mixture was treated with 1N HCl (20 mL) and extracted with ethyl acetate (5 x 25 mL). The organic fractions were dried over Na_2SO_4 , filtered, and concentrated to yield 4-bromophenethyl-4-methylbenzenesulfonate (0.60 g, 35%) as a yellowish liquid. $^1\text{H-NMR}$ (Acetone- d_6 , 300 MHz)

δ 7.64 (d, J = 8.4 Hz, 2H), 7.40-7.37 (d, J = 8.7 Hz, 4H), 7.09 (d, J = 8.5 Hz, 2H), 4.25 (t, J = 6.9 Hz, 2H), 2.92 (t, J = 6.3 Hz, 2H), 2.45 (s, 3H).

[00423] Step b: (4-Bromophenethyl)(methyl)sulfane

To a 20 mL round-bottom flask were added 4-bromophenethyl 4-methylbenzenesulfonate (0.354 g, 0.996 mmol) and CH_3SNa (0.10 g, 1.5 mmol), followed by the addition of THF (1.5 mL) and *N*-methyl-2-pyrrolidinone (1.0 mL). The mixture was stirred at room temperature for 48 hours, and then treated with a saturated aqueous solution of sodium bicarbonate (10 mL). The mixture was extracted with ethyl acetate (4 x 10 mL), dried over Na_2SO_4 , filtered, and concentrated to yield (4-bromophenethyl)(methyl)sulfane (0.30 g crude) as a yellowish oil. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.40 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 2.89-2.81 (m, 2H), 2.74-2.69 (m, 2H), 2.10 (s, 3H).

[00424] Step c: 1-Bromo-4-(2-methylsulfonyl)-ethylbenzene

To a 20 mL round-bottom flask were added (4-bromophenethyl)-(methyl)sulfane (0.311g, 1.34 mmol) and Oxone (3.1 g, 0.020 mol), followed by the addition of a 1:1 mixture of acetone/water (10 mL). The mixture was vigorously stirred at room temperature for 20 hours, before being concentrated. The aqueous mixture was extracted with ethyl acetate (3 x 15 mL) and dichloromethane (3 x 10 mL). The organic fractions were combined, dried with Na_2SO_4 , filtered, and concentrated to yield a white semisolid. Purification of the crude material by flash chromatography yielded 1-bromo-4-(2-methylsulfonyl)-ethylbenzene (0.283 g, 80%). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 300 MHz) δ 7.49 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 3.43 (m, 2H), 2.99 (m, 2H), 2.97 (s, 3H).

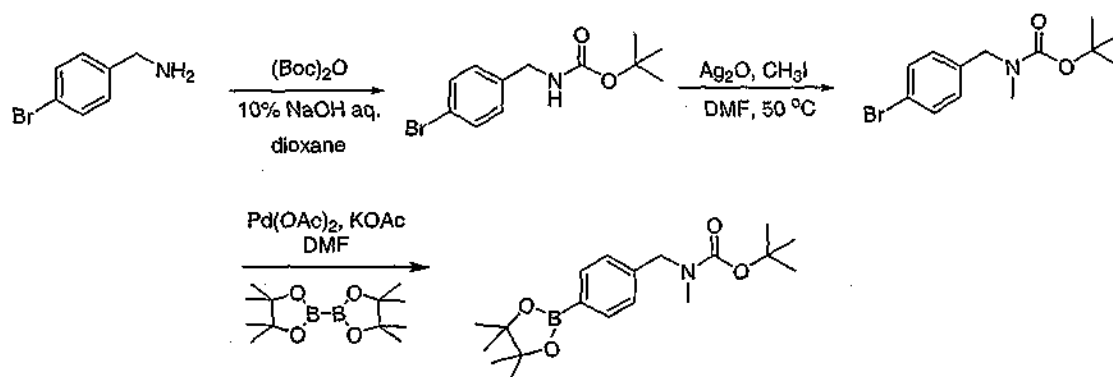
[00425] Step d: 4,4,5,5-Tetramethyl-2-(4-(2-(methylsulfonyl)ethyl)-phenyl)-1,3,2-dioxaborolane

4,4,5,5-Tetramethyl-2-(4-(2-(methylsulfonyl)ethyl)phenyl)-1,3,2-dioxaborolane was prepared in the same manner as described above for 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfonyl-piperazine, Preparation AA.

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CC. tert-Butyl methyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate



[00426] Step a: *tert*-Butyl-4-bromobenzylcarbamate

Commercially available *p*-bromobenzylamine hydrochloride (1 g, 4 mmol) was treated with 10% aq. NaOH (5 mL). To the clear solution was added (Boc)₂O (1.1 g, 4.9 mmol) dissolved in dioxane (10 mL). The mixture was vigorously stirred at room temperature for 18 hours. The resulting residue was concentrated, suspended in water (20 mL), extracted with ethyl acetate (4 x 20 mL), dried over Na₂SO₄, filtered, and concentrated to yield *tert*-butyl-4-bromobenzylcarbamate (1.23 g, 96%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 6 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.07 (d, *J* = 6.3 Hz, 2H), 1.38 (s, 9H).

[00427] Step b: *tert*-Butyl-4-bromobenzyl(methyl)carbamate

In a 60-mL vial, *tert*-butyl-4-bromobenzylcarbamate (1.25 g, 4.37 mmol) was dissolved in DMF (12 mL). To this solution was added Ag₂O (4.0 g, 17 mmol) followed by the addition of CH₃I (0.68 mL, 11 mmol). The mixture was stirred at 50 °C for 18 hours. The reaction mixture was filtered through a bed of celite and the celite was washed with methanol (2 x 20 mL) and dichloromethane (2 x 20 mL). The filtrate was concentrated to remove most of the DMF. The residue was treated with water (50 mL) and a white emulsion formed. This mixture was extracted with ethyl acetate (4 x 25 mL), dried over Na₂SO₄, and the solvent was evaporated to yield *tert*-butyl-4-bromobenzyl(methyl)carbamate (1.3 g, 98%) as a yellow oil. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.32 (s, 2H), 2.74 (s, 3H), 1.38 (s, 9H).

[00428] Step c: *tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylmethylcarbamate

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The coupling reaction was achieved in the same manner as described above for 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfonyl-piperazine, Preparation AA. The Boc protecting group was removed after the coupling reaction by treating the crude reaction mixture with 0.5 mL of 1N HCl in diethyl ether for 18 hours before purification by HPLC.

[00429] Additional examples of the invention were prepared following the above procedure with non-substantial changes but using aryl boronic acids given in Table 4.

[00430] Table 4: Additional exemplary compounds of formula I.

Compound No.	Amine	Boronic Acid
1	B-2	[2-(dimethylaminomethyl)phenyl]boronic acid
2	B-2	[4-(1-piperidyl)phenyl]boronic acid
3	B-2	(3,4-dichlorophenyl)boronic acid
4	B-2	(4-morpholinosulfonylphenyl)boronic acid
5	B-2	(3-chloro-4-methoxy-phenyl)boronic acid
6	B-2	(6-methoxy-3-pyridyl)boronic acid
7	B-2	(4-dimethylaminophenyl)boronic acid
8	B-2	(4-morpholinophenyl)boronic acid
9	B-2	[4-(acetylaminomethyl)phenyl]boronic acid
10	B-2	(2-hydroxyphenyl)boronic acid
11	B-1	2-dihydroxyboranylbenzoic acid
12	B-1	(6-methoxy-3-pyridyl)boronic acid
14	B-2	(2,4-dimethylphenyl)boronic acid
15	B-2	[3-(hydroxymethyl)phenyl]boronic acid
16	B-2	3-dihydroxyboranylbenzoic acid
17	B-2	(3-ethoxyphenyl)boronic acid
18	B-2	(3,4-dimethylphenyl)boronic acid
19	B-1	[4-(hydroxymethyl)phenyl]boronic acid
20	B-1	3-pyridylboronic acid
21	B-2	(4-ethylphenyl)boronic acid
23	B-2	4,4,5,5-tetramethyl-2-(4-(2-(methylsulfonyl)ethyl)phenyl)-1,3,2-dioxaborolane
24	B-1	benzo[1,3]dioxol-5-ylboronic acid
25	B-2	(3-chlorophenyl)boronic acid
26	B-2	(3-methylsulfonylaminophenyl)boronic acid
27	B-2	(3,5-dichlorophenyl)boronic acid
28	B-2	(3-methoxyphenyl)boronic acid
29	B-1	(3-hydroxyphenyl)boronic acid
31	B-2	phenylboronic acid
32	B-2	(2,5-difluorophenyl)boronic acid
33	B-8	phenylboronic acid
36	B-2	(2-methylsulfonylaminophenyl)boronic acid
37	B-1	1H-indol-5-ylboronic acid
38	B-2	2,2,2-trifluoro-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)acetamide
39	B-2	(2-chlorophenyl)boronic acid

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Compound No.	Amine	Boronic Acid
40	B-1	m-tolylboronic acid
41	B-2	(2,4-dimethoxypyrimidin-5-yl)boronic acid
42	B-2	(4-methoxycarbonylphenyl)boronic acid
43	B-2	<i>tert</i> -butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylmethylcarbamate ^(a)
44	B-2	(4-ethoxyphenyl)boronic acid
45	B-2	(3-methylsulfonylphenyl)boronic acid
46	B-2	(4-fluoro-3-methyl-phenyl)boronic acid
47	B-2	(4-cyanophenyl)boronic acid
48	B-1	(2,5-dimethoxyphenyl)boronic acid
49	B-1	(4-methylsulfonylphenyl)boronic acid
50	B-1	cyclopent-1-enylboronic acid
51	B-2	o-tolylboronic acid
52	B-1	(2,6-dimethylphenyl)boronic acid
53	B-8	2-chlorophenylboronic acid
54	B-2	(2,5-dimethoxyphenyl)boronic acid
55	B-2	(2-fluoro-3-methoxy-phenyl)boronic acid
56	B-2	(2-methoxyphenyl)boronic acid
57	B-9	phenylboronic acid
58	B-2	(4-isopropoxyphenyl)boronic acid
59	B-2	(4-carbamoylphenyl)boronic acid
60	B-2	(3,5-dimethylphenyl)boronic acid
61	B-2	(4-isobutylphenyl)boronic acid
62	B-1	(4-cyanophenyl)boronic acid
63	B-10	phenylboronic acid
64	B-2	<i>N</i> -ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzenesulfonamide
65	B-1	2,3-dihydrobenzofuran-5-ylboronic acid
66	B-2	(4-chlorophenyl)boronic acid
67	B-2	(4-chloro-3-methyl-phenyl)boronic acid
68	B-2	(2-fluorophenyl)boronic acid
69	B-2	benzo[1,3]dioxol-5-ylboronic acid
70	B-2	(4-morpholinocarbonylphenyl)boronic acid
71	B-1	cyclohex-1-enylboronic acid
72	B-2	(3,4,5-trimethoxyphenyl)boronic acid
73	B-2	[4-(dimethylaminomethyl)phenyl]boronic acid
74	B-2	m-tolylboronic acid
77	B-2	(3-cyanophenyl)boronic acid
78	B-2	[3-(<i>tert</i> -butoxycarbonylaminomethyl)phenyl]boronic acid ^(a)
79	B-2	(4-methylsulfonylphenyl)boronic acid
80	B-1	p-tolylboronic acid
81	B-2	(2,4-dimethoxyphenyl)boronic acid
82	B-2	(2-methoxycarbonylphenyl)boronic acid
83	B-2	(2,4-difluorophenyl)boronic acid
84	B-2	(4-isopropylphenyl)boronic acid
85	B-2	[4-(2-dimethylaminoethylcarbamoyl)phenyl]boronic acid
86	B-1	(2,4-dimethoxyphenyl)boronic acid

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Compound No.	Amine	Boronic Acid
87	B-1	benzofuran-2-ylboronic acid
88	B-2	2,3-dihydrobenzofuran-5-ylboronic acid
89	B-2	(3-fluoro-4-methoxy-phenyl)boronic acid
91	B-1	(3-cyanophenyl)boronic acid
92	B-1	(4-dimethylaminophenyl)boronic acid
93	B-2	(2,6-dimethoxyphenyl)boronic acid
94	B-2	(2-methoxy-5-methyl-phenyl)boronic acid
95	B-2	(3-acetylaminophenyl)boronic acid
96	B-1	(2,4-dimethoxypyrimidin-5-yl)boronic acid
97	B-2	(5-fluoro-2-methoxy-phenyl)boronic acid
98	B-1	[3-(hydroxymethyl)phenyl]boronic acid
99	B-1	(2-methoxyphenyl)boronic acid
100	B-2	(2,4,6-trimethylphenyl)boronic acid
101	B-2	[4-(dimethylcarbamoyl)phenyl]boronic acid
102	B-2	[4-(<i>tert</i> -butoxycarbonylaminomethyl)phenyl]boronic acid ^(a)
104	B-1	(2-chlorophenyl)boronic acid
105	B-1	(3-acetylaminophenyl)boronic acid
106	B-2	(2-ethoxyphenyl)boronic acid
107	B-2	3-furylboronic acid
108	B-2	[2-(hydroxymethyl)phenyl]boronic acid
110	B-9	2-chlorophenylboronic acid
111	B-2	(2-fluoro-6-methoxy-phenyl)boronic acid
112	B-2	(2-ethoxy-5-methyl-phenyl)boronic acid
113	B-2	1H-indol-5-ylboronic acid
114	B-1	(3-chloro-4-pyridyl)boronic acid
115	B-2	cyclohex-1-enylboronic acid
116	B-1	o-tolylboronic acid
119	B-2	(2-aminophenyl)boronic acid
120	B-2	(4-methoxy-3,5-dimethyl-phenyl)boronic acid
121	B-2	(4-methoxyphenyl)boronic acid
122	B-2	(2-propoxyphenyl)boronic acid
123	B-2	(2-isopropoxyphenyl)boronic acid
124	B-2	(2,3-dichlorophenyl)boronic acid
126	B-2	(2,3-dimethylphenyl)boronic acid
127	B-2	(4-fluorophenyl)boronic acid
128	B-1	(3-methoxyphenyl)boronic acid
129	B-2	(4-chloro-2-methyl-phenyl)boronic acid
130	B-1	(2,6-dimethoxyphenyl)boronic acid
131	B-2	(5-isopropyl-2-methoxy-phenyl)boronic acid
132	B-2	(3-isopropoxyphenyl)boronic acid
134	B-2	4-dihydroxyboranylbenzoic acid
135	B-2	(4-dimethylamino-2-methoxy-phenyl)boronic acid
136	B-2	(4-methylsulfinylphenyl)boronic acid
137	B-2	[4-(methylcarbamoyl)phenyl]boronic acid
138	B-1	8-quinolylboronic acid
139	B-2	cyclopent-1-enylboronic acid
140	B-2	p-tolylboronic acid
142	B-8	2-methoxyphenylboronic acid

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Compound No.	Amine	Boronic Acid
143	B-2	(2,5-dimethylphenyl)boronic acid
144	B-1	(3,4-dimethoxyphenyl)boronic acid
145	B-1	(3-chlorophenyl)boronic acid
146	B-2	[4-(morpholinomethyl)phenyl]boronic acid
147	B-10	4-(dimethylamino)phenylboronic acid
148	B-2	[4-(methylsulfamoyl)phenyl]boronic acid
149	B-1	4-dihydroxyboranylbenzoic acid
150	B-1	phenylboronic acid
151	B-2	(2,3-difluorophenyl)boronic acid
152	B-1	(4-chlorophenyl)boronic acid
153	B-9	2-methoxyphenylboronic acid
154	B-2	3-dihydroxyboranylbenzoic acid
155	B-10	2-methoxyphenylboronic acid
157	B-2	(3-chloro-4-fluoro-phenyl)boronic acid
158	B-2	(2,3-dimethoxyphenyl)boronic acid
159	B-2	[4-(<i>tert</i> -butoxycarbonylaminomethyl)phenyl]boronic acid
160	B-2	(4-sulfamoylphenyl)boronic acid
161	B-2	(3,4-dimethoxyphenyl)boronic acid
162	B-2	[4-(methylsulfonylaminomethyl)phenyl]boronic acid
166	B-1	4-(<i>N,N</i> -dimethylsulfamoyl)phenylboronic acid
167	B-6	2-isopropylphenylboronic acid
171	B-6	4-(methylcarbamoyl)phenylboronic acid
173	B-2	3-fluorophenylboronic acid
174	B-6	3-(<i>N,N</i> -dimethylsulfamoyl)phenylboronic acid
179	B-6	4-(<i>N</i> -methylsulfamoyl)phenylboronic acid
181	B-1	3-((<i>tert</i> -butoxycarbonylamino)methyl)phenylboronic acid
185	B-3	3-methoxyphenylboronic acid
186	B-6	2-chlorophenylboronic acid
187	B-7	3-(dimethylcarbamoyl)phenylboronic acid
188	B-6	3-(hydroxymethyl)phenylboronic acid
189	B-1	3-(<i>N,N</i> -dimethylsulfamoyl)phenylboronic acid
190	B-1	4-sulfamoylphenylboronic acid
191	B-1	2-isopropylphenylboronic acid
193	B-5	3-sulfamoylphenylboronic acid
194	B-3	4-isopropylphenylboronic acid
195	B-3	3-(<i>N,N</i> -dimethylsulfamoyl)phenylboronic acid
196	B-7	4-(methylcarbamoyl)phenylboronic acid
198	B-3	3-(dimethylcarbamoyl)phenylboronic acid
204	B-5	3-(dimethylcarbamoyl)phenylboronic acid
206	B-3	4-chlorophenylboronic acid
207	B-1	4-(<i>N</i> -methylsulfamoyl)phenylboronic acid
209	B-1	3-(methylcarbamoyl)phenylboronic acid
210	B-3	4-sulfamoylphenylboronic acid
213	B-5	3-isopropylphenylboronic acid
215	B-7	4-methoxyphenylboronic acid
216	B-6	3-chlorophenylboronic acid
217	B-7	<i>m</i> -tolylboronic acid

Compound No.	Amine	Boronic Acid
219	B-5	4-(hydroxymethyl)phenylboronic acid
222	B-6	m-tolylboronic acid
224	B-5	2-chlorophenylboronic acid
225	B-1	3-isopropylphenylboronic acid
227	B-6	4-(hydroxymethyl)phenylboronic acid
229	B-7	3-chlorophenylboronic acid
230	B-6	o-tolylboronic acid
231	B-1	2-(hydroxymethyl)phenylboronic acid
235	B-3	3-isopropylphenylboronic acid
238	B-5	3-carbamoylphenylboronic acid
241	B-2	4-(<i>N,N</i> -dimethylsulfamoyl)phenylboronic acid
243	B-7	2-methoxyphenylboronic acid
247	B-6	3-(dimethylcarbamoyl)phenylboronic acid
251	B-3	3-sulfamoylphenylboronic acid
252	B-1	4-methoxyphenylboronic acid
254	B-3	4-(<i>N</i> -methylsulfamoyl)phenylboronic acid
255	B-1	4-((<i>tert</i> -butoxycarbonylamino)methyl)phenylboronic acid
257	B-5	4-chlorophenylboronic acid
258	B-3	3-(methylcarbamoyl)phenylboronic acid
260	B-3	2-(hydroxymethyl)phenylboronic acid
263	B-4	4-(hydroxymethyl)phenylboronic acid
264	B-7	4-chlorophenylboronic acid
265	B-6	4-carbamoylphenylboronic acid
266	B-5	3-methoxyphenylboronic acid
269	B-7	phenylboronic acid
272	B-3	4-methoxyphenylboronic acid
274	B-6	2-(hydroxymethyl)phenylboronic acid
277	B-3	4-(hydroxymethyl)phenylboronic acid
278	B-3	3-(methylcarbamoyl)phenylboronic acid
280	B-3	4-(<i>N,N</i> -dimethylsulfamoyl)phenylboronic acid
283	B-3	4-carbamoylphenylboronic acid
286	B-1	4-(methylcarbamoyl)phenylboronic acid
287	B-2	4-(trifluoromethoxy)phenylboronic acid
288	B-5	4-(<i>N</i> -methylsulfamoyl)phenylboronic acid
289	B-3	phenylboronic acid
290	B-6	4-isopropylphenylboronic acid
291	B-3	3-(hydroxymethyl)phenylboronic acid
293	B-6	3-methoxyphenylboronic acid
294	B-7	2-(hydroxymethyl)phenylboronic acid
295	B-3	3-carbamoylphenylboronic acid
296	B-5	m-tolylboronic acid
297	B-1	4-(dimethylcarbamoyl)phenylboronic acid
298	B-3	2-methoxyphenylboronic acid
299	B-7	p-tolylboronic acid
300	B-3	o-tolylboronic acid
301	B-5	2-(hydroxymethyl)phenylboronic acid
303	B-6	2-methoxyphenylboronic acid
305	B-6	3-isopropylphenylboronic acid

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Compound No.	Amine	Boronic Acid
308	B-7	4-isopropylphenylboronic acid
309	B-3	4-(dimethylcarbamoyl)phenylboronic acid
310	B-5	4-(methylcarbamoyl)phenylboronic acid
313	B-7	o-tolylboronic acid
314	B-7	3-(methylcarbamoyl)phenylboronic acid
315	B-3	p-tolylboronic acid
320	B-1	3-(dimethylcarbamoyl)phenylboronic acid
321	B-5	4-sulfamoylphenylboronic acid
322	B-6	phenylboronic acid
323	B-5	o-tolylboronic acid
324	B-3	4-((tert-butoxycarbonylamino)methyl)phenylboronic acid ^(a)
326	B-5	4-(dimethylcarbamoyl)phenylboronic acid
327	B-5	2-methoxyphenylboronic acid
328	B-1	4-isopropylphenylboronic acid
329	B-5	2-isopropylphenylboronic acid
331	B-3	m-tolylboronic acid
333	B-6	4-methoxyphenylboronic acid
334	B-5	4-methoxyphenylboronic acid
337	B-6	p-tolylboronic acid
343	B-5	4-(N,N-dimethylsulfamoyl)phenylboronic acid
346	B-3	2-isopropylphenylboronic acid
348	B-6	4-((tert-butoxycarbonylamino)methyl)phenylboronic acid ^(a)
349	B-1	3-sulfamoylphenylboronic acid
350	B-3	3-((tert-butoxycarbonylamino)methyl)phenylboronic acid ^(a)
351	B-5	phenylboronic acid
352	B-7	2-isopropylphenylboronic acid
353	B-6	4-chlorophenylboronic acid
354	B-7	2-chlorophenylboronic acid
355	B-5	3-(N,N-dimethylsulfamoyl)phenylboronic acid
356	B-7	3-sulfamoylphenylboronic acid
357	B-7	4-(N-methylsulfamoyl)phenylboronic acid
359	B-1	4-carbamoylphenylboronic acid
361	B-3	3-chlorophenylboronic acid
365	B-1	3-carbamoylphenylboronic acid
367	B-7	3-(hydroxymethyl)phenylboronic acid
368	B-4	4-(dimethylcarbamoyl)phenylboronic acid
370	B-5	3-(hydroxymethyl)phenylboronic acid
371	B-5	3-(methylcarbamoyl)phenylboronic acid
374	B-6	4-sulfamoylphenylboronic acid
375	B-5	4-carbamoylphenylboronic acid
389	B-12	2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
390	B-11	3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
391	B-13	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid

Compound No.	Amine	Boronic Acid
392	B-11	3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
393	B-12	2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
394	B-12	3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
395	B-2	4-cyclohexylphenylboronic acid
396	B-12	3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
397	B-11	3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
398	B-12	3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
399	B-13	2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
400	B-13	3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
401	B-11	2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
402	B-12	2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
403	B-11	2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
404	B-11	2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
405	B-12	2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
406	B-13	2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
407	B-11	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
408	B-13	2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
410	B-2	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline
411	B-13	3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
412	B-2	2-methoxypyridin-3-ylboronic acid
414	B-11	3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
415	B-13	3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
417	B-12	2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
418	B-4	3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
419	B-11	2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
420	B-2	4-(hydroxymethyl)phenylboronic acid
421	B-11	2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid

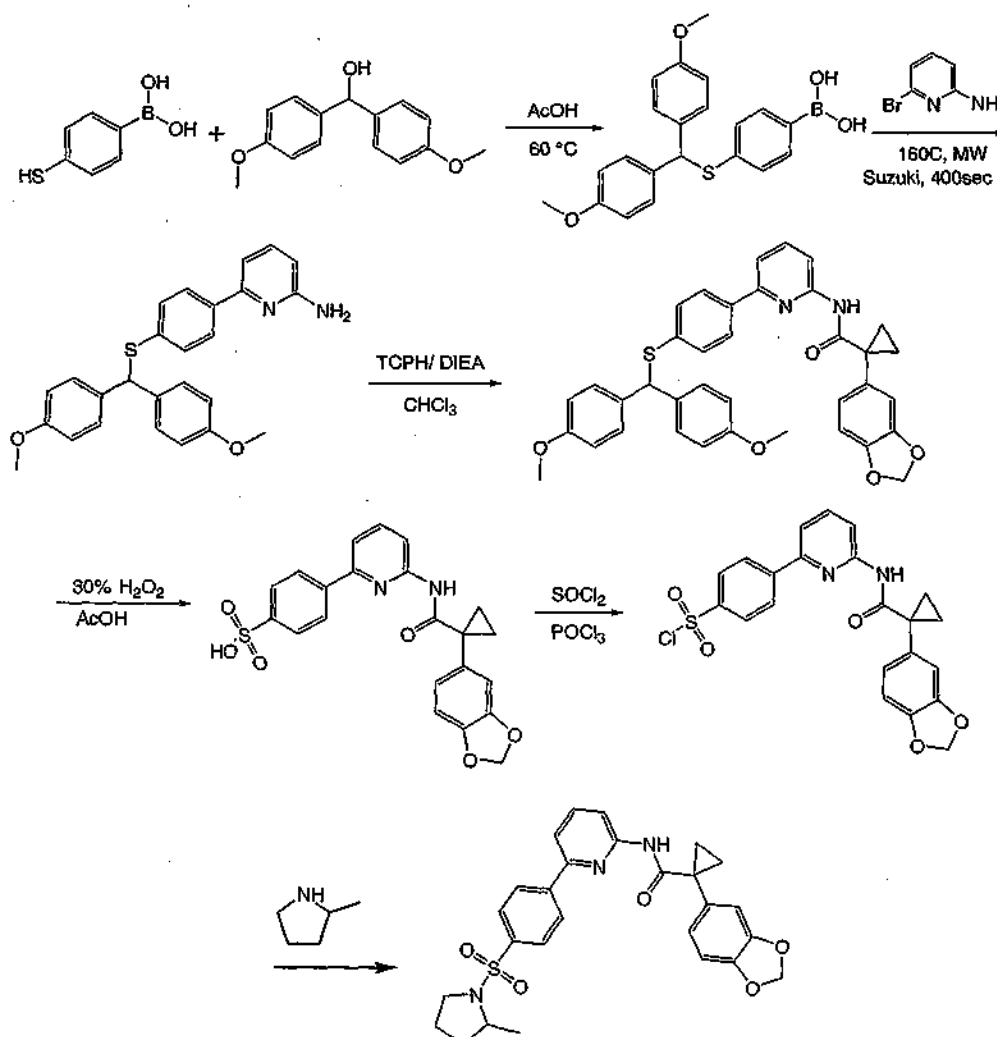
Compound No.	Amine	Boronic Acid
422	B-12	3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid

(a) The Boc protecting group was removed after the coupling reaction by treating the crude reaction mixture with 0.5 mL of 1N HCl in diethyl ether for 18 hours before purification by HPLC.

[00431] Further examples of the invention may be prepared by modification of intermediates as illustrated above.

Compound Derivatization After Coupling:

DD. 1-(Benzo[d][1,3]dioxol-5-yl)-N-(6-(4-(2-methylpyrrolidin-1-yl)sulfonyl)phenyl)pyridin-2-yl)cyclopropanecarboxamide



[00432] Step a: 4-(4,4'-Dimethoxybenzhydryl)-thiophenyl boronic acid

4,4'-Dimethoxybenzhydrol (2.7 g, 11 mmol) and 4-mercaptophenylboronic acid (1.54 g, 10 mmol) were dissolved in 20 mL AcOH and heated at 60 °C for 1h. Solvent was

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evaporated and the residue was dried under high vacuum. This material was used without further purification.

[00433] Step b: 6-(4-(Bis(4-methoxyphenyl)methylthio)phenyl)pyridin-2-amine

4-(4,4'-Dimethoxybenzhydryl)-thiophenyl boronic acid (10 mmol) and 2-amino-6-bromopyridine (1.73 g, 10 mmol) were dissolved in MeCN (40 mL) followed by addition of $\text{Pd}(\text{PPh}_3)_4$ (~50 mg) and aq. K_2CO_3 (1M, 22 mL). The reaction mixture was heated portion wise in a microwave oven (160 °C, 400 sec). The products were distributed between ethyl acetate and water. The organic layer was washed with water, brine and dried over MgSO_4 . Evaporation of the volatiles yielded an oil that was used without purification in the next step. ESI-MS m/z calc. 428.0, found 429.1 (M+1).

[00434] Step c: 1-(Benzo[d][1,3]dioxol-5-yl)-N-(6-(4-(bis(4-methoxyphenyl)methylthio)phenyl)-pyridin-2-yl)cyclopropanecarboxamide

6-[(4,4'-Dimethoxybenzhydryl)-4-thiophenyl]pyridin-2-ylamine (~10 mmol) and 1-benzo[1,3]dioxol-5-yl-cyclopropanecarboxylic acid (2.28 g, 11 mmol) were dissolved in chloroform (25 mL) followed by the addition of TCPH (4.1 g, 12 mmol) and DIEA (5 mL, 30 mmol). The reaction mixture was heated at 65 °C for 48 h before the volatiles were removed under reduced pressure. The residue was transferred to a separatory funnel and distributed between water (200 mL) and ethyl acetate (150 mL). The organic layer was washed with 5% NaHCO_3 (2 x 150 mL), water (1 x 150 mL), brine (1 x 150 mL) and dried over MgSO_4 . Evaporation of the solvent yielded crude 1-(benzo[d][1,3]dioxol-5-yl)-N-(6-(4-(bis(4-methoxyphenyl)-methylthio)phenyl)pyridin-2-yl)cyclopropanecarboxamide as a pale oil. ESI-MS m/z calc. 616.0, found 617.0 (M+1) (HPLC purity ~85%, UV254 nm).

[00435] Step d: 4-(6-(1-(Benzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)pyridin-2-yl)benzenesulfonic acid

1-(Benzo[d][1,3]dioxol-5-yl)-N-(6-(4-(bis(4-methoxyphenyl)methylthio)-phenyl)pyridin-2-yl)cyclopropanecarboxamide (~8.5 mmol) was dissolved in AcOH (75 mL) followed by the addition of 30% H_2O_2 (10 mL). Additional hydrogen peroxide (10 mL) was added 2h later. The reaction mixture was stirred at 35-45 °C overnight (~90% conversion, HPLC). The volume of reaction mixture was reduced to a third by evaporation (bath temperature below 40 °C). The reaction mixture was loaded directly onto a prep RP HPLC column (C-18) and purified. Fractions with 4-(6-(1-(benzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)pyridin-2-yl)benzenesulfonic acid were collected and evaporated

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(1.9 g, 4.3 mmol, cal. based on 4-mercaptophenylboronic acid). ESI-MS m/z calc. 438.0, found 438.9 ($M+1$).

[00436] Step e: 4-(6-(1-(Benzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)pyridin-2-yl)benzene-1-sulfonyl chloride

4-(6-(1-(Benzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)pyridin-2-yl)benzenesulfonic acid (1.9 g, 4.3 mmol) was dissolved in POCl_3 (30 mL) followed by the addition of SOCl_2 (3 mL) and DMF (100 μL). The reaction mixture was heated at 70-80 °C for 15 min. The volatiles were evaporated and then re-evaporated with chloroform-toluene. The residual brown oil was diluted with chloroform (22 mL) and used for sulfonylation immediately. ESI-MS m/z calc. 456.0, found 457.1 ($M+1$).

[00437] Step f: 1-(Benzo[d][1,3]dioxol-5-yl)-*N*-(6-(4-(2-methylpyrrolidin-1-yl)sulfonyl)phenyl)pyridin-2-yl)cyclopropanecarboxamide

4-(6-(1-(Benzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)pyridin-2-yl)benzene-1-sulfonyl chloride (~ 35 μmol , 400 μL solution in chloroform) was treated with 2-methylpyrrolidine followed by the addition of DIEA (100 μL). The reaction mixture was kept at room temperature for 1h, concentrated, then diluted with DMSO (400 μL). The resulting solution was subjected to HPLC purification. Fractions containing the desired material were combined and concentrated in vacuum centrifuge at 40° C to provide the trifluoroacetic salt of target material (ESI-MS m/z calc. 505.0, found 505.9 ($M+1$), retention time 4.06 min). ^1H NMR (250 MHz, $\text{DMSO}-d_6$) δ 1.15 (m, 2H), δ 1.22 (d, 3H, $J=6.3$ Hz), δ 1.41-1.47 (m, 2H), δ 1.51 (m, 2H), δ 1.52-1.59 (m, 2H), δ 3.12 (m, 1H), δ 3.33 (m, 1H), δ 3.64 (m, 1H), δ 6.07 (s, 2H), δ 6.96-7.06 (m, 2H), δ 7.13 (d, 1H, $J=1.3$ Hz), δ 7.78 (d, 1H, $J=8.2$ Hz), δ 7.88 (d, 2H, $J=8.5$ Hz), δ 7.94 (t, 1H, $J=8.2$ Hz), δ 8.08 (d, 1H, $J=8.2$ Hz), δ 8.16 (d, 2H, $J=8.5$ Hz), δ 8.53 (s, 1H).

[00438] The compounds in the following table were synthesized as described above using commercially available amines. Additional examples of the invention were prepared following the above procedure with non-substantial changes but using amines given in Table 5.

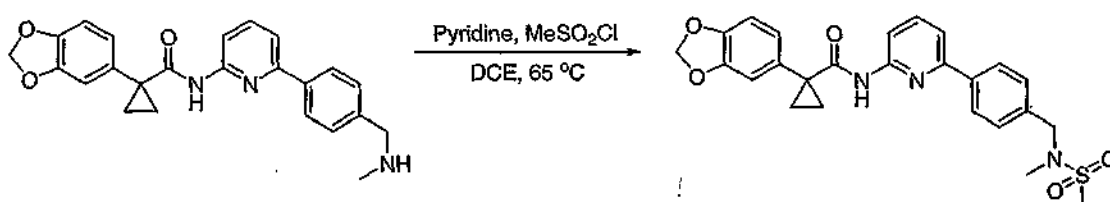
[00439] Table 5: Additional exemplary compounds of formula I.

Compound No.	Amine
13	1-methylpiperazine
22	2,6-dimethylmorpholine
30	piperidin-3-ylmethanol
34	2-(methylamino)ethanol
35	(R)-pyrrolidin-2-ylmethanol

Compound No.	Amine
75	2-(pyrrolidin-1-yl)ethanamine
76	pyrrolidine
90	piperidine
103	(tetrahydrofuran-2-yl)methanamine
109	piperidin-4-ol
117	2-methylpropan-2-amine
118	cyclopentanamine
125	(S)-2-(methoxymethyl)pyrrolidine
133	(R)-2-(methoxymethyl)pyrrolidine
141	piperidin-4-ylmethanol
156	N-methylpropanamine
163	pyrrolidin-3-ol
168	2-(2-aminoethoxy)ethanol
172	2-morpholinoethanamine
175	furan-2-ylmethanamine
176	piperidin-3-ol
178	2-(1-methylpyrrolidin-2-yl)ethanamine
180	3-methylpiperidine
182	(S)-pyrrolidine-2-carboxamide
184	(R)-1-aminopropan-2-ol
197	2-aminopropane-1,3-diol
199	2-amino-2-ethylpropane-1,3-diol
203	N ¹ ,N ¹ -dimethylethane-1,2-diamine
205	(R)-2-amino-3-methylbutan-1-ol
208	cyclohexanamine
212	piperazin-2-one
232	2-aminoethanol
233	piperidin-2-ylmethanol
234	2-(piperazin-1-yl)ethanol
244	N-(cyclopropylmethyl)propan-1-amine
249	3-morpholinopropan-1-amine
261	1-(piperazin-1-yl)ethanone
267	2-(1H-imidazol-4-yl)ethanamine
268	(R)-2-aminopropan-1-ol
270	2-methylpiperidine
273	2-(pyridin-2-yl)ethanamine
275	3,3-difluoropyrrolidine
276	2-amino-2-methylpropan-1-ol
285	3-(1H-imidazol-1-yl)propan-1-amine
304	piperidine-3-carboxamide
306	cyclobutanamine
307	(S)-3-aminopropane-1,2-diol
311	N-methylcyclohexanamine
312	N-methylprop-2-en-1-amine
316	2-amino-2-methylpropane-1,3-diol
325	(5-methylfuran-2-yl)methanamine
330	3,3-dimethylbutan-1-amine
332	2-methylpyrrolidine
335	2,5-dimethylpyrrolidine

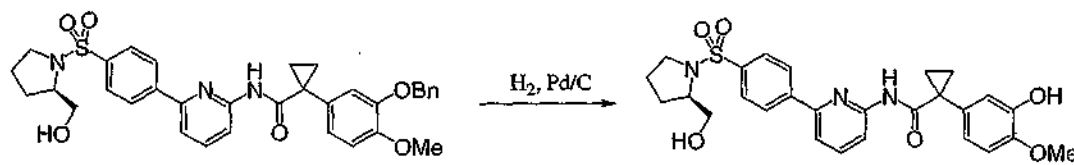
Compound No.	Amine
336	(R)-2-aminobutan-1-ol
338	propan-2-amine
339	N-methylbutan-1-amine
342	4-amino-3-hydroxybutanoic acid
344	3-(methylamino)propane-1,2-diol
347	N-(2-aminoethyl)acetamide
360	1-aminobutan-2-ol
364	(S)-pyrrolidine-2-carboxylic acid
366	1-(2-methoxyethyl)piperazine
373	(R)-2-aminopentan-1-ol

EE. 1-Benzo[1,3]dioxol-5-yl-N-[6-[4-[(methyl-methylsulfonyl-amino)methyl] phenyl]-2-pyridyl]-cyclopropane-1-carboxamide (Compound No. 292)



[00440] To the starting amine (brown semisolid, 0.100 g, ~ 0.2 mmol, obtained by treatment of the corresponding *t*-butyloxycarbonyl derivative by treatment with 1N HCl in ether) was added dichloroethane (DCE) (1.5 mL), followed by the addition of pyridine (0.063 mL, 0.78 mmol) and methansulfonyl chloride (0.03 mL, 0.4 mmol). The mixture was stirred at 65 °C for 3 hours. After this time, LC/MS analysis showed ~ 50 % conversion to the desired product. Two additional equivalents of pyridine and 1.5 equivalents of methansulfonyl chloride were added and the reaction was stirred for 2 hours. The residue was concentrated and purified by HPLC to yield 1-benzo[1,3]dioxol-5-yl-N-[6-[4-[(methyl-methylsulfonyl-amino)methyl]phenyl]-2-pyridyl]-cyclopropane-1-carboxamide (0.020 g, 21% yield) as a white solid. ESI-MS *m/z* calc. 479.2, found 480.1 (*M*+1)⁺.

FF. (R)-1-(3-(hydroxy-4-methoxyphenyl)-N-(6-(4-(2-(hydroxymethyl)-pyrrolidin-1-ylsulfonyl)phenyl)pyridin-2-yl)cyclopropanecarboxamide



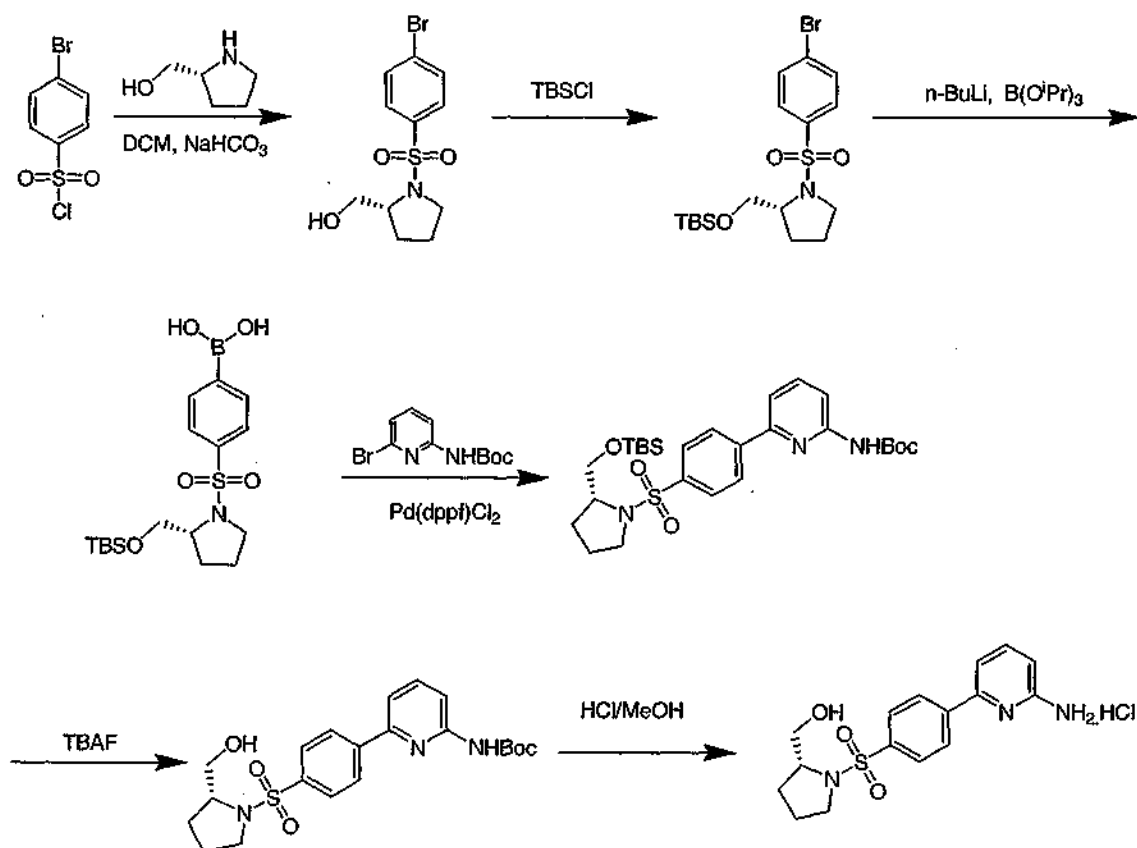
[00441] (R)-1-(3-(Benzyloxy)-4-methoxyphenyl)-N-(6-(4-(2-(hydroxymethyl)pyrrolidin-1-ylsulfonyl)phenyl)pyridin-2-yl)cyclopropanecarboxamide (28 mg, 0.046 mmol) was dissolved in ethanol (3 mL). Palladium on charcoal (10%, 20 mg) was added

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and the reaction was stirred overnight under 1 atm of hydrogen. The catalyst was filtered off and the product was isolated by silica gel chromatography (50-80% EtOAc in hexane) to provide (*R*)-1-(3-hydroxy-4-methoxyphenyl)-*N*-(6-(4-(2-(hydroxymethyl)pyrrolidin-1-yl)sulfonyl)phenyl)pyridin-2-yl)cyclopropanecarboxamide (8 mg, 34%). ESI-MS *m/z* calc. 523.4, found 524.3 (*M*+1)⁺. Retention time of 3.17 minutes.

[00442] 2-Amino-5-phenylpyridine (CAS [33421-40-8]) is C-1.

GG. (*R*)-(1-(4-(6-Aminopyridin-2-yl)phenylsulfonyl)pyrrolidin-2-yl) methanol hydrochloride (C-2)



[00443] Step a: (*R*)-(1-(4-Bromophenylsulfonyl)pyrrolidin-2-yl)methanol

To a mixture of sat aq. NaHCO₃ (44 g, 0.53 mol), CH₂Cl₂ (400 mL) and pyrrolidin-2-yl-methanol (53 g, 0.53 mol) was added a solution of 4-bromo-benzenesulfonyl chloride (127 g, 0.50 mol) in CH₂Cl₂ (100 mL). The reaction was stirred at 20 °C overnight. The organic phase was separated and dried over Na₂SO₄. Evaporation of the solvent under reduced pressure provided (*R*)-(1-(4-bromophenylsulfonyl)pyrrolidin-2-yl)methanol (145 g, crude), which was used in the next step without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 7.66-7.73 (m, 4 H), 3.59-3.71 (m, 3 H), 3.43-3.51 (m, 1 H), 3.18-3.26 (m, 1 H), 1.680-1.88 (m, 3 H), 1.45-1.53 (m, 1 H).

[00444] Step b: (*R*)-1-(4-Bromo-benzenesulfonyl)-2-(*tert*-butyl-dimethyl-silanyloxymethyl) pyrrolidine.

To a solution of [1-(4-bromo-benzenesulfonyl)-pyrrolidin-2-yl]-methanol (50.0 g, 0.16 mol) and 1H-imidazole (21.3 g, 0.31 mol) in CH₂Cl₂ (500 mL) was added *tert*-butylchlorodimethylsilane (35.5 g, 0.24 mol) in portions. After addition, the mixture was stirred for 1 hour at room temperature. The reaction was quenched with water (200 mL) and the separated aqueous layer was extracted with CH₂Cl₂ (100 mL × 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and evaporated under *vacuum* to give 1-(4-bromo-benzenesulfonyl)-2-(*tert*-butyldimethylsilanyloxymethyl)pyrrolidine (68.0 g, 99%). ¹H NMR (300 MHz, CDCl₃) δ 7.63-7.71 (m, 4 H), 3.77-3.81 (m, 1 H), 3.51-3.63 (m, 2 H), 3.37-3.43 (m, 1 H), 3.02-3.07 (m, 1 H), 1.77-1.91 (m, 2 H), 1.49-1.57 (m, 2 H), 0.87 (s, 9 H), 0.06 (d, *J* = 1.8 Hz, 6 H).

[00445] Step c: (*R*)-4-(2-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidin-1-ylsulfonyl) phenylboronic acid

To a solution of 1-(4-bromo-benzenesulfonyl)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)pyrrolidine (12.9 g, 29.7 mmol) and B(O^{*i*}Pr)₃ (8.4 g, 45 mmol) in dry THF (100 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 29.7 mL) at -70 °C. After addition, the mixture was warmed slowly to -10 °C and treated with HCl (1M, 50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and evaporated under *vacuum*. The organics were combined to give crude (*R*)-4-(2-((*tert*-butyldimethylsilyloxy)methyl) pyrrolidin-1-ylsulfonyl)phenylboronic acid (15.0 g), which was used directly in the next step.

[00446] Step d: (6-{4-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-pyrrolidine-1-sulfonyl] phenyl}pyridin-2-yl)carbamic acid *tert*-butyl ester

To a solution of (6-bromo-pyridin-2-yl)carbamic acid *tert*-butyl ester (24.6 g, 90.0 mmol) in DMF (250 mL) were added (*R*)-4-(2-((*tert*-butyldimethylsilyloxy)-methyl) pyrrolidin-1-ylsulfonyl)phenylboronic acid (45.0 g), Pd(PPh₃)₄ (10.4 g, 9.0 mmol), potassium carbonate (18.6 g, 135 mol) and water (200 mL). The resulting mixture was degassed by gently bubbling argon through the solution for 5 minutes at 20 °C. The reaction mixture was then heated at 80 °C overnight. DMF was removed under *vacuum*. To the residue was added EtOAc (300 mL). The mixture was filtered through a pad of silica gel, which was washed with EtOAc (50 mL × 3). The combined organic extracts were evaporated under *vacuum*. The crude residue was purified by column (Petroleum Ether/EtOAc 20:1) to give (6-{4-[2-(*tert*-butyl-dimethyl-

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silanyloxymethyl)pyrrolidine-1-sulfonyl} phenyl}pyridin-2-yl)carbamic acid *tert*-butyl ester

(22.2 g, 45% over 2-steps). ^1H NMR (300 MHz, CDCl_3) δ 8.09 (d, $J = 8.4$ Hz, 2 H), 7.88-7.96 (m, 3 H), 8.09 (t, $J = 7.8$ Hz, 1 H), 7.43-7.46 (m, 1 H), 7.38 (s, 1 H), 3.83-3.88 (m, 1 H), 3.64-3.67 (m, 1 H), 3.53-3.59 (m, 1 H), 3.41-3.47 (m, 1 H), 3.08-3.16 (m, 1 H), 1.82-1.91 (m, 2 H), 1.67-1.69 (m, 1 H), 1.53-1.56 (m, 10 H), 0.89 (s, 9 H), 0.08 (d, $J = 2.4$ Hz, 6 H).

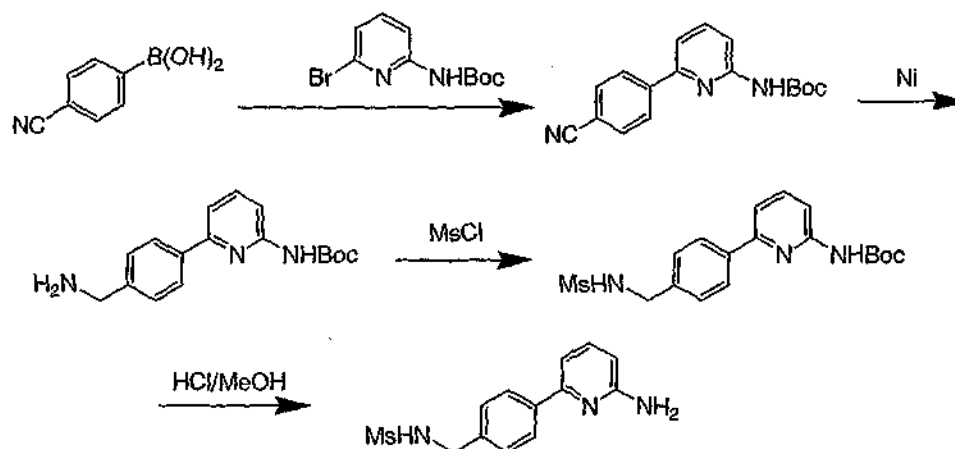
[00447] Step e: {6-[4-(2-Hydroxymethyl-pyrrolidine-1-sulfonyl)-phenyl]pyridin-2-yl} carbamic acid *tert*-butyl ester

A solution of crude (6-{4-[2-(*tert*-butyl-dimethyl-silanyloxymethyl)-pyrrolidine-1-sulfonyl]phenyl}-pyridin-2-yl)carbamic acid *tert*-butyl ester (22.2 g, 40.5 mmol) and TBAF (21.2 g, 81.0 mmol) in DCM (300 mL) was stirred at room temperature overnight. The mixture was washed with brine (100 mL \times 3), dried over Na_2SO_4 and evaporated under *vacuum* to give {6-[4-(2-hydroxymethyl-pyrrolidine-1-sulfonyl)-phenyl]pyridin-2-yl}carbamic acid *tert*-butyl ester (15.0 g, 86%), which was used directly in the next step.

[00448] Step f: (*R*)-(1-(4-(6-Aminopyridin-2-yl)phenylsulfonyl)-pyrrolidin-2-yl) methanol hydrochloride (C-2)

A solution of {6-[4-(2-hydroxymethyl-pyrrolidine-1-sulfonyl)-phenyl]pyridin-2-yl}carbamic acid *tert*-butyl ester (15.0 g, 34.6 mmol) in HCl/MeOH (50 mL, 2M) was heated at reflux for 2 h. After cooling to room temperature, the reaction mixture was evaporated under *vacuum* and washed with EtOAc to give (*R*)-(1-(4-(6-aminopyridin-2-yl)phenylsulfonyl)pyrrolidin-2-yl) methanol hydrochloride (C-2; 11.0 g, 86%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.18 (d, $J = 8.7$ Hz, 2 H), 7.93-7.99 (m, 3 H), 7.31 (d, $J = 7.2$ Hz, 1 H), 7.03 (d, $J = 8.7$ Hz, 1 H), 3.53-3.57 (m, 2 H), 3.29-3.5 (m, 2 H), 3.05-3.13 (m, 1 H), 1.77-1.78 (m, 2 H), 1.40-1.45 (m, 2 H). MS (ESI) m/z ($\text{M}+\text{H}$) $^+$ 334.2.

HH. *N*-(4-(6-Aminopyridin-2-yl)benzyl)methanesulfonamide (C-3)



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[00449]

Step a: [6-(4-Cyano-phenyl)-pyridin-2-yl]carbamic acid *tert*-butyl ester

A mixture of 4-cyanobenzenboronic acid (7.35 g, 50 mmol), (6-bromo-pyridin-2-yl)carbamic acid *tert*-butyl ester (13.8 g, 50 mmol), Pd(Ph₃P)₄ (5.8 g, 0.15 mmol) and K₂CO₃ (10.4 g, 75 mmol) in DMF/H₂O (1:1, 250 mL) was stirred under argon at 80 °C overnight. DMF was evaporated off under reduced pressure and the residue was dissolved in EtOAc (200 mL). The mixture was washed with water and brine, dried over Na₂SO₄, and concentrated to dryness. The residue was purified by column (Petroleum Ether/EtOAc 50:1) on silica gel to give [6-(4-cyano-phenyl)-pyridin-2-yl]carbamic acid *tert*-butyl ester (7.0 g, 60%). ¹H NMR (300 MHz, CDCl₃) δ 8.02-8.07 (m, 2 H), 7.95 (d, *J* = 8.4 Hz, 1 H), 7.71-7.79 (m, 3 H), 7.37-7.44 (m, 2 H), 1.53 (s, 9 H).

[00450]

Step b: [6-(4-Aminomethyl-phenyl)-pyridin-2-yl]-carbamic acid *tert*-butyl ester

A suspension of [6-(4-cyano-phenyl)-pyridin-2-yl]carbamic acid *tert*-butyl ester (7.0 g, 24 mmol), Raney Ni (1.0 g) in EtOH (500 mL) and NH₃·H₂O (10 mL) was hydrogenated under H₂ (50 psi.) at 50 °C for 6 h. The catalyst was filtered off and the filtrate was concentrated to dryness to give [6-(4-aminomethyl-phenyl)-pyridin-2-yl]-carbamic acid *tert*-butyl ester, which was used directly in next step. ¹H NMR (300 MHz, CDCl₃) δ 7.83-7.92 (m, 3H), 7.70 (t, *J* = 7.8 Hz, 1 H), 7.33-7.40 (m, 4 H), 3.92 (brs, 2 H), 1.53 (s, 9 H).

[00451]

Step c: {6-[4-(Methanesulfonylamino-methyl)-phenyl]-pyridin-2-yl}carbamic acid *tert*-butyl ester

To a solution of [6-(4-aminomethyl-phenyl)-pyridin-2-yl]-carbamic acid *tert*-butyl ester (5.7 g 19 mmol) and Et₃N (2.88 g, 29 mmol) in dichloromethane (50 mL) was added dropwise MsCl (2.7 g, 19 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 30 min, and then washed with water and brine, dried over Na₂SO₄ and concentrated to dryness. The residue was recrystallized with DCM/Petroleum Ether (1:3) to give {6-[4-(methanesulfonylamino-methyl)-phenyl]-pyridin-2-yl}carbamic acid *tert*-butyl ester (4.0 g, 44% over two steps). ¹H NMR (300 MHz, CDCl₃) δ 7.90-7.97 (m, 3 H), 7.75 (t, *J* = 8.4, 8.4 Hz, 1 H), 7.54-7.59 (m, 1 H), 7.38-7.44 (m, 3 H), 4.73 (br, 1 H), 4.37 (d, *J* = 6.0 Hz, 2 H), 2.90 (s, 3 H), 1.54 (s, 9 H).

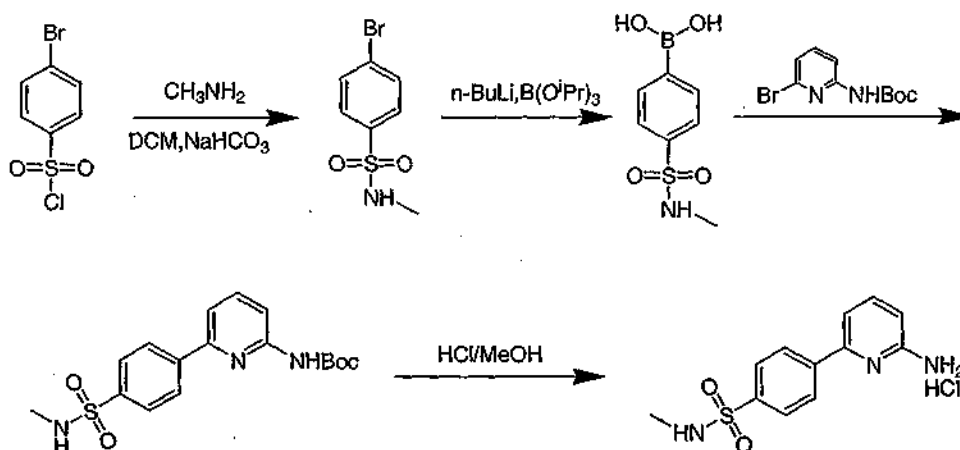
[00452]

Step d: N-(4-(6-Aminopyridin-2-yl)benzyl)methane-sulfonamide (C-3)

A mixture of {6-[4-(methanesulfonylamino-methyl)-phenyl]-pyridin-2-yl} carbamic acid *tert*-butyl ester (11 g, 29 mmol) in HCl/MeOH (4M, 300 mL) was stirred at room temperature overnight. The mixture was concentrated to dryness. The residue was filtered and

washed with ether to give *N*-(4-(6-aminopyridin-2-yl)benzyl)methane sulfonamide (C-3) (7.6 g, 80%) ^1H NMR (300 MHz, DMSO- d_6) δ 14.05 (br s, 1 H), 8.24 (br s, 2 H), 7.91-7.98 (m, 3 H), 7.70 (t, J = 6.0 Hz, 1 H), 7.53 (d, J = 8.1 Hz, 2 H), 7.22 (d, J = 6.9 Hz, 1 H), 6.96 (d, J = 9 Hz, 1 H), 4.23 (d, J = 5.7 Hz, 2 H), 2.89 (s, 3 H). MS (ESI) m/z ($M+H$) $^+$: 278.0,

II. 4-(6-Aminopyridin-2-yl)-*N*-methylbenzenesulfonamide hydrochloride (C-4)



[00453] Step a: 4-Bromo-*N*-methyl-benzenesulfonamide

To a mixture of sat aq. NaHCO_3 (42 g, 0.5 mol), CH_2Cl_2 (400 mL) and methylamine (51.7 g, 0.5 mol, 30% in methanol) was added a solution of 4-bromo-benzenesulfonyl chloride (127 g, 0.5 mol) in CH_2Cl_2 (100 mL). The reaction was stirred at 20 °C overnight. The organic phase was separated and dried over Na_2SO_4 . Evaporation of the solvent under reduced pressure provided the 4-bromo-*N*-methyl-benzenesulfonamide (121 g, crude), which was used in the next step without further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 7.64-7.74 (m, 4 H), 4.62-4.78 (m, 1 H), 2.65 (d, J = 5.4 Hz, 3 H).

[00454] Step b: 4-(*N*-Methylsulfamoyl)phenylboronic acid

To a solution of 4-bromo-*N*-methyl-benzene sulfonamide (24.9 g, 0.1 mol) and $\text{B}(\text{O}^i\text{Pr})_3$ (28.2 g, 0.15 mol) in THF (200 mL) was added $n\text{-BuLi}$ (100 mL, 0.25 mol) at -70 °C. The mixture was slowly warmed to 0 °C, then 10% HCl solution was added until pH 3~4. The resulting mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 , and evaporated under reduced pressure to give 4-(*N*-methylsulfamoyl)phenylboronic acid (22.5 g, 96%), which was used in the next step without further purification. ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.29 (s, 2 H), 7.92 (d, J = 8.1 Hz, 2 H), 7.69 (d, J = 8.4 Hz, 2 H), 2.36 (d, J = 5.1 Hz, 3 H).

[00455] Step c: *tert*-Butyl 6-(4-(*N*-methylsulfamoyl)phenyl)pyridin-2-ylcarbamate

To a solution of 4-(*N*-methylsulfamoyl)phenylboronic acid (17.2 g, 0.08 mol) and (6-bromo-pyridin-2-yl)carbamic acid *tert*-butyl ester (21.9 g, 0.08 mol) in DMF (125 mL) and H₂O (125 mL) were added Pd(PPh₃)₄ (9.2 g, 0.008 mol) and K₂CO₃ (16.6 g, 0.12 mol). The resulting mixture was degassed by gently bubbling argon through the solution for 5 minutes at 20 °C. The reaction mixture was then heated at 80 °C for 16 h. The mixture was evaporated under reduced pressure, then poured into H₂O, and extracted with EtOAc. The organic phase was dried over Na₂SO₄, and was evaporated under reduced pressure to give *tert*-butyl 6-(4-(*N*-methylsulfamoyl)phenyl)pyridin-2-ylcarbamate (21 g, 58%), which was used in the next step without further purification.

[00456] Step d: 4-(6-Aminopyridin-2-yl)-*N*-methylbenzenesulfonamide hydrochloride

To a solution of *tert*-butyl 6-(4-(*N*-methylsulfamoyl)phenyl)pyridin-2-ylcarbamate (8.5 g, 23.4 mmol) in MeOH (10 mL) was added HCl/MeOH (2M, 50 mL) at room temperature. The suspension was stirred at room temperature overnight. The solid product was collected by filtration, washed with MeOH, and dried to give 4-(6-aminopyridin-2-yl)-*N*-methylbenzenesulfonamide hydrochloride (5.0 g, 71%). ¹H NMR (300 Hz, DMSO-*d*₆) δ 8.12 (d, *J* = 8.4 Hz, 2 H), 7.91-7.96 (m, 3 H), 7.58-7.66 (m, 1 H), 7.31-7.53 (m, 1 H), 7.27 (d, *J* = 6.6, 1 H), 6.97 (d, *J* = 9.0, 1 H), 2.43 (d, *J* = 4.8 Hz, 3 H). MS (ESI) *m/z* (M+H)⁺ 264.0.

[00457] The compounds in the following table were synthesized as described above using commercially available or previously described carboxylic acids and amines.

[00458] Table 6: Additional exemplary compounds of formula I.

Compound No.	Carboxylic acid	Amine
164	A-9	C-1
165	A-3	C-2
169	A-17	C-3
170	A-3	C-4
177	A-2	C-3
183	A-13	C-4
192	A-8	C-2
200	A-14	C-2
201	A-4	C-3
202	A-15	C-2
211	A-15	C-3
214	A-6	C-2
218	A-2	C-4
220	A-4	C-2
221	A-10	C-2
223	A-17	C-4

Compound No.	Carboxylic acid	Amine
226	A-20	C-2
228	A-10	C-3
236	A-24	C-2
237	A-11	C-3
239	A-23	C-2
240	A-11	C-4
242	A-13	C-2
245	A-15	C-4
246	A-8	C-3
248	A-13	C-3
250	A-16	C-4
253	A-22	C-2
256	A-2	C-2
259	A-24	C-4
262	A-10	C-4
271	A-14	C-4
279	A-19	C-2
281	A-16	C-2
282	A-8	C-4
284	A-17	C-2
302	A-5	C-2
317	A-10	C-1
318	A-21	C-2
319	A-6	C-4
340	A-11	C-2
341	A-5	C-3
345	A-9	C-3
358	A-18	C-2
362	A-16	C-3
363	A-5	C-4
369	A-9	C-4
372	A-9	C-2
376	A-35	C-2
377	A-32	C-2
378	A-27	C-2
379	A-36	C-2
380	A-34	C-2
381	A-29	C-2
382	A-28	C-2
383	A-25	C-2
384	A-30	C-2
385	A-33	C-2
386	A-31	C-2
387	A-37	C-2
388	A-26	C-2
409	A-38	C-2
413	A-45	C-2

[00459] Physical data for examples of the invention are given in Table 7.

[00460] Additional exemplary compounds 164-388, as shown in Table 1, can also be prepared using appropriate starting materials and methods exemplified for the previously described compounds.

[00461] Table 7: Physical data for exemplary compounds.

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
1	416.3	2.39	
2	442.5	2.7	
3	427.1	4.1	
4	508.3	3.43	
5	423.3	3.72	
6	390.1	3.57	
7	402.5	2.96	¹ H NMR (400 MHz, CD ₃ CN) δ 1.21-1.29 (m, 2H), 1.62-1.68 (m, 2H), 3.05 (s, 6H), 6.06 (s, 2H), 6.86-6.97 (m, 3H), 7.04-7.08 (m, 2H), 7.53-7.55 (m, 1H), 7.76-7.82 (m, 3H), 7.86 (t, J = 8.0 Hz, 1H), 8.34 (br s, 1H)
8	444.5	3.09	
9	430.5	2.84	
10	375.3	3.39	
11	403.5	2.83	
12	390	3.14	
14	520.2	1.38	
15	387.3	3.71	
16	389.3	2.9	
17	403.5	3.33	
18	403.5	3.75	
19	387.1	3.76	
20	389	2.79	¹ H NMR (400 MHz, CD ₃ CN/ DMSO- <i>d</i> ₆) δ 1.15-1.23 (m, 2H), 1.56-1.61 (m, 2H), 4.60 (s, 2H), 6.05 (s, 2H), 6.94 (d, J = 8.3 Hz, 1H), 7.05-7.09 (m, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.57-7.62 (m, 2H), 7.92 (s, 1H), 8.00 (dd, J = 2.5, 8.6 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 8.48 (d, J = 1.8 Hz, 1H)
21	360	2.18	
22	387.3	3.77	
23	535.2	2.81	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
24	464.1	2.35	¹ H-NMR (DMSO- <i>d</i> ₆ , 300 MHz) δ 8.40(s, 1H), 7.96 (d, J= 8.4 Hz, 1H), 7.86 (m, 2H), 7.82 (m, 1H), 7.62 (d, J= 7.8 Hz, 1H), 7.36 (d, J= 7.8 Hz, 1H), 7.11 (d, J= 2.1 Hz, 1H), 7.00 (m, 2H), 6.05 (s, 2H), 3.42 (m, 2H, overlap with water), 3.03 (m, J= 5.4 Hz, 2H), 2.98 (t, 1H), 1.49 (m, 2H), 1.14 (m, 2H).
25	403	3.29	¹ H NMR (400 MHz, CD ₃ CN/ DMSO- <i>d</i> ₆) δ 1.14-1.17 (m, 2H), 1.52-1.55 (m, 2H), 6.01 (s, 2H), 6.03 (s, 2H), 6.89-6.96 (m, 2H), 7.01-7.12 (m, 3H), 7.15 (d, J = 1.8 Hz, 1H), 7.93 (dd, J = 8.7, 2.5 Hz, 1H), 8.05-8.11 (m, 2H), 8.39-8.41 (m, 1H)
26	393	3.88	
27	452.1	3.11	
28	427.1	4.19	
29	388.9	3.58	
30	375.3	2.95	
31	535.2	2.42	
32	359.1	3.48	
33	394.9	3.77	
34	360.3	2.96	
35	495.1	2.24	¹ H-NMR (300 MHz, CDCl ₃) δ 8.22 (d, J = 8.7 Hz, 1H), 7.98 (m, 3H), 7.80 (m, 3H), 7.45 (d, J = 7.5 Hz, 1H), 6.99 (dd, J = 8.1, 1.8 Hz, 2H), 6.95 (d, J = 1.5 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.02 (s, 2H), 3.77 (t, J = 5.1 Hz, 2H), 3.17 (m, J = 5.1 Hz, 2H), 2.85 (s, 3H), 1.70 (q, J = 3.6 Hz, 2H), 1.19 (q, J = 3.6 Hz, 2H).
36	521.2	2.36	¹ H-NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.51 (s, 1H), 8.15 (d, J = 9.0 Hz, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.92 (t, J = 7.8 Hz, 1H), 7.88 (d, J = 8.1Hz, 2H), 7.76 (d, J = 7.5 Hz, 1H), 7.11 (d, J = 1.2 Hz, 1H), 7.03 (dd, J = 7.8, 1.8 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.06 (s, 2H), 3.55 (m, 2H, overlap with water), 3.15 (m, 2H), 3.07 (m, 1H), 1.77 (m, 2H), 1.50 (dd, J = 7.2, 4.5 Hz, 2H), 1.43 (m, 2H), 1.15 (dd, J = 6.9, 3.9 Hz, 2H).

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
37	452.3	3.38	
38	398	3.02	
39	483.1	2.58	¹ H-NMR (DMSO- <i>d</i> ₆ , 300 MHz) δ 10.01 (t, J= 6.0 Hz, 1H), 8.39 (s, 1H), 7.97 (d, J= 7.8 Hz, 1H), 7.89 (d, J= 8.4 Hz, 1H), 7.83 (d, J= 7.8 Hz, 1H), 7.62 (d, J= 6.9 Hz, 1H), 7.33 (d, J= 8.4 Hz, 2H), 7.11 (d, J= 2.1 Hz, 1H), 7.03 (d, J= 1.5 Hz, 1H), 6.99 (dd, 7.8 Hz, 2H), 6.05 (s, 2H), 4.41 (d, J= 6 Hz, 2H), 1.48 (m, 2H), 1.14 (m, 2H).
40	393.1	3.89	
41	373.1	3.57	
42	421.1	3.33	
43	417.3	3.62	
44	401.2	1.26	
45	403.5	3.25	
46	437.3	3.19	
47	391.1	3.82	
48	384.3	3.74	
49	419.3	3.27	
50	437	3.02	
51	349	3.33	
52	373.1	3.58	¹ H NMR (400 MHz, CD ₃ CN) δ 1.17-1.20 (m, 2H), 1.58-1.61 (m, 2H), 2.24 (s, 3H), 6.01 (s, 2H), 6.90 (d, J = 8.4 Hz, 1H), 7.04-7.06 (m, 2H), 7.16 (dd, J = 7.5, 0.8 Hz, 1H), 7.23-7.33 (m, 4H), 7.79-7.89 (m, 2H), 8.10 (dd, J = 8.3, 0.8 Hz, 1H)
53	387	3.62	
54	394.1	3.06	
55	419.3	2.92	
56	407.5	3.55	
57	388.9	2.91	
58	360.2	3.74	
59	417.3	3.64	
60	402.5	3.07	
61	387.1	3.84	
62	415.3	4.1	
63	384	3.35	
64	360.3	3.58	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
65	465.1	2.47	¹ H-NMR (300 MHz, CDCl ₃) δ 8.19 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.92 (s, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.76 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 6.99 (m, 1H), 6.95 (br s, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.02 (s, 2H), 4.37 (t, J = 5.7 Hz, 1H), 3.02 (m, 2H), 1.70 (q, J = 3.9 Hz, 2H), 1.17 (q, J = 3.6 Hz, 2H), 1.11 (t, J = 7.2 Hz, 3H).
66	401	3.24	
67	393	3.88	
68	407.5	4.04	
69	377.1	3.26	
70	403.5	3.69	
71	472.3	3.02	
72	363	3.38	
73	449.3	3.4	
74	416.3	2.43	
75	373.1	3.69	
76	534.2	1.36	
77	491.2	2.7	
78	384.3	3.72	
79	388.3	2.32	
80	437.3	3.42	
81	373	3.51	¹ H NMR (400 MHz, CD ₃ CN/DMSO- <i>d</i> ₆) δ 1.07-1.27 (m, 2H), 1.50-1.67 (m, 2H), 2.36 (s, 3H), 6.10 (s, 2H), 6.92 (d, J = 7.9 Hz, 1H), 7.01-7.09 (m, 2H), 7.28 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.93-8.00 (m, 2H), 8.15 (d, J = 9.3 Hz, 1H), 8.44 (d, J = 2.5 Hz, 1H)
82	419	2.71	¹ H NMR (400 MHz, CD ₃ CN) δ 1.29-1.32 (m, 2H), 1.68-1.71 (m, 2H), 3.90 (s, 3H), 3.99 (s, 3H), 6.04 (s, 2H), 6.70-6.72 (m, 2H), 6.93 (d, J = 8.4 Hz, 1H), 7.03-7.05 (m, 2H), 7.59 (d, J = 8.2 Hz, 1H), 7.73 (t, J = 7.6 Hz, 2H), 8.01 (t, J = 8.1 Hz, 1H), 8.72 (br s, 1H)
83	417.3	3.41	
84	394.9	3.74	
85	401.3	3.97	
86	473.5	2.69	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
87	419.1	3.18	¹ H NMR (400 MHz, CD ₃ CN) δ 1.25-1.31 (m, 2H), 1.62-1.69 (m, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 6.04 (s, 2H), 6.62-6.70 (m, 2H), 6.92 (d, J = 8.4 Hz, 1H), 7.00-7.08 (m, 2H), 7.30 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 8.9 Hz, 1H), 8.14 (dd, J = 8.9, 2.3 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 8.65 (br s, 1H)
88	399	3.83	
89	401.3	3.62	
90	407.3	3.59	
91	505.2	2.88	
92	384	3.36	¹ H NMR (400 MHz, CD ₃ CN) δ 1.27-1.30 (m, 2H), 1.65-1.67 (m, 2H), 6.05 (s, 2H), 6.93 (d, J = 8.4 Hz, 1H), 7.04-7.09 (m, 2H), 7.67 (t, J = 7.7 Hz, 1H), 7.79-7.81 (m, 1H), 7.91-7.94 (m, 1H), 8.02-8.08 (m, 2H), 8.23 (dd, J = 8.9, 2.5 Hz, 1H), 8.50 (d, J = 1.9 Hz, 1H), 8.58 (br s, 1H)
93	402	2.73	¹ H NMR (400 MHz, CD ₃ CN) δ 1.16-1.24 (m, 2H), 1.57-1.62 (m, 2H), 6.05 (s, 2H), 6.95 (d, J = 7.6 Hz, 1H), 7.05-7.09 (m, 2H), 7.71-7.75 (m, 2H), 7.95 (br s, 1H), 8.04-8.10 (m, 3H), 8.22 (d, J = 8.7 Hz, 1H), 8.54 (d, J = 2.5 Hz, 1H)
94	419.3	2.8	
95	403.3	2.98	
97	416.5	3.22	
98	421	3	
99	407.1	3.32	
100	389	2.83	¹ H NMR (400 MHz, CD ₃ CN) δ 1.21-1.26 (m, 2H), 1.60-1.65 (m, 2H), 4.65 (s, 2H), 6.03 (s, 2H), 6.89-6.94 (m, 1H), 7.02-7.08 (m, 2H), 7.36-7.62 (m, 3H), 8.12 (s, 2H), 8.36 (br s, 1H), 8.45-8.47 (m, 1H)

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
101	388.9	3.27	¹ H NMR (400 MHz, CD ₃ CN) δ 1.22-1.24 (m, 2H), 1.61-1.63 (m, 2H), 3.82 (s, 3H), 6.04 (s, 2H), 6.92 (d, J = 8.4 Hz, 1H), 7.04-7.12 (m, 4H), 7.34 (dd, J = 7.6, 1.7 Hz, 1H), 7.38-7.43 (m, 1H), 8.03 (dd, J = 8.7, 2.3 Hz, 1H), 8.10 (dd, J = 8.7, 0.7 Hz, 1H), 8.27 (br s, 1H), 8.37-8.39 (m, 1H)
102	401.3	3.77	
103	430.5	3.04	
104	388.3	2.32	
105	521.2	2.46	
106	393	3.63	
107	416	2.84	¹ H NMR (400 MHz, CD ₃ CN/DMSO- <i>d</i> ₆) δ 1.13-1.22 (m, 2H), 1.53-1.64 (m, 2H), 2.07 (s, 3H), 6.08 (s, 2H), 6.90-6.95 (m, 1H), 7.01-7.09 (m, 2H), 7.28 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 1.6 Hz, 1H), 7.95 (dd, J = 2.5, 8.7 Hz, 1H), 8.03 (br s, 1H), 8.16 (d, J = 8.7 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 9.64 (s, 1H)
108	403.3	3.07	
109	349.1	3.29	
110	389.2	3.15	
111	521.2	2.27	
112	394	3.82	
113	407.5	3.3	
114	417.1	3.17	
115	398.1	3.22	
116	394	3.1	¹ H NMR (400 MHz, CD ₃ CN) δ 1.18-1.26 (m, 2H), 1.59-1.64 (m, 2H), 6.05 (s, 2H), 6.95 (d, J = 8.4 Hz, 1H), 7.06-7.11 (m, 2H), 7.40 (d, J = 4.9 Hz, 1H), 7.92-7.96 (m, 2H), 8.26 (d, J = 9.3 Hz, 1H), 8.36 (d, J = 1.7 Hz, 1H), 8.56 (d, J = 5.0 Hz, 1H), 8.70 (s, 1H)
117	363.3	3.48	
118	374.3	3.54	
119	494.3	3.59	
120	505.2	2.9	
121	374.3	2.55	
122	417.3	3.63	
123	389.3	3.47	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
124	417.1	3.29	
125	417.3	3.08	
126	427.3	3.89	
127	535.2	2.76	
128	386.9	3.67	
129	377.1	3.67	
130	389.1	3.4	¹ H NMR (400 MHz, CD ₃ CN) δ 1.22-1.24 (m, 2H), 1.61-1.63 (m, 2H), 3.86 (s, 3H), 6.05 (s, 2H), 6.93 (d, J = 8.4 Hz, 1H), 6.97-7.00 (m, 1H), 7.05-7.08 (m, 2H), 7.16-7.21 (m, 2H), 7.41 (t, J = 8.0 Hz, 1H), 8.07-8.17 (m, 3H), 8.48-8.48 (m, 1H)
131	407.3	3.49	
132	419	3.09	¹ H NMR (400 MHz, CD ₃ CN) δ 1.17-1.25 (m, 2H), 1.57-1.64 (m, 2H), 3.72 (s, 6H), 6.04 (s, 2H), 6.74 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 1H), 7.05-7.08 (m, 2H), 7.35 (t, J = 8.4 Hz, 1H), 7.75 (d, J = 10.5 Hz, 1H), 8.07-8.14 (m, 3H)
133	431.3	3.27	
135	417.3	3.81	
136	535.2	2.75	
137	403.5	3.35	
138	432.5	2.76	¹ H NMR (400 MHz, CD ₃ CN) δ 1.30-1.35 (m, 2H), 1.69-1.74 (m, 2H), 3.09 (s, 6H), 4.05 (s, 3H), 6.04 (s, 2H), 6.38 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 9.0, 2.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.03-7.06 (m, 2H), 7.31 (d, J = 7.7 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.97 (t, J = 8.3 Hz, 1H)
139	421.1	2.71	
140	416.5	2.92	
141	410	2.83	¹ H NMR (400 MHz, CD ₃ CN) δ 1.28-1.37 (m, 2H), 1.66-1.73 (m, 2H), 6.05 (s, 2H), 6.91-6.97 (m, 1H), 7.05-7.09 (m, 2H), 7.69-7.74 (m, 1H), 7.82 (t, J = 7.7 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.37 (d, J = 8.8 Hz, 1H), 8.58-8.65 (m, 2H), 8.82 (br s, 1H), 8.94 (d, J = 6.2 Hz, 1H)
142	349.3	3.33	
143	373.1	3.68	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
144	535.2	2.33	
145	390.3	3.4	
146	386.9	3.72	
147	419.1	3.13	¹ H NMR (400 MHz, CD ₃ CN) δ 1.23-1.26 (m, 2H), 1.62-1.64 (m, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 6.04 (s, 2H), 6.93 (d, J = 8.4 Hz, 1H), 7.03-7.07 (m, 3H), 7.17-7.19 (m, 2H), 8.06-8.15 (m, 2H), 8.38 (br s, 1H), 8.45-8.46 (m, 1H)
148	393.1	3.72	¹ H NMR (400 MHz, CD ₃ CN) δ 1.20-1.27 (m, 2H), 1.58-1.67 (m, 2H), 6.05 (s, 2H), 6.94 (d, J = 8.4 Hz, 1H), 7.05-7.09 (m, 2H), 7.41-7.50 (m, 2H), 7.55-7.59 (m, 1H), 7.66-7.69 (m, 1H), 8.07 (d, J = 11.2 Hz, 1H), 8.11 (br s, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.48 (d, J = 1.9 Hz, 1H)
149	458.5	2.42	
150	403.5	3.04	
151	452.3	3.44	¹ H NMR (400 MHz, MeOD) δ 1.30-1.36 (m, 2H), 1.71-1.77 (m, 2H), 2.58 (s, 3H), 6.04 (s, 2H), 6.93 (dd, J = 0.8, 7.5 Hz, 1H), 7.04-7.08 (m, 2H), 7.86 (dd, J = 0.8, 7.7 Hz, 1H), 8.00-8.02 (m, 2H), 8.08-8.12 (m, 3H), 8.19-8.23 (m, 1H)
152	403	2.97	
153	359.1	3.36	¹ H NMR (400 MHz, CD ₃ CN) δ 1.24-1.26 (m, 2H), 1.62-1.65 (m, 2H), 6.05 (s, 2H), 6.93 (d, J = 8.4 Hz, 1H), 7.05-7.08 (m, 2H), 7.42-7.46 (m, 1H), 7.49-7.53 (m, 2H), 7.63-7.66 (m, 2H), 8.10-8.16 (m, 2H), 8.33 (br s, 1H), 8.48-8.48 (m, 1H)
154	395.1	3.34	
155	393	3.7	
156	390.2	3.7	
157	403.5	3.33	
158	390.2	3.58	
159	493.2	2.85	
160	411.3	3.94	
161	419.1	3.2	
162	488.1	3.62	
163	438.1	3	
164	314.1	3.38	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
165	538.5	3.28	
166	466.1	2.9	
167	429.3	2.95	
168	526.3	3.189189	
169	498.3	3.7	
170	468.3	3.27	
171	444.5	2.24	
172	551.1	2.849824	
173	377	3.7	
174	493.9	2.69	
175	517.9	3.423179	
176	522.3	3.49262	
177	502.1	3.43	
178	549.1	2.906129	
179	480.1	2.51	
180	520.3	4.295395	
181	488.2	3.07	
182	535.1	3.267469	
183	436.3	3.62	
184	496.3	3.265482	
185	403.5	2.88	
186	420.9	2.86	
187	444.3	2.39	
188	417.3	2.24	
189	466.1	2.88	
190	438.1	2.39	
191	401.1	3.44	
192	552.3	3.18	
193	452.3	2.55	
194	415	4	
195	479.1	1.08	
196	430.5	2.34	
197	512.3	2.961206	
198	444.5	2.75	H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 1.11-1.19 (m, 2H), 1.46-1.52 (m, 2H), 2.31 (s, 3H), 2.94 (s, 3H), 2.99 (s, 3H), 6.08 (s, 2H), 6.97-7.05 (m, 2H), 7.13 (d, J = 1.6 Hz, 1H), 7.35 (t, J = 1.5 Hz, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H)
199	540.3	3.18	
200	520.3	3.79	
201	452.3	3.22	
202	536.5	3.63	
203	509.1	2.82	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
204	444.5	2.5	
205	524.3	3.48	
206	407.5	3.6	
207	452.1	2.62	
208	520.3	4.06	
209	416.1	2.3	
210	452.3	2.8	H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 1.11-1.19 (m, 2H), 1.47-1.52 (m, 2H), 2.31 (s, 6.08 (s, 2H), 6.96-7.07 (m, 2H), 7.13 (d, J = 1.6 Hz, 1H), 7.43 (s, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 7.99 (d, J = 8.4 Hz, 1H), 8.38 (s, 1H)
211	480.3	3.33	
212	521.1	3.23	
213	415.3	3.4	
214	562.3	3.71	
215	403.3	2.67	
216	421.1	2.91	
217	387.1	2.89	
218	488.3	3.73	
219	403.7	2.43	
220	508.5	3.46	
221	508.3	3.46	
222	401.1	2.76	
223	484.5	3.95	
224	407.5	3.23	
225	401.2	3.49	
226	608.3	3.58	
227	417.1	2.24	
228	452.3	3.21	
229	407.1	3.08	
230	401.3	2.68	
231	389.1	2.36	
232	481.9	3.155919	
233	535.9	3.58	
234	551.1	2.90	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
235	415.3	3.71	H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 1.12-1.17 (m, 2H), 1.23 (d, J = 6.9 Hz, 6H), 1.47-1.51 (m, 2H), 2.30 (s, 3H), 2.92 (septet, J = 6.9 Hz, 1H), 6.08 (s, 2H), 6.97-7.05 (m, 2H), 7.12-7.17 (m, 2H), 7.20-7.22 (m, 1H), 7.24-7.26 (m, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.32 (s, 1H)
236	540.3	3.85	
237	456.5	3.35	
238	416.5	2.35	
239	529.3	2.29	
240	442.3	3.57	
241	466.3	3.5	
242	506.3	3.67	
243	403.3	2.69	
244	534.3	3.93	
245	466.3	3.6	
246	496.3	2.9	
247	458.5	2.3	
248	450.3	3.01	
249	565.2	2.89	
250	480.5	3.74	
251	452.1	1.07	
252	389.1	2.82	
253	530.3	2.8	
254	466.1	1.06	
255	488.2	3.05	
256	558.3	3.46	
257	407.5	3.27	
258	430.5	2.66	H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 1.12-1.18 (m, 2H), 1.47-1.54 (m, 2H), 2.30 (s, 3H), 2.79 (d, J = 4.5 Hz, 3H), 6.08 (s, 2H), 6.96-7.07 (m, 2H), 7.13 (d, J = 1.6 Hz, 1H), 7.48-7.57 (m, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 1.5 Hz, 1H), 7.84 (dt, J = 7.3, 1.7 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 8.36 (s, 1H), 8.50-8.51 (m, 1H)
259	470.3	3.82	
260	403.1	2.27	
261	549.1	3.39	
262	438.1	3.43	
263	403.3	2.8	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
264	407.1	3.04	
265	430.5	2.18	
266	403.3	2.96	
267	531.9	2.81	
268	496.3	3.24	
269	373.5	2.76	
270	520.3	4.21	
271	450.3	3.77	
272	403.2	1.09	
273	543.1	2.89	
274	417.3	2.26	
275	527.9	3.91	
276	510.3	3.37	
277	403.1	2.2	
278	430.5	2.68	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 1.12-1.19 (m, 2H), 1.47-1.51 (m, 2H), 2.31 (s, 3H), 2.80 (d, J = 4.5 Hz, 3H), 6.08 (s, 2H), 6.97-7.05 (m, 2H), 7.13 (d, J = 1.6 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.3 Hz, 1H), 8.35 (s, 1H), 8.50 (q, J = 4.5 Hz, 1H)
279	536.5	3.19	
280	480.3	3.25	
281	550.5	3.78	
282	482.5	3.15	
283	416.3	2.58	
284	554.3	3.99	
285	546.3	2.87	
286	416.1	2.29	
287	443	4.02	
288	466.3	2.76	
289	373.1	2.84	
290	429.3	3	
291	403.1	2.24	
292	479.2	2.49	
293	417.3	2.65	
294	403.5	2.39	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
295	416.3	2.61	H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 1.14-1.18 (m, 2H), 1.46-1.54 (m, 2H), 2.31 (s, 3H), 6.08 (s, 2H), 6.97-7.05 (m, 2H), 7.13 (d, J = 1.6 Hz, 1H), 7.44 (s, 1H), 7.49-7.56 (m, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.83-7.85 (m, 1H), 7.87-7.91 (m, 1H), 7.99 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 8.39 (s, 1H)
296	387.1	3.09	
297	430.2	2.38	
298	403.2	2.72	
299	387.3	2.86	
300	387.3	3.03	
301	403.5	2.44	
302	508.3	3.45	
303	417.3	2.58	
304	549.1	3.35	
305	429.5	3.01	
306	492.3	3.81	
307	512.3	2.97	
308	415.3	2.85	
309	444.5	2.75	
310	430.5	2.41	
311	534.3	3.92	
312	492.3	3.99	
313	387.3	2.84	
314	430.5	2.37	
315	387	1.12	
316	526.3	3.08	
317	344.2	3.35	
318	536.5	3.17	
319	492.3	3.69	
320	430.2	2.38	
321	452.3	2.55	
322	387.1	2.6	
323	387.1	3.01	
324	402.5	2.14	
325	531.9	3.83	
326	444.5	2.5	
327	403.3	2.83	
328	401.1	3.48	
329	415.3	3.36	
330	522.3	4.14	
331	387.1	3.01	
332	505.9	4.06	
333	417.1	2.58	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
334	403.5	2.92	
335	520.3	4.22	
336	510.3	3.36	
337	401.1	2.73	
338	479.9	3.44	
339	508.3	3.83	
340	512.5	3.6	
341	452.3	3.15	
342	540.3	3.07	
343	480.3	3	
344	526.3	3.15	
345	422.1	3.21	
346	415	4.05	
347	523.1	3.10	
348	416.3	1.87	
349	438.1	2.4	
350	402.5	2.18	
351	373.1	3.08	
352	415.7	3.13	
353	420.9	2.9	
354	407.3	3.03	
355	480.3	2.96	
356	452.3	2.47	
357	466.3	2.63	
358	536.5	3.26	
359	402.1	2.2	
360	510.3	3.42	
361	407	3.11	
362	494.5	3.45	
363	438.1	3.42	
364	535.9	3.44	
365	402.1	2.21	
366	565.2	3.01	
367	403.5	2.36	
368	444.5	2.97	
369	408.5	3.43	
370	403.3	2.45	
371	430.5	2.43	
372	478.3	3.47	
373	524.3	3.50	
374	466.3	2.35	
375	416.5	2.36	
376	552.3	3.42	
377	524.5	3.17	
378	538.5	3.07	
379	528.3	3.33	
380	548.3	3.75	

Compound No.	LCMS [M+H] ⁺	LCMS RT	NMR
381	526.3	3.46	
382	520.5	3.48	
383	518.1	3.55	
384	542.3	3.59	
385	550.5	3.69	
386	524.3	3.15	
387	522.5	3.78	
388	542.2	3.6	
389	467.3	1.93	
390	469.3	1.99	
391	507.5	2.12	
392	453.5	1.99	
393	487.3	2.03	
394	483.5	1.92	
395	441.3	4.33	
396	453.3	1.93	
397	439.5	1.94	
398	471.3	2	
399	537.5	2.1	
400	525.3	2.19	
401	453.5	1.96	
402	483.3	1.87	
403	457.5	1.99	
404	469.5	1.95	
405	471.3	1.98	
406	525.3	2.15	
407	439.4	1.97	
408	525.1	2.14	
409	618.7	3.99	
410	374.5	2.46	
411	507.5	2.14	
412	390.1	3.09	
413	552.3	4.04	
414	457.5	2.06	
415	521.5	2.14	
416	319	3.32	
417	471.3	1.96	
418	417.3	1.75	
419	473.3	2.04	
420	389.3	2.94	
421	457.5	1.99	
422	467.3	1.96	

ASSAYSAssays for Detecting and Measuring $\Delta F508$ -CFTR Correction Properties of CompoundsJJ. Membrane potential optical methods for assaying $\Delta F508$ -CFTR modulation properties of compounds

[00462] The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" *Biophys J* 69(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" *Chem Biol* 4(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" *Drug Discov Today* 4(9): 431-439).

[00463] These voltage sensitive assays are based on the change in fluorescence resonant energy transfer (FRET) between the membrane-soluble, voltage-sensitive dye, DiSBAC₂(3), and a fluorescent phospholipid, CC2-DMPE, which is attached to the outer leaflet of the plasma membrane and acts as a FRET donor. Changes in membrane potential (V_m) cause the negatively charged DiSBAC₂(3) to redistribute across the plasma membrane and the amount of energy transfer from CC2-DMPE changes accordingly. The changes in fluorescence emission were monitored using VIPRTM II, which is an integrated liquid handler and fluorescent detector designed to conduct cell-based screens in 96- or 384-well microtiter plates.

1. Identification of Correction Compounds

[00464] To identify small molecules that correct the trafficking defect associated with $\Delta F508$ -CFTR; a single-addition HTS assay format was developed. The cells were incubated in serum-free medium for 16 hrs at 37 °C in the presence or absence (negative control) of test compound. As a positive control, cells plated in 384-well plates were incubated for 16 hrs at 27 °C to "temperature-correct" $\Delta F508$ -CFTR. The cells were subsequently rinsed 3X with Krebs Ringers solution and loaded with the voltage-sensitive dyes. To activate $\Delta F508$ -CFTR, 10 μM forskolin and the CFTR potentiator, genistein (20 μM), were added along with Cl⁻-free medium to each well. The addition of Cl⁻-free medium promoted Cl⁻ efflux in response to $\Delta F508$ -CFTR activation and the resulting membrane depolarization was optically monitored using the FRET-based voltage-sensor dyes.

2. Identification of Potentiator Compounds

[00465] To identify potentiators of $\Delta F508$ -CFTR, a double-addition HTS assay format was developed. During the first addition, a Cl^- -free medium with or without test compound was added to each well. After 22 sec, a second addition of Cl^- -free medium containing 2 - 10 μM forskolin was added to activate $\Delta F508$ -CFTR. The extracellular Cl^- concentration following both additions was 28 mM, which promoted Cl^- efflux in response to $\Delta F508$ -CFTR activation and the resulting membrane depolarization was optically monitored using the FRET-based voltage-sensor dyes.³ Solutions Bath Solution #1: (in mM) NaCl 160, KCl 4.5, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, pH 7.4 with NaOH.

Chloride-free bath solution: Chloride salts in Bath Solution #1 are substituted with gluconate salts.

CC2-DMPE: Prepared as a 10 mM stock solution in DMSO and stored at $-20^\circ C$.

DiSBAC₂(3): Prepared as a 10 mM stock in DMSO and stored at $-20^\circ C$.

4. Cell Culture

[00467] NIH3T3 mouse fibroblasts stably expressing $\Delta F508$ -CFTR are used for optical measurements of membrane potential. The cells are maintained at $37^\circ C$ in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 10 % fetal bovine serum, 1 X NEAA, β -ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For all optical assays, the cells were seeded at 30,000/well in 384-well matrigel-coated plates and cultured for 2 hrs at $37^\circ C$ before culturing at $27^\circ C$ for 24 hrs for the potentiator assay. For the correction assays, the cells are cultured at $27^\circ C$ or $37^\circ C$ with and without compounds for 16 - 24 hours Electrophysiological Assays for assaying $\Delta F508$ -CFTR modulation properties of compounds

1. Using Chamber Assay

[00468] Using chamber experiments were performed on polarized epithelial cells expressing $\Delta F508$ -CFTR to further characterize the $\Delta F508$ -CFTR modulators identified in the optical assays. FRT ^{$\Delta F508$ -CFTR} epithelial cells grown on Costar Snapwell cell culture inserts were mounted in an Ussing chamber (Physiologic Instruments, Inc., San Diego, CA), and the monolayers were continuously short-circuited using a Voltage-clamp System (Department of Bioengineering, University of Iowa, IA, and, Physiologic Instruments, Inc., San Diego, CA). Transepithelial resistance was measured by applying a 2-mV pulse. Under these conditions, the

FRT epithelia demonstrated resistances of $4 \text{ K}\Omega/\text{cm}^2$ or more. The solutions were maintained at 27°C and bubbled with air. The electrode offset potential and fluid resistance were corrected using a cell-free insert. Under these conditions, the current reflects the flow of Cl^- through $\Delta\text{F508-CFTR}$ expressed in the apical membrane. The I_{SC} was digitally acquired using an MP100A-CE interface and AcqKnowledge software (v3.2.6; BIOPAC Systems, Santa Barbara, CA).

2. Identification of Correction Compounds

[00469] Typical protocol utilized a basolateral to apical membrane Cl^- concentration gradient. To set up this gradient, normal ringer was used on the basolateral membrane, whereas apical NaCl was replaced by equimolar sodium gluconate (titrated to pH 7.4 with NaOH) to give a large Cl^- concentration gradient across the epithelium. All experiments were performed with intact monolayers. To fully activate $\Delta\text{F508-CFTR}$, forskolin ($10 \mu\text{M}$) and the PDE inhibitor, IBMX ($100 \mu\text{M}$), were applied followed by the addition of the CFTR potentiator, genistein ($50 \mu\text{M}$).

[00470] As observed in other cell types, incubation at low temperatures of FRT cells stably expressing $\Delta\text{F508-CFTR}$ increases the functional density of CFTR in the plasma membrane. To determine the activity of correction compounds, the cells were incubated with $10 \mu\text{M}$ of the test compound for 24 hours at 37°C and were subsequently washed 3X prior to recording. The cAMP- and genistein-mediated I_{SC} in compound-treated cells was normalized to the 27°C and 37°C controls and expressed as percentage activity. Preincubation of the cells with the correction compound significantly increased the cAMP- and genistein-mediated I_{SC} compared to the 37°C controls.

3. Identification of Potentiator Compounds

[00471] Typical protocol utilized a basolateral to apical membrane Cl^- concentration gradient. To set up this gradient, normal ringers was used on the basolateral membrane and was permeabilized with nystatin ($360 \mu\text{g/ml}$), whereas apical NaCl was replaced by equimolar sodium gluconate (titrated to pH 7.4 with NaOH) to give a large Cl^- concentration gradient across the epithelium. All experiments were performed 30 min after nystatin permeabilization. Forskolin ($10 \mu\text{M}$) and all test compounds were added to both sides of the cell culture inserts. The efficacy of the putative $\Delta\text{F508-CFTR}$ potentiators was compared to that of the known potentiator, genistein.

4. Solutions

Basolateral solution (in mM): NaCl (135), CaCl₂ (1.2), MgCl₂ (1.2), K₂HPO₄ (2.4), KHPO₄ (0.6), N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (10), and dextrose (10). The solution was titrated to pH 7.4 with NaOH.

Apical solution (in mM): Same as basolateral solution with NaCl replaced with Na Gluconate (135).

5. Cell Culture

[00472] Fisher rat epithelial (FRT) cells expressing $\Delta F508$ -CFTR (FRT ^{$\Delta F508$ -CFTR}) were used for Ussing chamber experiments for the putative $\Delta F508$ -CFTR modulators identified from our optical assays. The cells were cultured on Costar Snapwell cell culture inserts and cultured for five days at 37 °C and 5% CO₂ in Coon's modified Ham's F-12 medium supplemented with 5% fetal calf serum, 100 U/ml penicillin, and 100 µg/ml streptomycin. Prior to use for characterizing the potentiator activity of compounds, the cells were incubated at 27 °C for 16 - 48 hrs to correct for the $\Delta F508$ -CFTR. To determine the activity of correction compounds, the cells were incubated at 27 °C or 37 °C with and without the compounds for 24 hours.

6. Whole-cell recordings

[00473] The macroscopic $\Delta F508$ -CFTR current ($I_{\Delta F508}$) in temperature- and test compound-corrected NIH3T3 cells stably expressing $\Delta F508$ -CFTR were monitored using the perforated-patch, whole-cell recording. Briefly, voltage-clamp recordings of $I_{\Delta F508}$ were performed at room temperature using an Axopatch 200B patch-clamp amplifier (Axon Instruments Inc., Foster City, CA). All recordings were acquired at a sampling frequency of 10 kHz and low-pass filtered at 1 kHz. Pipettes had a resistance of 5 – 6 MΩ when filled with the intracellular solution. Under these recording conditions, the calculated reversal potential for Cl⁻ (E_{Cl}) at room temperature was -28 mV. All recordings had a seal resistance > 20 GΩ and a series resistance < 15 MΩ. Pulse generation, data acquisition, and analysis were performed using a PC equipped with a Digidata 1320 A/D interface in conjunction with Clampex 8 (Axon Instruments Inc.). The bath contained < 250 µl of saline and was continuously perfused at a rate of 2 ml/min using a gravity-driven perfusion system.

7. Identification of Correction Compounds

[00474] To determine the activity of correction compounds for increasing the

density of functional $\Delta F508$ -CFTR in the plasma membrane, we used the above-described perforated-patch-recording techniques to measure the current density following 24-hr treatment with the correction compounds. To fully activate $\Delta F508$ -CFTR, 10 μM forskolin and 20 μM genistein were added to the cells. Under our recording conditions, the current density following 24-hr incubation at 27°C was higher than that observed following 24-hr incubation at 37 °C. These results are consistent with the known effects of low-temperature incubation on the density of $\Delta F508$ -CFTR in the plasma membrane. To determine the effects of correction compounds on CFTR current density, the cells were incubated with 10 μM of the test compound for 24 hours at 37°C and the current density was compared to the 27°C and 37°C controls (% activity). Prior to recording, the cells were washed 3X with extracellular recording medium to remove any remaining test compound. Preincubation with 10 μM of correction compounds significantly increased the cAMP- and genistein-dependent current compared to the 37°C controls.

8. Identification of Potentiator Compounds

[00475] The ability of $\Delta F508$ -CFTR potentiators to increase the macroscopic $\Delta F508$ -CFTR Cl^- current ($I_{\Delta F508}$) in NIH3T3 cells stably expressing $\Delta F508$ -CFTR was also investigated using perforated-patch-recording techniques. The potentiators identified from the optical assays evoked a dose-dependent increase in $I_{\Delta F508}$ with similar potency and efficacy observed in the optical assays. In all cells examined, the reversal potential before and during potentiator application was around -30 mV, which is the calculated E_{Cl} (-28 mV).

9. Solutions

Intracellular solution (in mM): Cs-aspartate (90), CsCl (50), $MgCl_2$ (1), HEPES (10), and 240 $\mu g/ml$ amphotericin-B (pH adjusted to 7.35 with CsOH).

Extracellular solution (in mM): *N*-methyl-D-glucamine (NMDG)-Cl (150), $MgCl_2$ (2), $CaCl_2$ (2), HEPES (10) (pH adjusted to 7.35 with HCl).

10. Cell Culture

[00476] NIH3T3 mouse fibroblasts stably expressing $\Delta F508$ -CFTR are used for whole-cell recordings. The cells are maintained at 37 °C in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 10 % fetal bovine serum, 1 X NEAA, β -ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For whole-cell recordings, 2,500 - 5,000 cells were seeded on poly-L-lysine-coated glass coverslips

and cultured for 24 - 48 hrs at 27 °C before use to test the activity of potentiators; and incubated with or without the correction compound at 37 °C for measuring the activity of correctors.

11. Single-channel recordings

[00477] The single-channel activities of temperature-corrected $\Delta F508$ -CFTR stably expressed in NIH3T3 cells and activities of potentiator compounds were observed using excised inside-out membrane patch. Briefly, voltage-clamp recordings of single-channel activity were performed at room temperature with an Axopatch 200B patch-clamp amplifier (Axon Instruments Inc.). All recordings were acquired at a sampling frequency of 10 kHz and low-pass filtered at 400 Hz. Patch pipettes were fabricated from Corning Kovar Sealing #7052 glass (World Precision Instruments, Inc., Sarasota, FL) and had a resistance of 5 - 8 M Ω when filled with the extracellular solution. The $\Delta F508$ -CFTR was activated after excision, by adding 1 mM Mg-ATP, and 75 nM of the cAMP-dependent protein kinase, catalytic subunit (PKA; Promega Corp. Madison, WI). After channel activity stabilized, the patch was perfused using a gravity-driven microperfusion system. The inflow was placed adjacent to the patch, resulting in complete solution exchange within 1 - 2 sec. To maintain $\Delta F508$ -CFTR activity during the rapid perfusion, the nonspecific phosphatase inhibitor F (10 mM NaF) was added to the bath solution. Under these recording conditions, channel activity remained constant throughout the duration of the patch recording (up to 60 min). Currents produced by positive charge moving from the intra- to extracellular solutions (anions moving in the opposite direction) are shown as positive currents. The pipette potential (V_p) was maintained at 80 mV.

[00478] Channel activity was analyzed from membrane patches containing ≤ 2 active channels. The maximum number of simultaneous openings determined the number of active channels during the course of an experiment. To determine the single-channel current amplitude, the data recorded from 120 sec of $\Delta F508$ -CFTR activity was filtered "off-line" at 100 Hz and then used to construct all-point amplitude histograms that were fitted with multigaussian functions using Bio-Patch Analysis software (Bio-Logic Comp. France). The total microscopic current and open probability (P_o) were determined from 120 sec of channel activity. The P_o was determined using the Bio-Patch software or from the relationship $P_o = I/i(N)$, where I = mean current, i = single-channel current amplitude, and N = number of active channels in patch.

12. Solutions

Extracellular solution (in mM): NMDG (150), aspartic acid (150), CaCl_2 (5), MgCl_2 (2), and HEPES (10) (pH adjusted to 7.35 with Tris base).

Intracellular solution (in mM): NMDG-Cl (150), MgCl_2 (2), EGTA (5), TES (10), and Tris base (14) (pH adjusted to 7.35 with HCl).

13. Cell Culture

[00479] NIH3T3 mouse fibroblasts stably expressing $\Delta F508$ -CFTR are used for excised-membrane patch-clamp recordings. The cells are maintained at 37 °C in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 10 % fetal bovine serum, 1 X NEAA, β -ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For single channel recordings, 2,500 - 5,000 cells were seeded on poly-L-lysine-coated glass coverslips and cultured for 24 - 48 hrs at 27 °C before use.

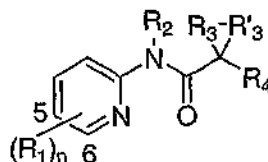
[00480] The exemplified compounds of Table 1 have an activity with a range of about 100 nM and 20 μM as measured using the assays described hereinabove. The exemplified compounds of Table 1 are found to be sufficiently efficacious as measured using the assays described hereinabove.

OTHER EMBODIMENTS

[00481] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

Each R_1 is an optionally substituted C_{1-6} aliphatic, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted C_{3-10} cycloaliphatic, an optionally substituted 3 to 10 membered heterocycloaliphatic, carboxy, amido, amino, halo, or hydroxy, provided that at least one R_1 is an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl attached to the 5- or 6- position of the pyridyl ring;

Each R_2 is hydrogen, an optionally substituted C_{1-6} aliphatic, an optionally substituted C_{3-6} cycloaliphatic, an optionally substituted phenyl, or an optionally substituted heteroaryl;

Each R_3 and R'_3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7} cycloaliphatic or an optionally substituted heterocycloaliphatic;

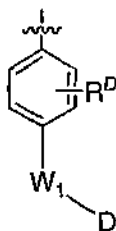
Each R_4 is an optionally substituted aryl or an optionally substituted heteroaryl; and

Each n is 1, 2, 3 or 4.

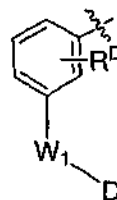
2. The compound according to claim 1, wherein one R_1 that is attached to 5- or 6- position of the pyridyl ring is aryl or heteroaryl, each optionally substituted with 1, 2, or 3 of R^D ; wherein R^D is $-Z^D R_9$; wherein each Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-\text{CO}-$, $-\text{CS}-$, $-\text{CONR}^E-$, $-\text{CONR}^E \text{NR}^E-$, $-\text{CO}_2-$, $-\text{OCO}-$, $-\text{NR}^E \text{CO}_2-$, $-\text{O}-$, $-\text{NR}^E \text{CONR}^E-$, $-\text{OCONR}^E-$, $-\text{NR}^E \text{NR}^E-$, $-\text{NR}^E \text{CO}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^E-$, $-\text{SO}_2 \text{NR}^E-$, $-\text{NR}^E \text{SO}_2-$, or $-\text{NR}^E \text{SO}_2 \text{NR}^E-$; each R_9 is independently R^E , halo, $-\text{OH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, or $-\text{OCF}_3$; and each R^E is independently hydrogen, an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

3. The compound according to claim 2, wherein the one R_1 attached to the 5- or 6- position of the pyridyl ring is phenyl optionally substituted with 1, 2, or 3 of R^D .
4. The compound according to claim 3, wherein the one R_1 attached to the 5- or 6- position of the pyridyl ring is a phenyl optionally substituted with 1 R^D , wherein R^D is $-Z^D R_9$; each Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-O-$, $-NHC(O)-$, $-C(O)NR^E-$, $-SO_2-$, $-NHSO_2-$, $-NHC(O)-$, $-NR^E SO_2-$, $-SO_2NH-$, $-SO_2NR^E-$, $-NH-$, or $-C(O)O-$.
5. The compound according to claim 2, wherein one carbon unit of Z^D is replaced by $-O-$, $-NHC(O)-$, $-C(O)NR^E-$, $-SO_2-$, $-NHSO_2-$, $-NHC(O)-$, $-SO-$, $-NR^E SO_2-$, $-SO_2NH-$, $-SO_2NR^E-$, $-NH-$, or $-C(O)O-$.
6. The compound according to claim 4, wherein R_9 is independently an optionally substituted aliphatic, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, an optionally substituted heteroaryl, H, or halo.
7. The compound according to claim 2, wherein the one R_1 attached to the 5- or 6- position of the pyridyl ring is heteroaryl optionally substituted with 1, 2, or 3 of R^D .
8. The compound according to claim 7, wherein one R_1 attached to the 5- or 6- position of the pyridyl ring is a 5 or 6 membered heteroaryl having 1, 2, or 3 heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the heteroaryl is substituted with 1 of R^D , wherein R^D is $-Z^D R_9$; each Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-O-$, $-NHC(O)-$, $-C(O)NR^E-$, $-SO_2-$, $-NHSO_2-$, $-NHC(O)-$, $-NR^E SO_2-$, $-SO_2NH-$, $-SO_2NR^E-$, $-NH-$, or $-C(O)O-$.
9. The compound according to claim 7, wherein one carbon unit of Z^D is replaced by $-O-$, $-NHC(O)-$, $-C(O)NR^E-$, $-SO_2-$, $-NHSO_2-$, $-NHC(O)-$, $-SO-$, $-NR^E SO_2-$, $-SO_2NH-$, $-SO_2NR^E-$, $-NH-$, or $-C(O)O-$.
10. The compound according to claim 8, wherein R_9 is independently an optionally substituted aliphatic, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl, H, or halo.

11. The compound according to claim 1, wherein R_1 that is attached to the 5- or 6- position of the pyridyl ring is:



(Z-1),



or (Z-2).

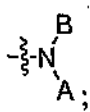
wherein

W_1 is $-C(O)-$, $-SO_2-$, or $-CH_2-$;

D is H, hydroxyl, or an optionally substituted group selected from aliphatic, cycloaliphatic, alkoxy, and amino; and

R^D is defined above.

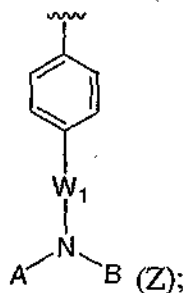
12. The compound according to claim 11, D is OH, an optionally substituted C_{1-6} aliphatic, an optionally substituted C_3-C_8 cycloaliphatic, an optionally substituted alkoxy, or an optionally substituted amino.

13. The compound according to claim 12, D is ;

wherein each of A and B is independently H, an optionally substituted C_{1-6} aliphatic, an optionally substituted C_3-C_8 cycloaliphatic, or

A and B , taken together, form an optionally substituted 3-7 membered heterocycloaliphatic ring.

14. The compound according to claim 1, wherein R_1 that is attached to the 5- or 6- position of the pyridyl ring is:



wherein:

W_1 is $-C(O)-$, $-SO_2-$, or $-CH_2-$;

Each of A and B is independently H, an optionally substituted C₁₋₆ aliphatic, an optionally substituted C₃₋₈ cycloaliphatic; or

A and B, taken together, form an optionally substituted 3-7 membered heterocycloaliphatic ring.

15. The compound according to claim 13, wherein A is H and B is C₁₋₆ aliphatic optionally substituted with 1, 2, or 3 of halo, oxo, alkyl, hydroxy, hydroxyalkyl, alkoxyalkyl, and an optionally substituted heterocycloaliphatic.

16. The compound according to claim 13, wherein A and B, taken together with the nitrogen atom to which they are attached, form an optionally substituted 3-7 membered heterocycloaliphatic ring.

17. The compound according to claim 16, wherein A and B, taken together with the nitrogen atom to which they are attached, form an optionally substituted pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl.

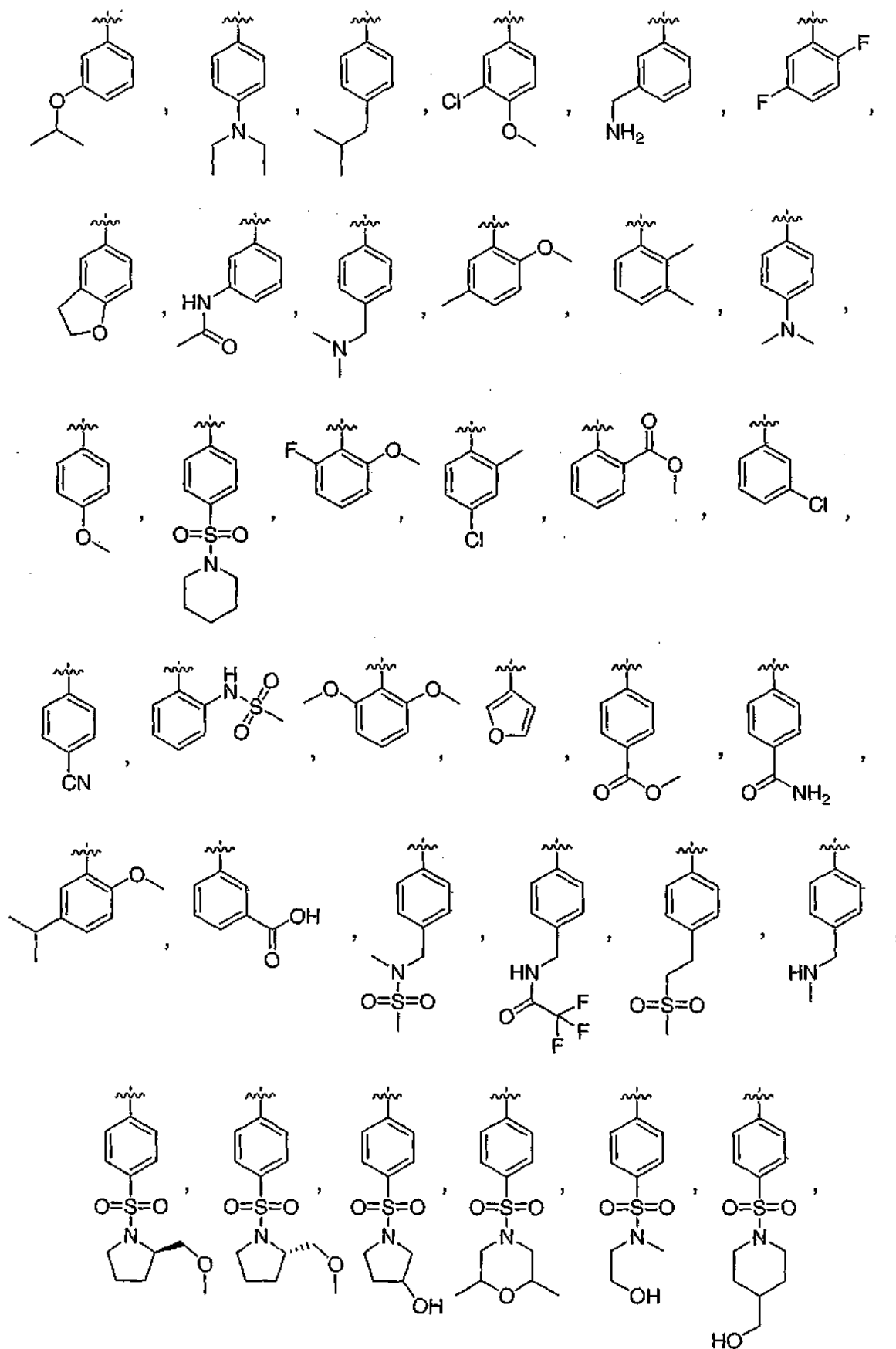
18. The compound according to claim 16, wherein the heterocycloaliphatic ring is optionally substituted with 1, 2, or 3 of halo, oxo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, amido, or carboxy.

19. The compound according to claim 1, wherein one R₁ that is attached to the 5- or 6-position of the pyridyl ring is cycloaliphatic or heterocycloaliphatic, each optionally substituted with 1, 2, or 3 of R^D; wherein R^D is -Z^DR₉; wherein each Z^D is independently a bond or an optionally substituted branched or straight C₁₋₆ aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by -CO-, -CS-, -CONR^E-, -CONR^ENR^E-, -CO₂-, -OCO-, -NR^ECO₂-, -O-, -NR^ECONR^E-, -OCONR^E-, -NR^ENR^E-, -NR^ECO-, -S-, -SO-, -SO₂-, -NR^E-, -SO₂NR^E-, -NR^ESO₂-, or -NR^ESO₂NR^E-; each R₉ is independently R^E, halo, -OH, -NH₂, -NO₂, -CN, -CF₃, or -OCF₃; and each R^E is independently hydrogen, an optionally substituted C₁₋₈ aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

20. The compound according to claim 19, wherein one R₁ that is attached to the 5- or 6-position of the pyridyl ring is an optionally substituted C₃₋₈ cycloaliphatic.

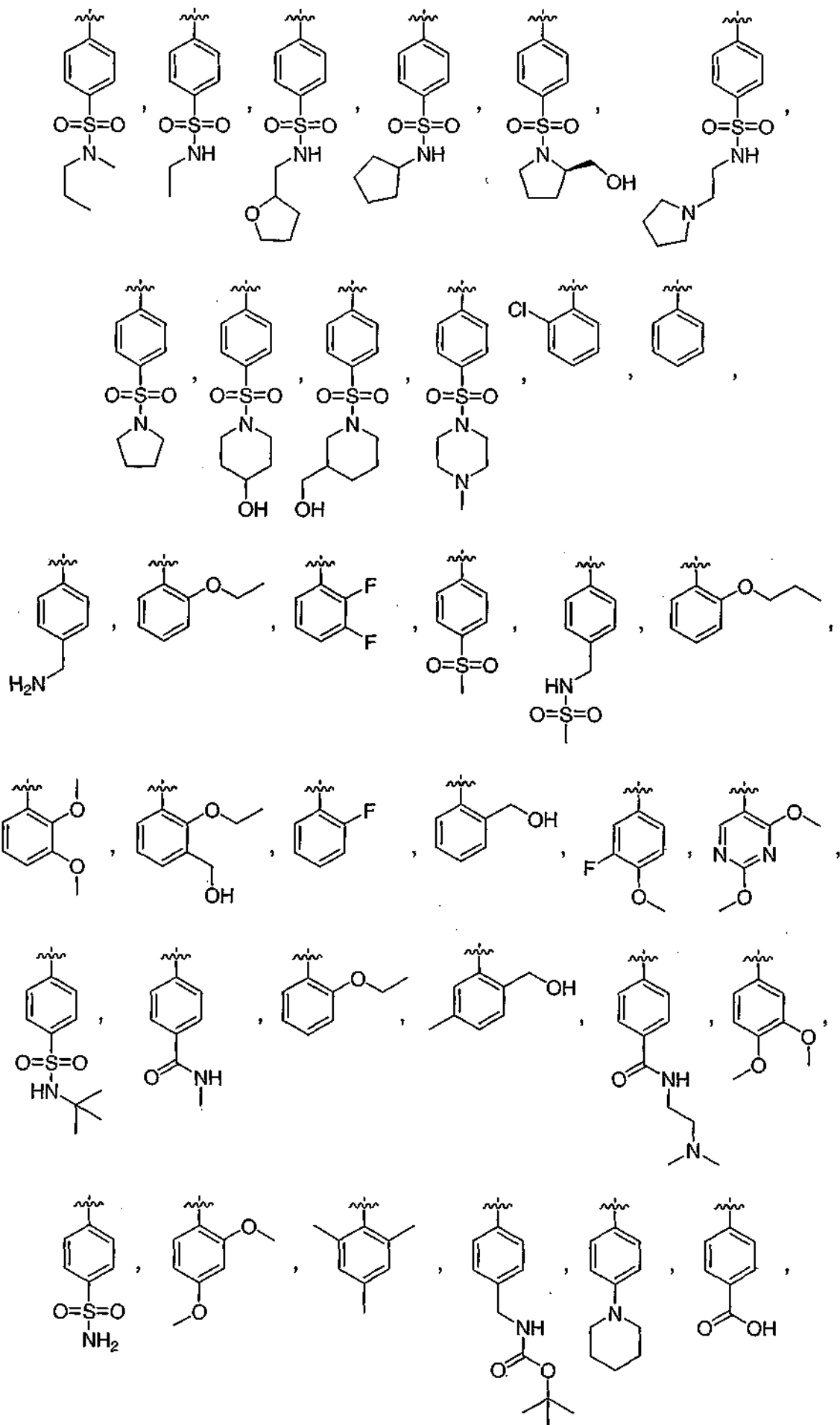
21. The compound according to claim 20, wherein one R₁ that is attached to the 5- or 6-position of the pyridyl ring is an optionally substituted C₃₋₈ cycloalkyl or an optionally substituted C₃₋₈ cycloalkenyl.

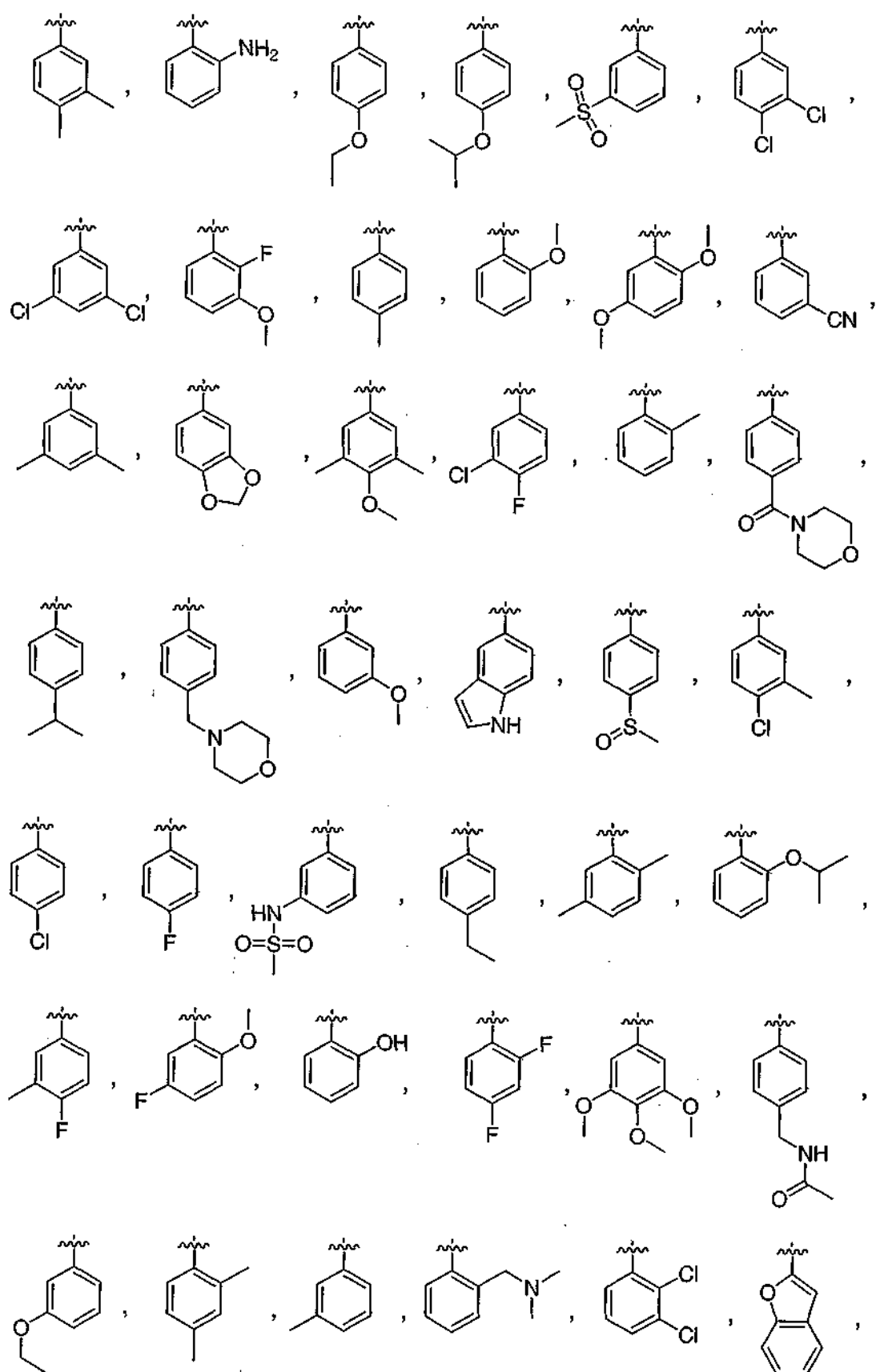
22. The compound according to claim 1, wherein the one R_1 attached to the 5- or 6- position of the pyridyl ring is selected from the group consisting of



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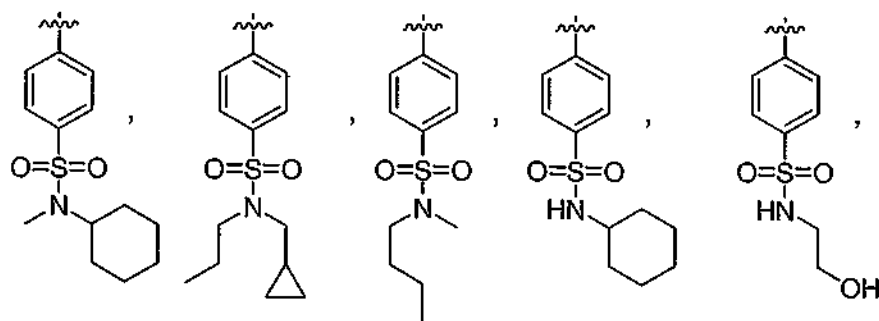
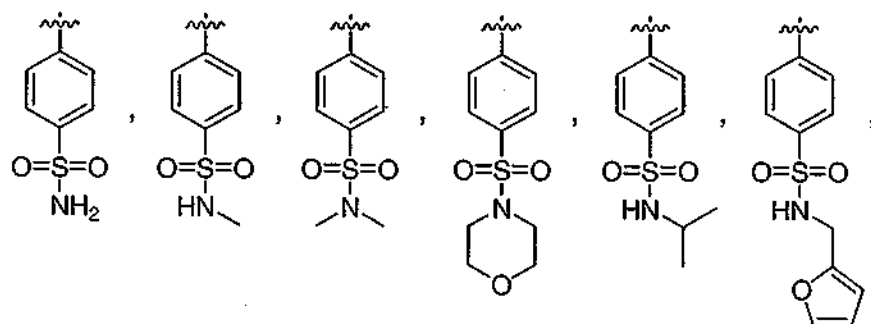
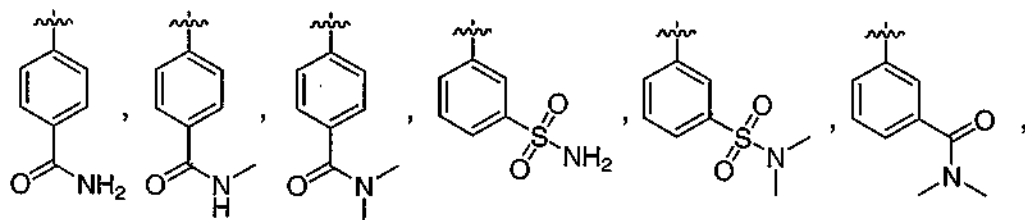
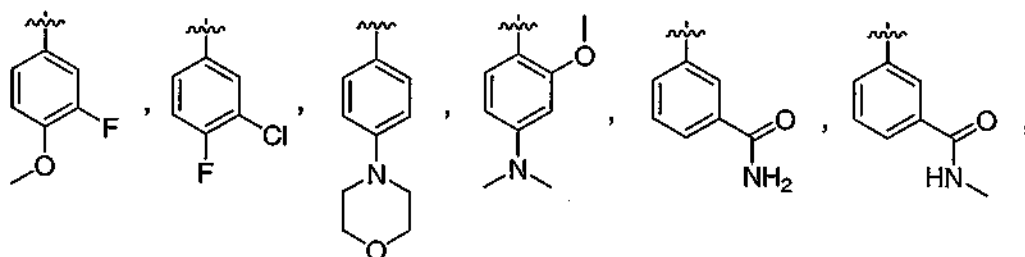
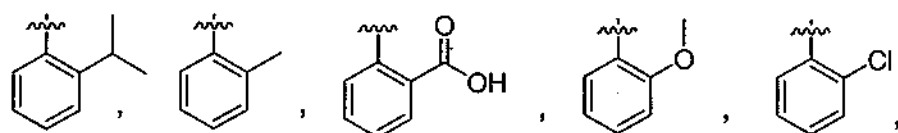
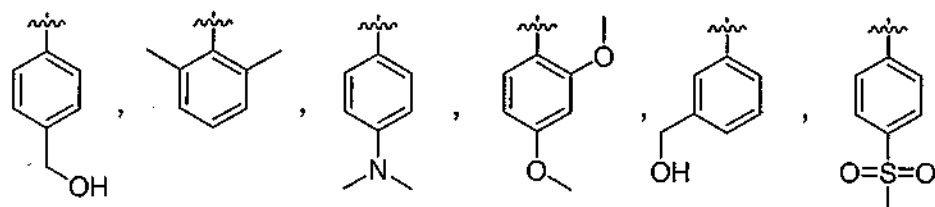
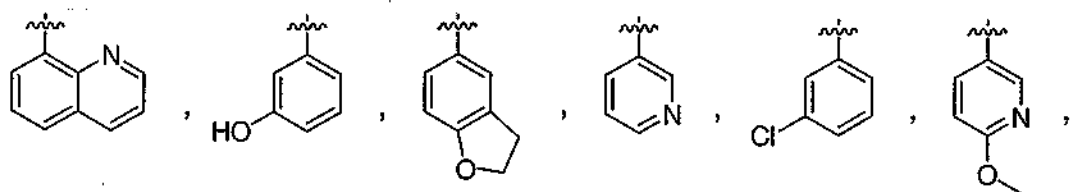
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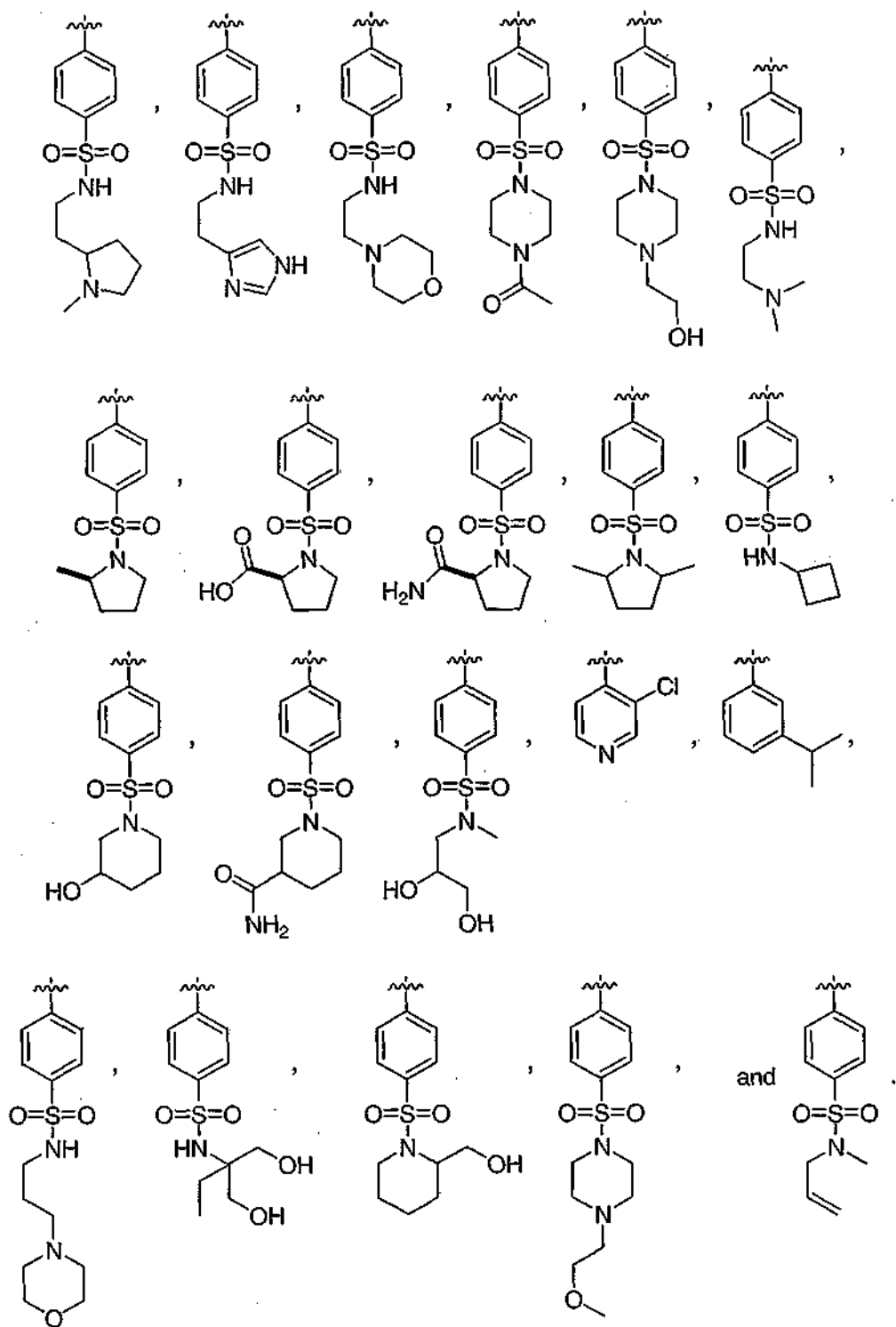




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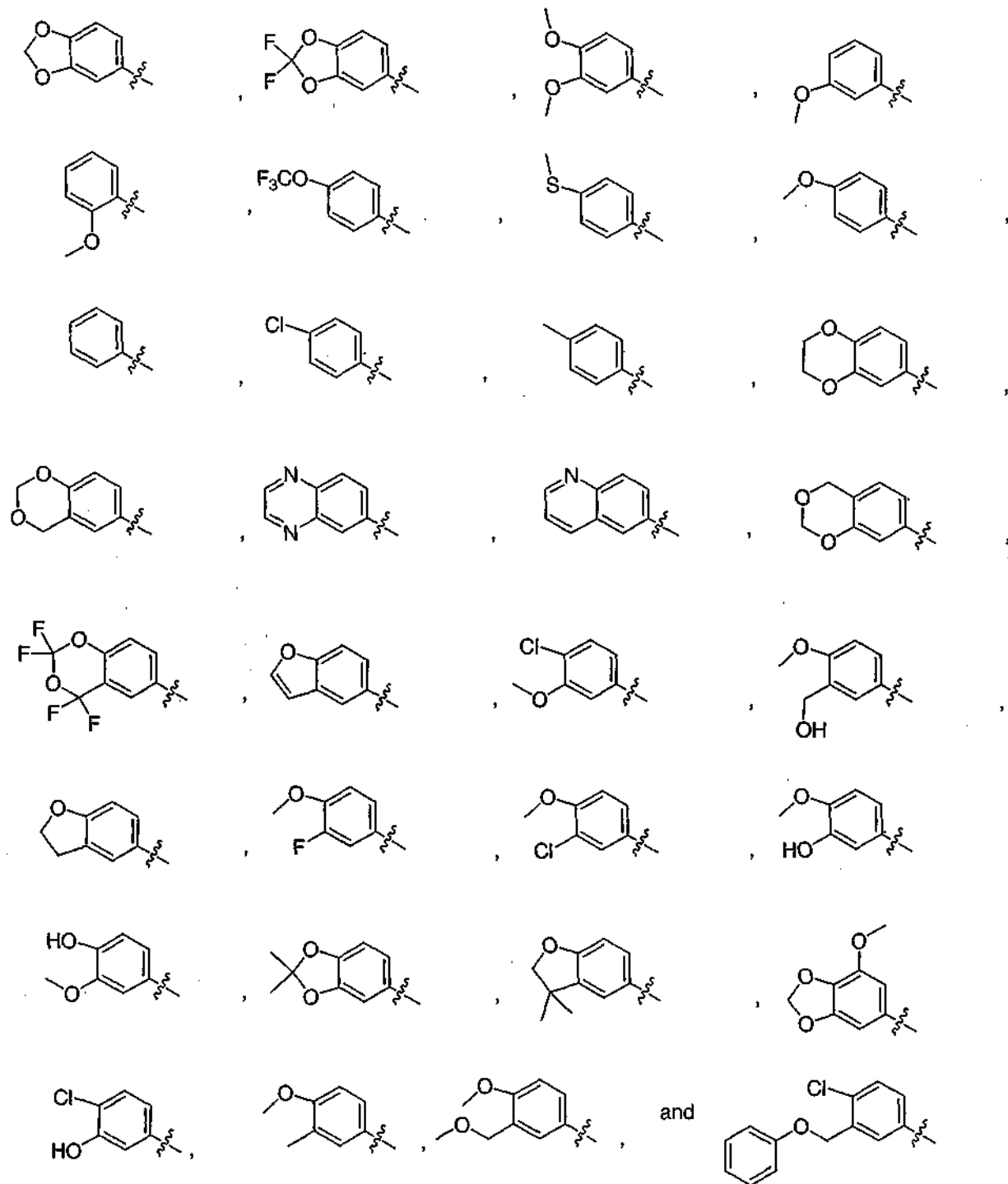
23. The compound according to claim 1, wherein R_2 is hydrogen.

24. The compound according to claim 1, wherein R_3 and R'_3 together with the carbon atom to which they are attached form an unsubstituted C_{3-7} cycloaliphatic or an unsubstituted heterocycloaliphatic.

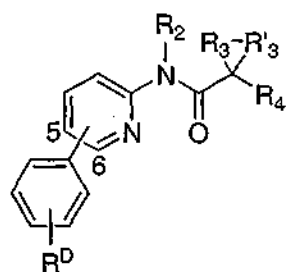
25. The compound according to claim 24, wherein R_3 and R'_3 together with the carbon atom to which they are attached form an unsubstituted cyclopropyl, an unsubstituted cyclopentyl, or an unsubstituted cyclohexyl.
26. The compound according to claim 1, wherein R_4 is an aryl or heteroaryl optionally substituted with 1, 2, or 3 of $-Z^C R_8$, wherein each Z^C is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^C are optionally and independently replaced by $-\text{CO}-$, $-\text{CS}-$, $-\text{CONR}^C-$, $-\text{CONR}^C \text{NR}^C-$, $-\text{CO}_2-$, $-\text{OCO}-$, $-\text{NR}^C \text{CO}_2-$, $-\text{O}-$, $-\text{NR}^C \text{CONR}^C-$, $-\text{OCONR}^C-$, $-\text{NR}^C \text{NR}^C-$, $-\text{NR}^C \text{CO}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^C-$, $-\text{SO}_2 \text{NR}^C-$, $-\text{NR}^C \text{SO}_2-$, or $-\text{NR}^C \text{SO}_2 \text{NR}^C-$; each R_8 is independently R^C , halo, $-\text{OH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CN}$, or $-\text{OCF}_3$; and each R^C is independently an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.
27. The compound according to claim 26, wherein R_4 is an aryl optionally substituted with 1, 2, or 3 of $-Z^C R_8$.
28. The compound according to claim 27, wherein R_4 is an optionally substituted phenyl.
29. The compound according to claim 26, wherein R_4 is a heteroaryl optionally substituted with 1, 2, or 3 of $-Z^C R_8$.
30. The compound according to claim 26, wherein R_4 is one selected from

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31. The compound according to claim 1, wherein said compound has formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

R^D is $-Z^D R_9$, wherein each Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-CO-$, $-CS-$, $-CONR^E-$, $-CONR^E NR^E-$, $-CO_2-$, $-OCO-$, $-NR^E CO_2-$, $-O-$, $-NR^E CONR^E-$, $-OCONR^E-$, $-NR^E NR^E-$, $-NR^E CO-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^E-$, $-SO_2 NR^E-$, $-NR^E SO_2-$, or $-NR^E SO_2 NR^E-$;

R_9 is independently R^E , halo, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-CF_3$, or $-OCF_3$;

Each R^E is independently hydrogen, an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl;

R_2 is C_{1-4} aliphatic, C_{3-6} cycloaliphatic, phenyl, or heteroaryl, each of which is optionally substituted, or R_2 is hydrogen;

R_3 and R'_3 together with the carbon atom to which they are attached form a C_{3-7} cycloaliphatic or a C_{3-7} heterocycloaliphatic, each of which is optionally substituted with 1, 2, or 3 of $-Z^B R_7$, wherein each Z^B is independently a bond, or an optionally substituted branched or straight C_{1-4} aliphatic chain wherein up to two carbon units of Z^B are optionally and independently replaced by $-CO-$, $-CS-$, $-CONR^B-$, $-CONR^B NR^B-$, $-CO_2-$, $-OCO-$, $-NR^B CO_2-$, $-O-$, $-NR^B CONR^B-$, $-OCONR^B-$, $-NR^B NR^B-$, $-NR^B CO-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^B-$, $-SO_2 NR^B-$, $-NR^B SO_2-$, or $-NR^B SO_2 NR^B-$;

Each R_7 is independently R^B , halo, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-CF_3$, or $-OCF_3$;

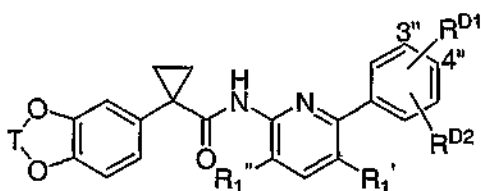
Each R^B is independently hydrogen, an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl;

Each R_4 is an aryl or heteroaryl, each of which is optionally substituted with 1, 2, or 3 of $-Z^C R_8$, wherein each Z^C is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^C are optionally and independently replaced by $-CO-$, $-CS-$, $-CONR^C-$, $-CONR^C NR^C-$, $-CO_2-$, $-OCO-$, $-NR^C CO_2-$, $-O-$, $-NR^C CONR^C-$, $-OCONR^C-$, $-NR^C NR^C-$, $-NR^C CO-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^C-$, $-SO_2 NR^C-$, $-NR^C SO_2-$, or $-NR^C SO_2 NR^C-$;

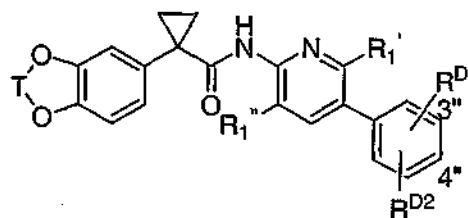
Each R_8 is independently R^C , halo, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-CF_3$, or $-OCF_3$; and

Each R^C is independently an optionally substituted C_{1-8} aliphatic group, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl.

32. The compound according to claim 31, wherein Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein one carbon unit of Z^D is optionally replaced by $-SO_2-$, $-CONR^E-$, $-NR^ESO_2-$, or $-SO_2NR^E-$.
33. The compound according to claim 32, wherein Z^D is an optionally substituted branched or straight C_{1-6} aliphatic chain wherein one carbon unit of Z^D is optionally replaced by $-SO_2-$.
34. The compound according to claim 31, wherein R_9 is an optionally substituted heteroaryl or an optionally substituted heterocycloaliphatic.
35. The compound according to claim 33, wherein R_9 is an optionally substituted heterocycloaliphatic having 1 or 2 nitrogen atoms and R_9 attaches directly to $-SO_2-$ via one ring nitrogen.
36. The compound according to claim 1, wherein said compound has formula V-A or formula V-B:



V-A



V-B

or a pharmaceutically acceptable salt thereof,

wherein:

T is an optionally substituted C_{1-2} aliphatic chain, wherein each of the carbon units is optionally and independently replaced by $-CO-$, $-CS-$, $-COCO-$, $-SO_2-$, $-B(OH)-$, or $-B(O(C_{1-6} \text{ alkyl}))-$;

Each of R_1' and R_1'' is an optionally substituted C_{1-6} aliphatic, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted 3 to 10 membered cycloaliphatic, an optionally substituted 3 to 10 membered heterocycloaliphatic, carboxy, amido, amino, halo, or hydroxy;

R^{D1} is attached to carbon number 3'' or 4'';

each R^{D1} and R^{D2} is $-Z^D R_9$, wherein each Z^D is independently a bond or an optionally substituted branched or straight C_{1-6} aliphatic chain wherein up to two carbon units of Z^D are optionally and independently replaced by $-CO-$, $-CS-$, $-CONR^E-$, $-CONR^E NR^E-$, $-CO_2-$, $-OCO-$, $-NR^E CO_2-$, $-O-$, $-NR^E CONR^E-$, $-OCONR^E-$, $-NR^E NR^E-$, $-NR^E CO-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^E-$, $-SO_2 NR^E-$, $-NR^E SO_2-$, or $-NR^E SO_2 NR^E-$;

R_9 is independently R^E , halo, -OH, -NH₂, -NO₂, -CN, -CF₃, or -OCF₃;
 or R^{D1} and R^{D2} , taken together with atoms to which they are attached, form a 3-8
 membered saturated, partially unsaturated, or aromatic ring with up to 3 ring members
 independently selected from the group consisting of O, NH, NR^E , and S; and
 each R^E is independently hydrogen, an optionally substituted C₁₋₈ aliphatic group, an
 optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an
 optionally substituted aryl, or an optionally substituted heteroaryl.

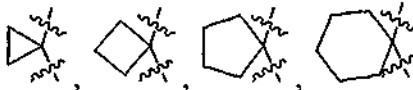
37. The compound according to claim 36, wherein up to two methylene units of T are
 optionally substituted by -CO-, -CS-, -B(OH), or -B(O(C₁₋₆ alkyl)).

38. The compound according to claim 36, wherein T is an optionally substituted chain
 selected from the group consisting of -CH₂- and -CH₂CH₂-.

39. The compound according to claim 36, wherein T is optionally substituted by -Z^ER₁₀;
 wherein each Z^E is independently a bond or an optionally substituted branched or straight C₁₋₆
 aliphatic chain wherein up to two carbon units of Z^E are optionally and independently replaced
 by -CO-, -CS-, -CONR^F-, -CONR^FNR^F-, -CO₂-, -OCO-, -NR^FCO₂-, -O-, -NR^FCONR^F-, -
 OCONR^F-, -NR^FNR^F-, -NR^FCO-, -S-, -SO-, -SO₂-, -NR^F-, -SO₂NR^F-, -NR^FSO₂-, or -
 NR^FSO₂NR^F-; R₁₀ is independently R^F, halo, -OH, -NH₂, -NO₂, -CN, -CF₃, or -OCF₃; each R^F is
 independently hydrogen, an optionally substituted C₁₋₈ aliphatic group, an optionally substituted
 cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or
 an optionally substituted heteroaryl.

40. The compound according to claim 39, wherein T is optionally substituted by F, Cl, C₁₋₆
 alkyl, C₃₋₈ cycloalkyl, phenyl, naphthyl, -O-(C₁₋₆ alkyl), -O-(C₃₋₈ cycloalkyl), -O-phenyl, or C₃₋₈
 spiroaliphatic.

41. The compound according to claim 36, wherein T is selected from the group consisting of

-CH₂-, -CH₂CH₂-, -CF₂-, -C(CH₃)₂-, -C(O)-, , -C(Phenyl)₂-, -
 B(OH)-, and -CH(OEt)-.

42. The compound according to claim 41, wherein T is selected from the group consisting of
 -CH₂-, -CF₂-, and -C(CH₃)₂-.

43. The compound according to claim 36, wherein Z^D is independently a bond or an
 optionally substituted branched or straight C₁₋₆ aliphatic chain wherein one carbon unit of Z^D is

optionally replaced by $-\text{CO}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{COO}-$, $-\text{OCO}-$, $-\text{CONR}^E$, $-\text{NR}^E\text{CO}-$, NR^ECO_2- , $-\text{O}-$, $-\text{NR}^E\text{SO}_2-$, or $-\text{SO}_2\text{NR}^E$.

44. The compound according to claim 36, wherein R^{D1} is $-\text{Z}^{\text{D}}\text{R}_9$, wherein R_9 is halo, $-\text{OH}$, $-\text{NH}_2$, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, or an optionally substituted group selected from the group consisting of C_{1-6} aliphatic, C_{3-8} cycloaliphatic, 3-8 membered heterocycloaliphatic, C_{6-10} aryl, and 5-10 membered heteroaryl.

45. The compound according to claim 44, wherein R_9 is F, Cl, $-\text{OH}$, $-\text{CN}$, $-\text{CF}_3$, or $-\text{OCF}_3$.

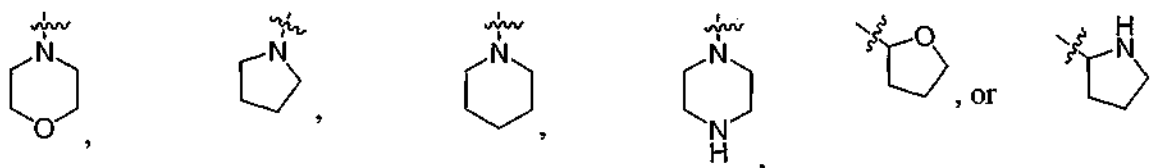
46. The compound according to claim 44, wherein R_9 is selected from the group consisting of C_{1-6} straight or branched alkyl or C_{2-6} straight or branched alkenyl; wherein said alkyl or alkenyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of R^E , oxo, halo, $-\text{OH}$, $-\text{NR}^E\text{R}^E$, $-\text{OR}^E$, $-\text{COOR}^E$, and $-\text{CONR}^E\text{R}^E$.

47. The compound according to claim 44, wherein R_9 is C_{3-8} cycloaliphatic optionally substituted by 1 or 2 substituents independently selected from the group consisting of R^E , oxo, halo, $-\text{OH}$, $-\text{NR}^E\text{R}^E$, $-\text{OR}^E$, $-\text{COOR}^E$, and $-\text{CONR}^E\text{R}^E$.

48. The compound according to claim 47, wherein R_9 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

49. The compound according to claim 44, wherein R^9 is a 3-8 membered heterocyclic with 1 or 2 heteroatoms independently selected from the group consisting of O, NH, NR^E , and S; wherein said heterocyclic is optionally substituted by 1 or 2 substituents independently selected from the group R^E , oxo, halo, $-\text{OH}$, $-\text{NR}^E\text{R}^E$, $-\text{OR}^E$, $-\text{COOR}^E$, and $-\text{CONR}^E\text{R}^E$.

50. The compound according to claim 49, wherein R^9 is an optionally substituted 3-8 membered heterocyclic is

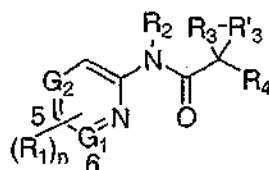


51. The compound according to claim 49, wherein R^9 is optionally substituted by 1 or 2 substituents independently selected from the group consisting of oxo, F, Cl, methyl, ethyl, *i*-propyl, *t*-butyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{O}(\text{C}_{1-6} \text{ alkyl})$, $-\text{CH}_2\text{CH}_2\text{O}(\text{C}_{1-6} \text{ alkyl})$, and $-\text{C}(\text{O})(\text{C}_{1-6} \text{ alkyl})$.

52. The compound according to claim 44, wherein R^9 is 5-8 membered heteroaryl with 1 or two ring atom independently selected from the group consisting of O, S, and NR^E ; wherein said

58. The compound according to claim 36, wherein R^{D2} is selected from the group consisting of H, C_{1-6} aliphatic, halo, -CN, -NH₂, -CH₂NH₂, -OH, -O(C_{1-6} aliphatic), -CH₂OH, -SO₂(C_{1-6} aliphatic), -NH-SO₂(C_{1-6} aliphatic), -C(O)O(C_{1-6} aliphatic), -C(O)OH, -NHC(O)(C_{1-6} aliphatic), -C(O)NH₂, -C(O)NH(C_{1-6} aliphatic), and -C(O)N(C_{1-6} aliphatic)₂.

59. A compound of formula (I'):



(I')

or a pharmaceutically acceptable salt thereof,

wherein:

one of G_1 and G_2 is N and the other of G_1 and G_2 is CH;

Each R_1 is an optionally substituted C_{1-6} aliphatic, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted 3 to 10 membered cycloaliphatic, an optionally substituted 3 to 10 membered heterocycloaliphatic, carboxy, amido, amino, halo, or hydroxy, provided that at least one R_1 is an optionally substituted aryl or an optionally substituted heteroaryl attached to the 5- or 6- position of the pyridyl ring;

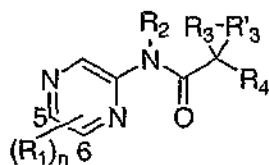
Each R_2 is hydrogen, an optionally substituted C_{1-6} aliphatic, an optionally substituted C_{3-6} cycloaliphatic, an optionally substituted phenyl, or an optionally substituted heteroaryl;

Each R_3 and R'_3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7} cycloaliphatic or an optionally substituted heterocycloaliphatic;

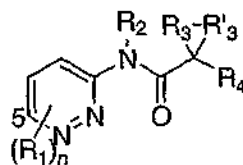
Each R_4 is an optionally substituted aryl or an optionally substituted heteroaryl; and

Each n is 1, 2, 3, or 4.

60. The compound according to claim 59, wherein the compound has formula (I'-A) or formula (I'-B).



(I'-A)

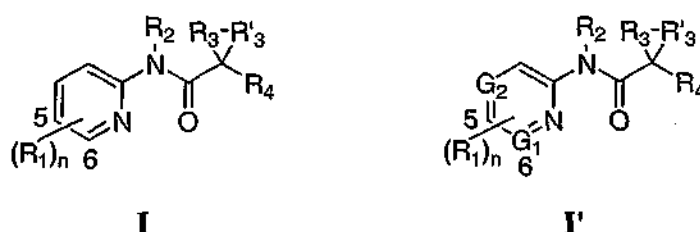


(I'-B)

or a pharmaceutically acceptable salt thereof,

wherein R_1 , R_2 , R_3 , R'_3 , R_4 , and n are defined above.

61. A compound according to any one of claims 1-59, wherein the compound is selected from Table 1.
62. A pharmaceutical composition comprising:
- (i) a compound according to any one of claims 1-61; and
 - (ii) a pharmaceutically acceptable carrier.
63. The composition according to claim 62, optionally further comprising a mucolytic agent, a bronchodilator, an antibiotic, an anti-infective agent, an anti-inflammatory agent, a CFTR modulator, or a nutritional agent.
64. A method according to modulating ABC transporter activity comprising the step of contacting said ABC transporter with a compound of formula (I) or formula (I'):



wherein:

one of G_1 and G_2 is a nitrogen, and the other is a carbon;

each R_1 is an optionally substituted C_{1-6} aliphatic, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted C_{3-10} cycloaliphatic, an optionally substituted 3 to 10 membered heterocycloaliphatic, carboxy, amido, amino, halo, or hydroxy, provided that at least one R_1 is an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl attached to the 5- or 6- position of the pyridyl ring;

each R_2 is hydrogen, an optionally substituted C_{1-6} aliphatic, an optionally substituted C_{3-6} cycloaliphatic, an optionally substituted phenyl, or an optionally substituted heteroaryl;

each R_3 and R'_3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7} cycloaliphatic or an optionally substituted heterocycloaliphatic;

each R_4 is an optionally substituted aryl or an optionally substituted heteroaryl; and

each n is 1-4.

65. The method according to claim 64, wherein the ABC transporter is CFTR.
66. A method of treating or lessening the severity of a disease in a patient, wherein said disease is selected from cystic fibrosis, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary

angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myeloperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders asuch as Huntington, spinocerebular ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, or Sjogren's disease, said method comprising the step of administering to said patient an effective amount of a compound of formula I or formula I' according to any oe of claims 1-61.

67. A kit for use in measuring the activity of an ABC transporter or a fragment thereof in a biological sample *in vitro* or *in vivo*, comprising:

(i) a composition comprising a compound of formula (I) or formula (I') according to any one of claims 1-61; and

(ii) instructions for:

- a) contacting the composition with the biological sample; and
- b) measuring activity of said ABC transporter or a fragment thereof.

68. The kit according to claim 67, further comprising instructions for

- a) contacting an additional composition with the biological sample;
- b) measuring the activity of said ABC transporter or a fragment thereof in the presence of said additional compound, and
- c) comparing the activity of the ABC transporter in the presence of the additional compound with the density of the ABC transporter in the presence of a composition of formula (I) or formula (I').

69. The kit according to claim 68, wherein the kit is used to measure the density of CFTR.

A. CLASSIFICATION OF SUBJECT MATTERINV. C07D405/12 C07D405/14 C07D213/75 A61K31/5585 A61K31/4418
A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/075435 A (VERTEX PHARMA [US]; HADIDA RUAH SARAH S [US]; GROOTENHUIS PETER D J [U] 18 August 2005 (2005-08-18) claim 1; compound 245 -----	1-69

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

1 March 2007

Date of mailing of the international search report

09/03/2007

Name and mailing address of the ISA/

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Authorized officer

Johnson, Claire

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/043289

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 64-66 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/043289

495

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005075435 A	18-08-2005	AU 2005210474 A1	18-08-2005
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Phenylglycine and Sulfonamide Correctors of Defective $\Delta F508$ and G551D Cystic Fibrosis Transmembrane Conductance Regulator Chloride-Channel Gating^[S]

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ABSTRACT

Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel cause cystic fibrosis. The $\Delta F508$ mutation produces defects in channel gating and cellular processing, whereas the G551D mutation produces primarily a gating defect. To identify correctors of gating, 50,000 diverse small molecules were screened at 2.5 μM (with forskolin, 20 μM) by an iodide uptake assay in epithelial cells coexpressing $\Delta F508$ -CFTR and a fluorescent halide indicator (yellow fluorescent protein-H148Q/I152L) after $\Delta F508$ -CFTR rescue by 24-h culture at 27°C. Secondary analysis and testing of >1000 structural analogs yielded two novel classes of correctors of defective $\Delta F508$ -CFTR gating ("potentiators") with nanomolar potency that were active in human $\Delta F508$ and G551D cells. The most potent compound of the phenylglycine class, 2-[(2-1*H*-indol-3-yl-acetyl)-methylamino]-*N*-(4-isopropylphenyl)-2-phenylacetamide, reversibly activated $\Delta F508$ -

CFTR in the presence of forskolin with $K_a \sim 70$ nM and also activated the CFTR gating mutants G551D and G1349D with K_a values of ~ 1100 and 40 nM, respectively. The most potent sulfonamide, 6-(ethylphenylsulfamoyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid cycloheptylamide, had $K_a \sim 20$ nM for activation of $\Delta F508$ -CFTR. In cell-attached patch-clamp experiments, phenylglycine-01 (PG-01) and sulfonamide-01 (SF-01) increased channel open probability >5-fold by the reduction of interburst closed time. An interesting property of these compounds was their ability to act in synergy with cAMP agonists. Microsome metabolism studies and rat pharmacokinetic analysis suggested significantly more rapid metabolism of PG-01 than SF-03. Phenylglycine and sulfonamide compounds may be useful for monotherapy of cystic fibrosis caused by gating mutants and possibly for a subset of $\Delta F508$ subjects with significant $\Delta F508$ -CFTR plasma-membrane expression.

Cystic fibrosis (CF), a relatively common hereditary disease in white populations, can produce chronic lung infection and deterioration of lung function, pancreatic insufficiency, male infertility, and meconium ileus (Pilewski and Frizzell, 1999). CF is caused by mutations in the cystic fibrosis trans-

membrane conductance regulator (CFTR) protein, a cAMP-activated Cl^- channel expressed in airway, pancreatic, intestinal, testicular, and other epithelia (Sheppard and Welsh, 1999). $\Delta F508$ is by far the most common CFTR mutation causing CF, being present in $\sim 60\%$ of CF genes and in $\sim 90\%$ of CF subjects as at least one allele (Bobadilla et al., 2002). The $\Delta F508$ mutation is believed to produce Cl^- -impermeable epithelial cells by aberrant protein folding and consequent defects in cellular processing and channel gating (Dalemans et al., 1991; Denning et al., 1992; Haws et al., 1996; Kopito, 1999). Most $\Delta F508$ -CFTR protein is retained at the endoplasmic reticulum and is degraded rapidly (Jensen et al., 1995;

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ABBREVIATIONS: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; YFP, yellow fluorescent protein; PG, phenylglycine; SF, sulfonamide; MDR-1, multidrug resistance protein 1; FRT, Fischer rat thyroid; DMSO, dimethyl sulfoxide; PBS, phosphate-buffered saline; DMAP, 4-(*N,N*-dimethylamino)pyridine; EDCI, 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide; LCMS, liquid chromatography/mass spectrometry; HPLC, high-performance liquid chromatography; SAR, structure-activity relationship; P_o , open-channel probability; T_o , mean channel open time; T_c , mean channel closed time.

Ward et al., 1995). Many other CFTR mutations causing CF are targeted to the cell plasma membrane but produce chloride-impermeable cells by a primary defect in channel gating. The most common of the CFTR gating mutants is G551D, with a worldwide frequency of 3.1% among CF chromosomes (Hamosh et al., 1992), although people of Celtic descent have frequencies as high as 8% (Cashman et al., 1995).

Small-molecule activators/correctors of mutant CFTRs may provide a strategy for treatment of CF that corrects the underlying defect. Activation of mutant CFTRs avoids potential concerns about treating the wrong cells and/or losing physiological CFTR regulation as might occur with gene therapy or activation of alternative chloride channels. Restoration of cAMP-regulated chloride permeability in epithelial cells expressing $\Delta F508$ -CFTR would probably require compound(s) that correct the underlying defects in cellular processing and channel gating, although there may exist a subset of subjects with enough plasma membrane $\Delta F508$ -CFTR expression (Penque et al., 2000; Sermet-Gaudelus et al., 2002) to be benefited by a corrector of defective channel gating ("potentiator"). Potentiators may also be useful as monotherapy for CF caused by gating mutants of CFTR such as G551D.

Various small molecules have been found to have potentiator activity for correction of the $\Delta F508$ -CFTR gating defect. Relatively high concentrations of flavones such as genistein ($>50 \mu\text{M}$) and xanthines such as isobutylmethylxanthine ($>1 \text{ mM}$) can restore normal or near-normal $\Delta F508$ -CFTR channel gating when given with cAMP agonists (Drumm et al., 1991; Haws et al., 1996; Hwang et al., 1997). Flavones at high concentrations also are able to correct defective gating in G551D-CFTR (Ilek et al., 1999; Zegar-Moran et al., 2002). We identified previously a benzothienophene class of $\Delta F508$ -CFTR potentiators by high-throughput screening of 100,000 small molecules (Yang et al., 2003). After compound optimization by structure-activity studies, benzothienophenes were identified that rapidly restored near-normal $\Delta F508$ -CFTR channel gating with $K_a \sim 0.5 \mu\text{M}$, as measured by short-circuit current analysis. However, activation required high concentrations of cAMP agonists, and the benzothienophenes did not activate CFTR gating mutants such as G551D.

In this study, we carried out high-throughput screening to identify novel classes of correctors of defective $\Delta F508$ -CFTR channel gating, focusing on compounds with very high potency, potentiator activity in human airway epithelial cells from CF subjects, and activity against other CFTR gating mutants. Two novel classes of potentiators emerged from primary screening and secondary evaluation: phenylglycines and sulfonamides. These compounds were potent in $\Delta F508$ -CFTR-transfected and natively expressing human cells, active in the presence of relatively low concentrations of cAMP agonists, and active against multiple CFTR gating mutants, including G551D. To evaluate their potential usefulness for drug development, the phenylglycines and sulfonamides were subject to analysis of structure-activity relationships, single-channel electrophysiology, and metabolic stability/in vivo pharmacology.

Materials and Methods

Cell Lines. Fischer rat thyroid (FRT) epithelial cells stably coexpressing human $\Delta F508$ -CFTR and the high-sensitivity halide-sens-

ing green fluorescent analog YFP-H148Q/I152L (Galiotta et al., 2001a) were generated as described previously (Yang et al., 2003). FRT cells were cultured on plastic in Coon's modified F-12 medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 100 U/ml penicillin, and 100 $\mu\text{g/ml}$ streptomycin. For primary screening, cells were plated using a multidrop dispenser (Thermo Electron Corp., Woburn, MA) into black 96-well microplates (Corning-Costar, Acton, MA) at 50,000 cells/well. Screening was done 18 to 24 h after plating. For short-circuit current measurements, cells were cultured on Snapwell permeable supports (Corning-Costar) at 500,000 cells/insert. Human nasal epithelial cells from subjects with CF were cultured on Snapwell inserts and were allowed to differentiate in a hormone-supplemented medium as described previously (Galiotta et al., 1998). Some measurements were done using stably transfected FRT cells expressing YFP-H148Q and wild-type or G551D-CFTR (Galiotta et al., 2001b). Patch-clamp experiments were done on $\Delta F508$ -CFTR expressing FRT cells plated on 35-mm Petri dishes.

Compounds. A collection of 50,000 diverse drug-like compounds ($>90\%$ with molecular size of 250–500 Da; ChemDiv, San Diego, CA) was used for initial screening. The compounds were cherry-picked for favorable drug-like properties, maximal chemical diversity, and minimal overlap with 100,000 compounds tested previously. For optimization, >1000 analogs of activators identified in the primary screen were purchased from ChemDiv. Compounds were prepared as 10 mM stock solutions in DMSO. Secondary plates containing one or four compounds per well were prepared for screening (1 mM in DMSO). Compounds for secondary analysis were resynthesized, purified, and confirmed by NMR and liquid chromatography/mass spectrometry.

Screening Procedures. Screening was carried out using a Beckman integrated system containing a 3-m robotic arm, a CO_2 incubator containing microplate carousel, plate washer, liquid-handling workstation, barcode reader, delidding station, plate sealer, and two Fluostar fluorescence plate readers (Optima; BMG LABTECH, Durham, NC), each equipped with dual syringe pumps and HQ500/20X ($500 \pm 10 \text{ nm}$) excitation and HQ535/30M ($535 \pm 15 \text{ nm}$) emission filters (Chroma Technology Corp., Brattleboro, VT). For assay of $\Delta F508$ -CFTR potentiator activity, FRT cells were incubated at 27°C (90% humidity, 5% CO_2) to allow the rescue of mutant CFTR. After 18- to 24-h incubation, plates (40–50 per day) were washed with PBS, and cells were incubated with 60 μl of PBS containing forskolin (20 μM) and test compounds (2.5 μM). After 15 min, the 96-well plate was transferred to a plate reader for fluorescence assay. Each well was assayed individually for I^- influx by recording fluorescence continuously (200 ms per point) for 2 s (baseline) and then for 12 s after rapid ($<1 \text{ s}$) addition of 165 μl of PBS, in which 137 mM Cl^- was replaced by I^- . I^- influx rate was computed by fitting the final 11.5 s of the data to an exponential for extrapolation of initial slope and normalizing for total fluorescence (background-subtracted initial fluorescence). All compound plates contained negative controls (DMSO vehicle alone) and positive controls (genistein, 5 and 50 μM). Assay analysis indicated a Z' factor (Zhang et al., 1999) of >0.7 .

Synthetic Chemistry. ^1H spectra were obtained in CDCl_3 or d_6 -DMSO using a Mercury 400 MHz spectrometer. Flash-column chromatography was done using EM silica gel (230–400 mesh). Thin-layer chromatography was carried out on Merck silica gel 60 F254 plates and visualized under a UV lamp. Microwave reactions were carried out on a synthesizer (Emrys, Charlottesville, VA). Representative synthetic schemes for a phenylglycine and sulfonamide follow (Fig. 2A).

For synthesis of phenylglycine-01 (PG-01), to a solution of *N*-tert-butoxycarbonyl-*N*-methylphenylglycine (compound I) (1.26 g, 4.75 mmol) at room temperature was added *p*-isopropylaniline (705 mg, 5.22 mmol), 4-(*N,N*-dimethylamino)pyridine (DMAP) (116 mg, 0.92 mmol) in CH_2Cl_2 (25 ml) and 1-ethyl-3-[3-(dimethylamino)-propyl]-carbodiimide (EDCI; 1.00 g, 5.22 mmol). The reaction mixture was stirred for 2 h and then quenched by pouring over saturated NH_4Cl . After extraction with CH_2Cl_2 , the organic layer was washed succes-

sively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the crude residue gave [(4-isopropylphenylcarbamoyl)-phenylmethyl]-methylcarbamic acid *tert*-butyl ester (compound IIA) as a white solid (1.67 g, 92%). Compound IIA (300 mg, 0.785 mmol) was dissolved in a minimal quantity of trifluoroacetic acid, maintained at room temperature for 15 min, poured over aqueous NaHCO_3 , and extracted with CH_2Cl_2 . Washing, drying, and evaporation of the organic layer gave compound II as a yellow oil (218 mg, 98%). To a mixture of compound II (177 mg, 0.620 mmol), indole-3-acetic acid (114 mg, 0.651 mmol) and DMAP (15 mg, 0.124 mmol) in CH_2Cl_2 (5 ml), EDCI (131 mg, 0.682 mmol) was added at room temperature. The reaction mixture was worked up as for compound IIA and recrystallized from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1) to give PG-01 as a white solid (1.67 g, 92%). Mass (ES+): $m/z = 440$ [$M + 1$] $^+$; ^1H NMR δ 1.21 (d, 6H, $J = 6.9$ Hz), 2.85 (sep, 1H, $J = 6.9$ Hz), 2.95 (s, 3H), 3.91 (s, 2H), 6.55 (s, 1H), 7.08 to 7.40 (m, 13H), 7.59 (d, 1H, $J = 7.8$ Hz), 7.88 (bs, 1H), 8.13 (bs, 1H).

For synthesis of sulfonamide-03 (SF-03), compound III (Blus, 1999) (2.21 g, 8.0 mmol) and diethylethoxymethylenemalonate (1.81 g, 8.4 mmol) were dissolved in tetrahydrofuran (4 ml), and the solution was heated to 140°C for 30 min until the tetrahydrofuran and ethanol by-product evaporated. The residue was diluted with ethyl acetate, washed with brine, dried with Na_2SO_4 , and evaporated to dryness. Flash chromatography gave light yellow solid compound IIIB (3.29 g, 90%). To a solution of phenyl ether (Ph_2O , 3 ml) and compound IIIB (130 mg, 0.30 mmol) in an Emrys microwave reaction vessel was added 4-chlorobenzoic acid (1 mg, 0.02 mmol). The solution was microwave-irradiated at 250°C for 75 min. The white precipitate was filtered and washed with hexane to yield compound IV (48 mg, 42%). To an Emrys microwave reaction vessel (0.2–0.5 ml) containing compound IV (65 mg, 0.083 mmol) was added *o*-methoxybenzyl amine (200 mg, 1.4 mmol) and microwave-irradiated at 180°C for 30 min. The resulting solution was diluted with dichloromethane

and water and extracted with ethyl acetate three times. After washing, drying, and evaporation, the residue was purified by flash chromatography giving SF-03 as a white powder (27 mg, 35%). Mass (ES+): $m/z = 492$ [$M + 1$] $^+$; ^1H NMR CDCl_3 δ 1.08 (t, 3H, $J = 7.2$ Hz), 3.65 (q, 2H, $J = 7.2$ Hz), 3.79 (s, 3H), 4.70 (d, 2H, $J = 6.0$ Hz), 6.81 (m, 2H), 7.02 (m, 2H), 7.16 (td, 1H, $J = 8.0, 1.6$ Hz), 7.23 (d, 1H, $J = 7.2$ Hz), 7.29 (m, 2H), 7.37 (d, 1H, $J = 8.4$ Hz), 7.53 (dd, 1H, $J = 8.8, 2.0$ Hz), 8.77 (d, 1H, $J = 2.0$ Hz), 8.83 (d, 1H, $J = 6.4$ Hz), 10.74 (t, 1H, $J = 5.6$ Hz), 12.30 (d, 1H, $J = 4.4$ Hz).

Assays of cAMP. cAMP activity was measured using the BIO-TRAK enzymatic immunoassay (Amersham Biosciences Inc., Piscataway, NJ) on FRT cell lysates after incubation with activators for 10 min in the presence of 0.5 μM forskolin.

Short-Circuit Current Measurements. For Ussing chamber experiments, $\Delta F508$ -CFTR-expressing FRT cells were seeded on Snapwell inserts and cultured for 7 to 9 days. The basolateral solution contained 130 mM NaCl, 2.7 mM KCl, 1.5 mM KH_2PO_4 , 1 mM CaCl_2 , 0.5 mM MgCl_2 , 10 mM glucose, and 10 mM sodium HEPES, pH 7.3. In the apical bathing solution, 65 mM NaCl was replaced by sodium gluconate, and CaCl_2 was increased to 2 mM. Solutions were bubbled with air and maintained at 37°C . The basolateral membrane was permeabilized with 250 $\mu\text{g}/\text{ml}$ amphotericin B. For human bronchial epithelial cells, apical and basolateral chambers contained 126 mM NaCl, 0.38 mM KH_2PO_4 , 2.1 mM K_2HPO_4 , 1 mM MgSO_4 , 1 mM CaCl_2 , 24 mM NaHCO_3 , and 10 mM glucose (basolateral membrane not permeabilized). Hemichambers were connected to a DVC-1000 voltage clamp (World Precision Instruments, Inc., Sarasota, FL) via Ag/AgCl electrodes and 1 M KCl agar bridges for recording short-circuit current.

Patch-Clamp Analysis. Experiments were performed in the cell-attached configuration of the patch-clamp technique on FRT cells expressing $\Delta F508$ -CFTR. Cells were plated at a density of 10^4 cells/well, grown at 37°C for 24 to 48 h, and then incubated for 24 to 48 h

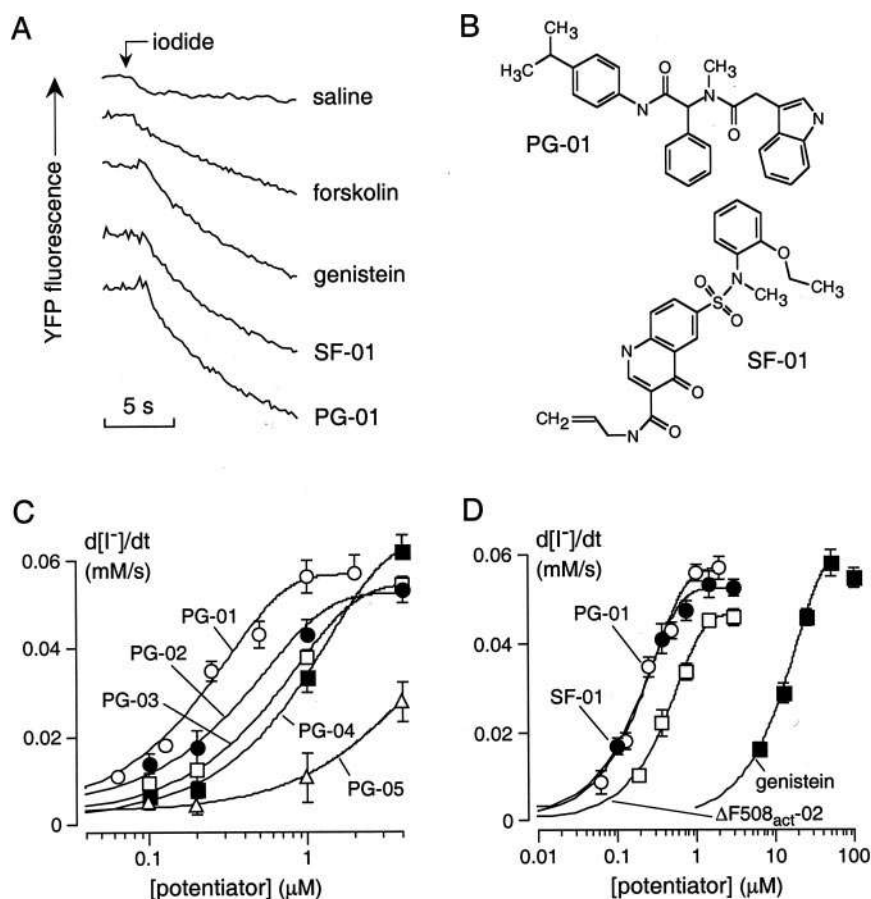


Fig. 1. Identification of $\Delta F508$ -CFTR potentiators by high-throughput screening. A, original traces showing quenching of cellular YFP fluorescence by I^- addition with saline alone and after additions of forskolin (20 μM) alone or forskolin plus genistein (50 μM), SF-01 (2.5 μM), or PG-01 (2.5 μM). B, chemical structures of potent PG-01 and SF-01 compounds. C and D, dose-response analysis of indicated compounds (mean \pm S.E., $n = 4$), including the tetrahydrobenzothiophene $\Delta F508_{\text{act-02}}$ (Yang et al., 2003).

at 27°C to allow trafficking of the $\Delta F508$ protein to the plasma membrane.

Single channel recordings were obtained using an EPC-7 patch-clamp amplifier (List Medical Instruments, Darmstadt, Germany). Data were filtered at 250 Hz and digitized at 500 Hz using an ITC-16 data translation interface (InstruTECH Corporation, Port Washington, NY). The pipette solution contained 120 mM CsCl, 10 mM TEA chloride, 0.5 mM EGTA, 1 mM $MgCl_2$, 40 mM mannitol, and 10 mM cesium HEPES, pH 7.3. The bath solution contained 130 mM KCl, 2 mM NaCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, 10 mM glucose, 20 mM mannitol, and 10 mM sodium HEPES, pH 7.3. Channel activity in the patches was recorded before and after stimulation with forskolin (20 μM), with and without potentiators. Most experiments were done with a pipette voltage of -60 mV (referred to the bath). Analysis of open-channel probability (P_o), mean channel open time (T_o), and mean channel closed time (T_c) was done using recordings of at least 3 min as described previously (Taddei et al., 2004).

Pharmacokinetics. To increase compound solubility, potentiators were dissolved in a liposomal formulation containing 5 mg of potentiator in 21.3 mg of hydrogenated soy phosphatidylcholine, 5.2 mg of cholesterol, 8.4 mg of distearoylphosphatidylglycerol, and 90 mg of sucrose in 5 ml of PBS. A bolus of potentiator-containing solution (5 mg/kg) was administered intravenously in rats over 1 min (male Sprague-Dawley rats, 360–420 g) by a jugular vein catheter. Arterial blood samples (~ 1 ml) were obtained at predetermined times for liquid chromatography/mass spectrometry (LCMS) analy-

sis. Animal procedures were approved by the University of California, San Francisco, Committee on Animal Research.

LCMS. For analysis of blood samples, collected plasma was chilled on ice, and ice-cold acetonitrile (2:1, v/v) was added to precipitate proteins. Samples were centrifuged at 4°C at 20,000g for 10 min. Supernatants (supplemented with sulforhodamine 101 as internal standard) were analyzed for PG-01 and SF-03 by extraction with C-18 reversed-phase cartridges (1 ml; Alltech Associates, Inc., Deerfield, IL) by standard procedures. The eluate was evaporated, and the residue was reconstituted in 100 μl of mobile phase for HPLC analysis. Reversed-phase HPLC separations were carried out using a C18 column (2.1 \times 100 mm, 3 μm particle size; Supelco, Bellefonte, PA) connected to a solvent delivery system (model 2690; Waters, Milford, MA). The solvent system consisted of a linear gradient from 20% CH_3CN /10 mM KH_2PO_4 , pH 3, to 95% CH_3CN /10 mM KH_2PO_4 , pH 3, over 10 min, followed by 6 min at 95% CH_3CN /20 mM NH_4OAc (0.2 ml/min flow rate). PG-01 and SF-03 were detected at 256 nm, after establishing a linear standard calibration curve in the range of 20 to 5000 nM. The detection limit was 10 nM, and recovery was >90%. Mass spectra were acquired on a mass spectrometer (Alliance HT 2790 + ZQ; Waters) using positive ion detection, scanning from 200 to 800 Da as described previously (Sonawane et al., 2004).

Stability in Hepatic Microsomes. PG-01 and SF-03 (10 μM each) were incubated separately with a phosphate-buffered (100 mM) solution of rat liver microsomes (2 mg of protein/ml; Sigma-Aldrich, St. Louis, MO) containing NADPH (0 or 1 mM) for 60 min at

TABLE 1

Structure-activity relationship analysis of phenylglycine and sulfonamide $\Delta F508$ -CFTR potentiators

Compound	Phenylglycines		Sulfonamides		K_a μM
	R1	R2	R3	R4	
PG-01	4-Isopropyl-Ph	H	Me	Indol-3-actyl	0.30
PG-02	2,3-diH-1,4-benzodioxin-6-yl	H	Me	Ac-NHCH ₂ CO-	0.30
PG-03	4-Isopropyl-Ph	4-OMe	Me	Indol-3-actyl	0.34
PG-04	2,3-diH-1,4-benzodioxin-6-yl	H	Me	Indol-3-acetyl	0.40
PG-05	4-OMe-Ph	H	Me	Indol-3-acetyl	0.70
PG-06	4-Isopropyl-Ph	H	H	Indol-3-acetyl	0.88
PG-07	1,3-benzodioxol-5-yl	4-Me	Me	Indol-3-acetyl	1.33
PG-08	4-OMe-Ph	4-OMe	Me	Indol-3-acetyl	2.13
PG-09	2,3-diH-1,4-benzodioxin-6-yl	4-Me	H	Indol-2-acetyl	2.33
PG-10	2,3-diH-1,4-benzodioxin-6-yl	4-OMe	Me	Indol-3-acetyl	2.71
SF-01	2-OEt-Ph	Me	2-Propenyl		0.30
SF-02	Ph	Et	Cycloheptyl		0.02
SF-03	Ph	Et	2-OMe-Ph-methyl		0.03
SF-04	Ph	Et	Cyclohexyl		0.03
SF-05	OMe-Ph	Me	n-Pentyl		0.06
SF-06	Ph	2-Propenyl	n-Butyl		0.11
SF-07	Ph	2-Propenyl	Cycloheptyl		0.12
SF-08	2,5-di-Me-Ph	Me	2-Pyridinylmethyl		0.13
SF-09	Ph	Et	(3-OMe)-propyl		0.14
SF-10	CH ₂ -CH ₂ -CH(Me)-CH ₂ -CH ₂ -		3(N-(n-butyl)phenylamino)propyl		0.14
SF-11	Ph	2-propenyl	2-Pyridinylmethyl		0.16
SF-12	Ph	2-Propenyl	n-Hexyl		0.19
SF-13	2-Me-Ph	Me	n-Butyl		0.20
SF-14	2-EtO-Ph	Me	(Tetrahydro-2-furanyl)methyl		0.20
SF-15	3-Me-Ph	Me	n-Pentyl		0.22
SF-16	Ph	Et	2-(1-Cyclohexen-1-yl)ethyl		0.24
SF-17	Ph	Et	(Tetrahydro-2-furanyl)methyl		0.24
SF-18	2-Et-Ph	Me	2-Pyridinylmethyl		0.27
SF-19	2,5-di-Me-Ph	Me	3-OMe-propyl		0.29
SF-20	2,6-di-Me-Ph	Me	n-Butyl		0.33

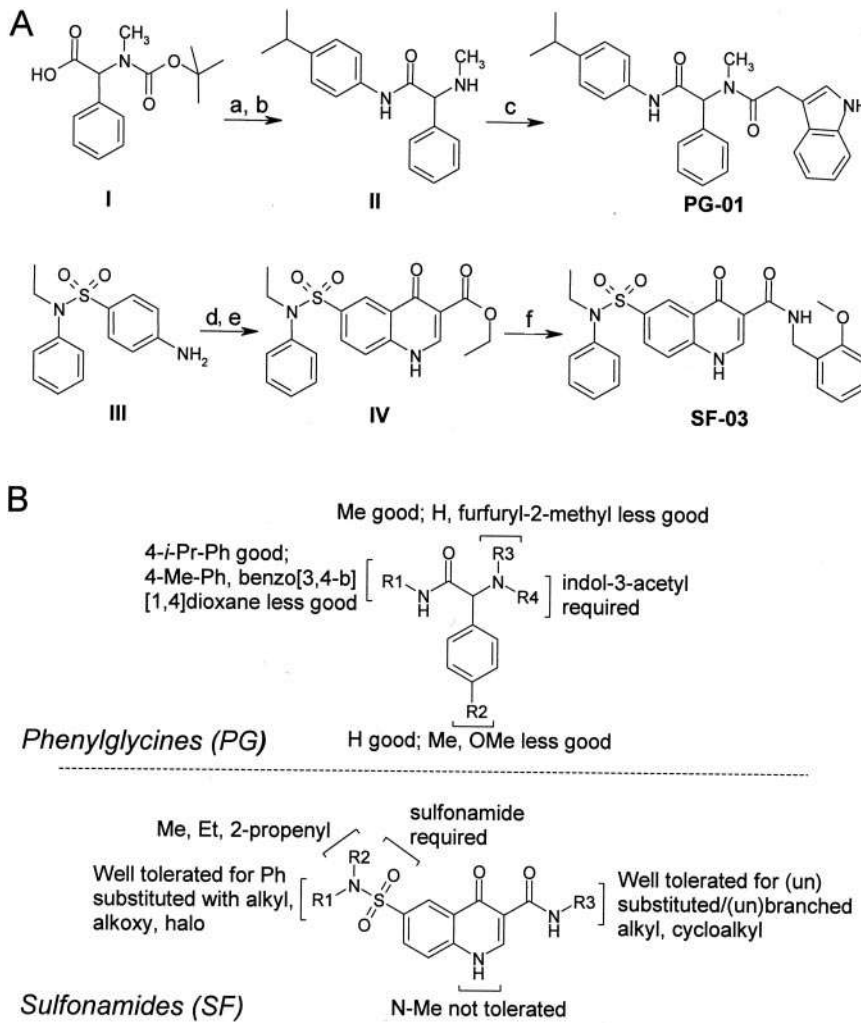


Fig. 2. Synthesis and structure-activity analysis of $\Delta F508$ -CFTR potentiators. A, top, synthesis of phenylglycine PG-01. Conditions: a, *p*-isopropylaniline, EDCI, catalytic amount DMAP, CH_2Cl_2 , 22°C, 2 h, yield 92%; b, trifluoroacetic acid, 22°C, 15 min, 98%; c, indole-3-acetic acid, EDCI, catalytic amount DMAP, CH_2Cl_2 , 22°C, 2 h, 92%. Bottom, synthesis of sulfonamide SF-03. Conditions: d, diethyl ethoxymethylene-malonate, 140°C, 1 h, 95%; e, catalytic amount *p*-chlorobenzoic acid, Ph_2O , 250°C, 45%; f, *o*-methoxybenzyl-amine, neat, 180°C, 35%. B, conclusions from SAR analysis of PG and SF analogs. See Results for explanations.

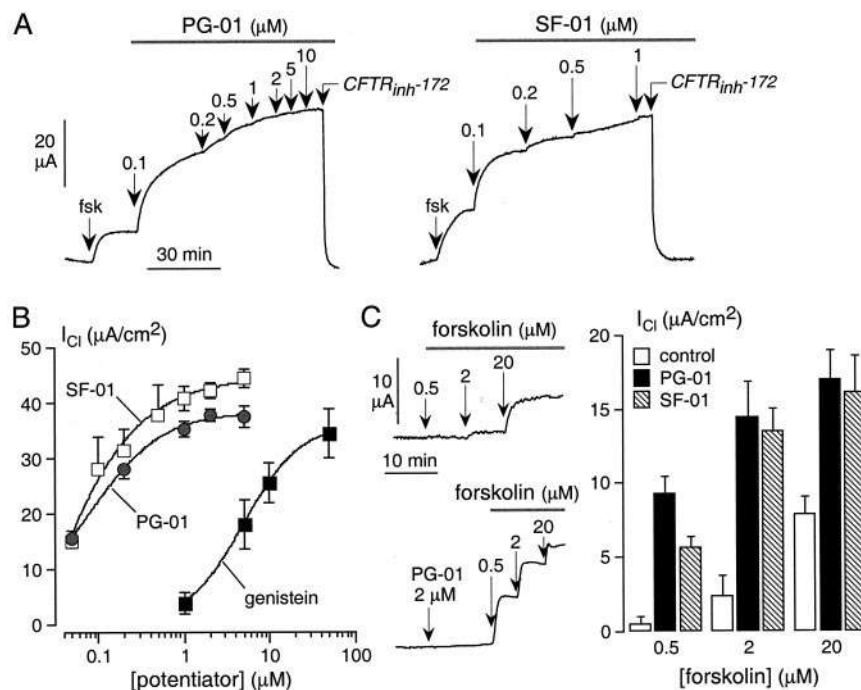


Fig. 3. Activation of cell-membrane Cl^- current by $\Delta F508$ -CFTR potentiators. Apical membrane Cl^- current measured in FRT cells expressing $\Delta F508$ -CFTR after low-temperature rescue. A, representative traces showing currents activated by forskolin (fsk, 20 μM) and $\Delta F508$ -CFTR potentiators PG-01 and SF-01 and inhibited by $\text{CFTR}_{\text{inh}}-172$. B, average dose-responses for potentiators, with genistein data shown for comparison (S.E., $n = 4$). C, representative curves (left) and averaged data (S.E., $n = 4$, right) from experiments showing forskolin dose-response with versus without the prior addition of potentiators (2 μM).

37°C. After 60 min, the mixture was chilled on ice, and 0.5 ml of ice-cold acetonitrile was added to precipitate the proteins for LCMS analysis as described above.

Results

Compounds were screened at a concentration of 2.5 μM (in the presence of forskolin, 20 μM) in ΔF508 -CFTR-expressing FRT cells after low-temperature rescue. CFTR-dependent I^- influx was determined from the time course of decreasing cellular YFP fluorescence. The screening revealed many compounds that at 2.5 μM increased I^- influx as much as the reference compound genistein at 50 μM and substantially greater than forskolin (20 μM) alone (Fig. 1A). Most of these active compounds had PG and SF scaffolds (Fig. 1B); in addition, some active compounds were related structurally to

tetrahydrobenzothiophene potentiators identified previously (Yang et al., 2003). Dose-response analysis of more than 1000 analogs of each chemical class not included in the primary library established a structure-activity relationship database. An example of dose-response analysis of phenylglycine analogs is shown in Fig. 1C, with compounds having a wide range of activating potencies. Dose-response data from the fluorescence assay for the most active compound of each class is shown in Fig. 1D, with data for comparison shown for genistein and the tetrahydrobenzothiophene $\Delta\text{F508}_{\text{act-02}}$. Activation of ΔF508 -CFTR was confirmed for each of the compounds by showing no activity on nontransfected FRT cells and near-complete inhibition of the increased I^- influx by the thiazolidinone CFTR_{inh}-172 (Ma et al., 2002a) at 10 μM (data not shown).

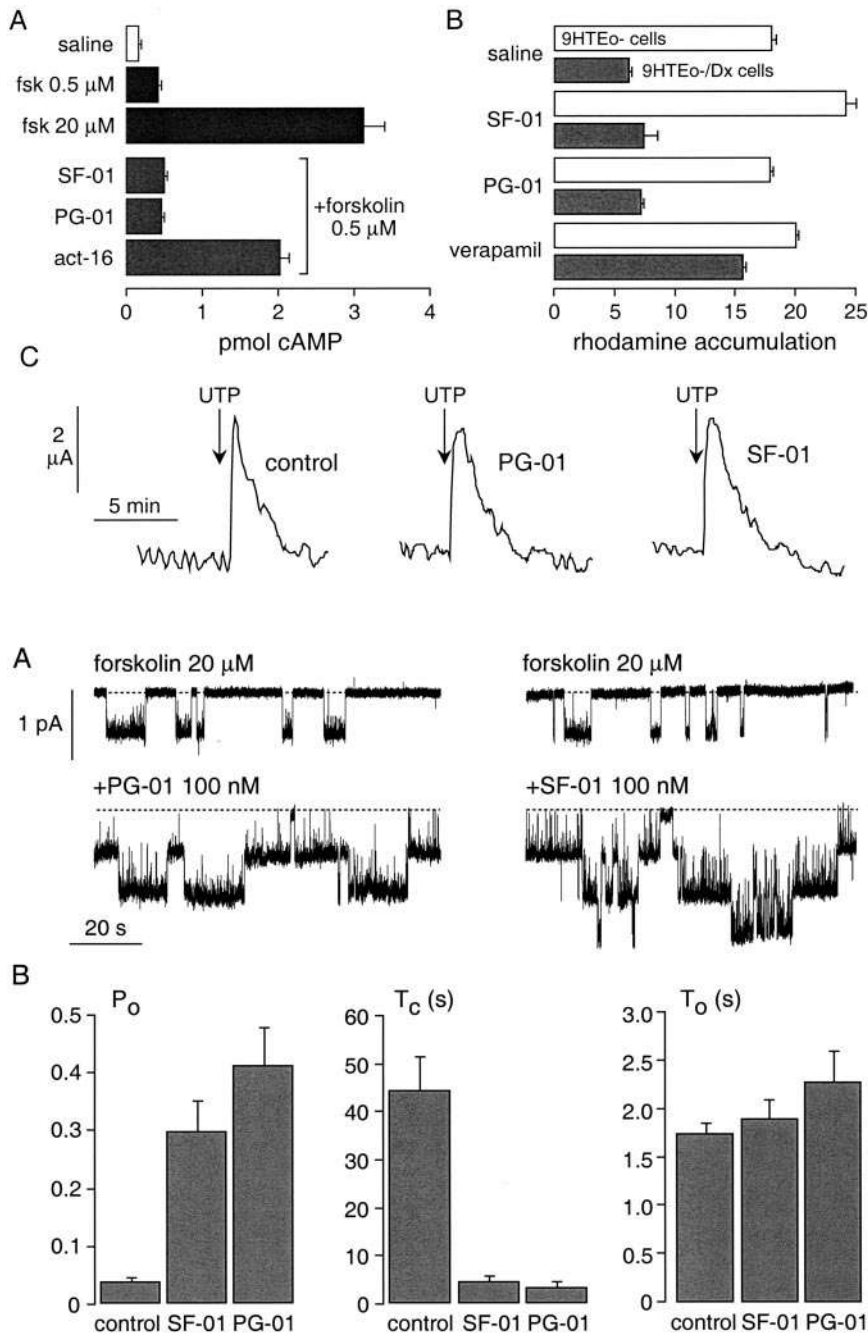


Fig. 4. Specificity of ΔF508 -CFTR potentiators. A, intracellular cAMP concentration after forskolin addition without and with potentiators (2 μM). Effects of PG-01 and SF-01 not significant. B, MDR-1 activity shown as rhodamine-123 accumulation in multidrug-sensitive (9HTEo-) and multidrug-resistant (9HTEo-/Dx) cells. Significant accumulation was found in 9HTEo-/Dx cells for verapamil (100 μM) but not for the potentiators (5 μM). C, activation of Cl^- current by apical UTP in polarized human bronchial epithelia. Pretreatment with ΔF508 -CFTR activators (2 μM) did not affect the maximum current or time course of the UTP response.

Fig. 5. Single-channel patch-clamp analysis of ΔF508 -CFTR channel stimulation by potentiators. A, representative recordings showing activity in multichannel patches. Broken line indicates current with channels closed. Pipette voltage was -60 mV. Downward deflections represent channel openings (Cl^- ions moving from pipette to cell). B, mean P_o , T_c , and T_o in the presence of forskolin alone or in combination with indicated potentiators.

Table 1 summarizes structure-activity relationship (SAR) data for the most potent PG and SF analogs; data for a larger series of less-active analogs is provided as Supplemental Table S1. Fig. 2B summarizes the principal conclusions from SAR analysis. Active PGs contained a disubstituted glycyl amine with amide of aromatic amines. Substitutions at R1 had relatively little effect on compound activity. Most active compounds had as R1 4-isopropylphenyl, with reduced activity for R1 as 2,3-diH-1,4-benzodioxin-6-yl in (PG-02 and -04) or 4-methoxyphenyl (PG-05). Evaluation of R2 substitutions indicated that replacement of hydrogen by methyl (PG-07) or methoxy (PG-10) strongly reduced potency. The R2 phenyl group seemed to be important for activity because its replacement by indol-3-methyl reduced activity. All potent compounds had as R3 a methyl, because its replacement by hydrogen (PG-06) or furfuryl-2-methyl reduced activity. Most active compounds had as R4 an indolyl-3-acetyl, because substitution by thiophene-2-acetyl or diphenyl acetyl resulted in loss of activity. Thus, the greatest $\Delta F508$ -CFTR-activating potency was produced by hydrophobic R1, R2, and R3, with R4 as indolyl-2 (or 3)-acetyl.

SAR analysis of sulfonamides supported the requirement of 3-carboxamide and 6-aminosulfo groups. All active quinolone compounds had as R1 hydrophobic groups such as

alkoxy-, dialkyl-, alkyl-, and halo-substituted phenyl or cyclohexyl (SF-10) groups. The greatest activity was found for R2 as nonpolar alkyl chains (ethyl, methyl, 2-propenyl). The most potent compounds (SF-02 to -04) contained an ethyl group at R2 in combination with phenyl as R1 and an alkyl group as R3. Substitutions at R3 with nonpolar linear or branched alkyl or cycloalkyl groups improved activity. In general, the greatest potency was found with hydrophobic-nonpolar substitutions on sulfonamide and carboxamide moieties.

Apical membrane current in FRT cells was measured to verify the activation of $\Delta F508$ -CFTR Cl^- conductance and to determine compound potency. Apical membrane current was measured after permeabilization of the basolateral membrane with amphotericin B in the presence of a Cl^- gradient (apical, 65 mM Cl^- ; basolateral, 130 mM). After maximal forskolin (20 μM), test compounds were added at increasing concentrations as shown in Fig. 3A, followed by CFTR_{inh}-172. The small effect of forskolin alone demonstrated defective $\Delta F508$ -CFTR gating, because a 10-fold lower concentrations of forskolin fully activated wild-type CFTR in this assay (Galietta et al., 2001c). PG-01 and SF-01 gave $\Delta F508$ -CFTR Cl^- currents with potencies greater than 100 nM (Fig. 3B), and maximal currents comparable with or greater than that

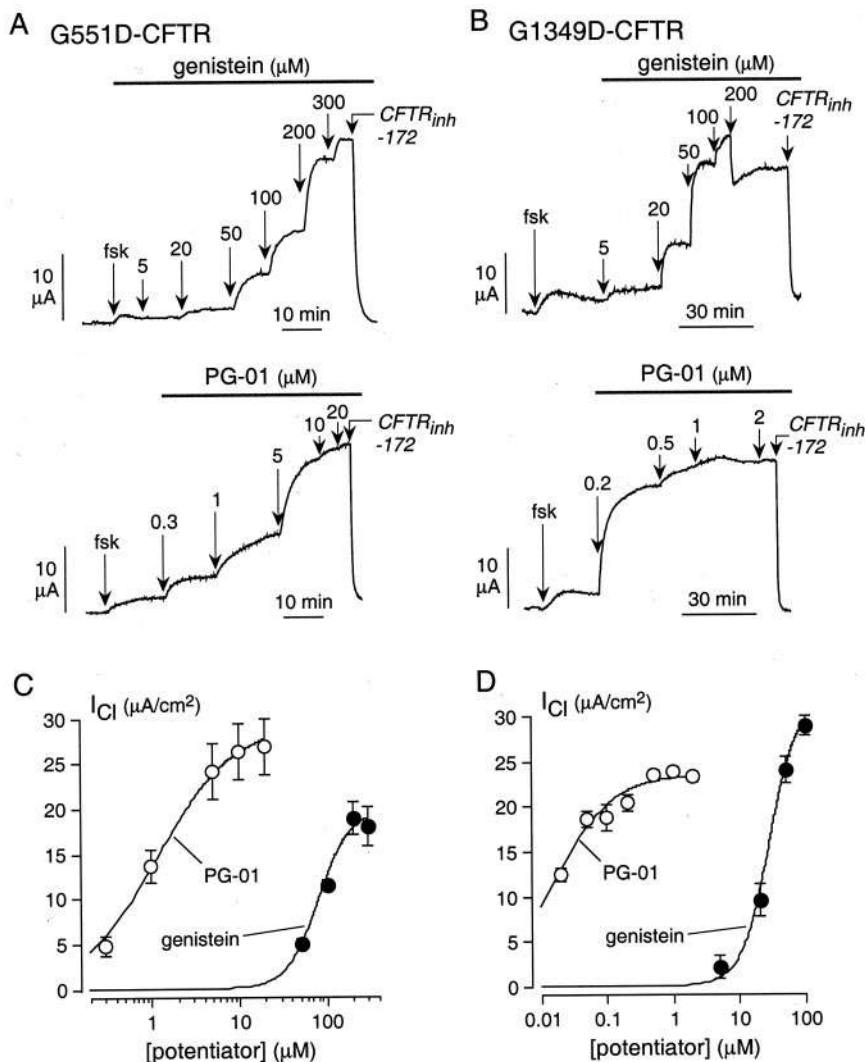


Fig. 6. Activation of G551D- and G1349D-CFTR mutants. A and B, stimulation of apical membrane Cl^- current by genistein (top) and PG-01 (bottom) in G551D- and G1349D-CFTR-expressing FRT cells. Cells were pretreated with forskolin (fsk, 20 μM). C and D, dose-responses for the PG-01 and genistein for activation of G551D- and G1349D-CFTR (S.E., $n = 4$).

produced by 50 μM genistein. It is interesting that these compounds were substantially less effective for the activation of wild-type CFTR. When stimulated with submaximal forskolin, PG-01 and SF-01 produced only a fraction (40–60%) of the current elicited by genistein (data not shown).

Experiments were also done by adding the potentiator first, followed by increasing concentrations of forskolin. Forskolin alone at 0.5 and 2 μM gave little apical membrane current (Fig. 3C, top left). However, PG-01, which did not itself activate ΔF508 -CFTR, produced substantial ΔF508 -CFTR Cl^- current after the addition of 0.5 and 2 μM forskolin (Fig. 3C, bottom left). Data are summarized in Fig. 3C (right), showing significant synergy of these potentiators with forskolin. The correction of ΔF508 -CFTR gating in the presence of relatively low concentrations of cAMP agonists is a desirable property of these compounds (see *Discussion*).

An initial analysis of compound specificity was done. Cells were incubated with potentiators in the presence of a low concentration of forskolin (0.5 μM), lysed, and assayed for cAMP. PG-01 and SF-01 did not increase cAMP above the level induced by forskolin 0.5 μM alone (Fig. 4A), whereas the compound CFTR_{act}-16, an indirect activator of CFTR (Ma et al., 2002b), strongly increased cAMP. MDR-1 activity was assayed by intracellular accumulation of the fluorescent probe rhodamine-123. Two cell lines were used, the parental human tracheal cell line 9HTEo-, and its multidrug-resistant subclone 9HTEo-/Dx that strongly expresses MDR-1 (Rasola et al., 1994). 9HTEo-/Dx cells accumulate much less rhodamine-123 than 9HTEo- cells as a consequence of MDR-1-

mediated dye extrusion. Dye accumulation was increased significantly by the MDR-1 inhibitor verapamil but was not affected by PG-01 or SF-01 (Fig. 4B). Last, effects on the UTP/calcium-activated Cl^- channel were measured from short-circuit current measurements on human bronchial epithelial cells. There was no effect of PG-01 or SF-01 on the magnitude or kinetics of the calcium-activated Cl^- current (Fig. 4C).

The ΔF508 -CFTR-activating mechanism was investigated by cell-attached patch-clamp measurements. The addition of 20 μM forskolin produced low channel activity, with a P_o of 0.04 (Fig. 5A). Channel openings were separated by long-duration closures, in agreement with previous observations on ΔF508 -CFTR (Dalemans et al., 1991; Haws et al., 1996). Although all patches contained more than one channel, simultaneous channel openings were rarely seen because of the low P_o . PG-01 or SF-01 at 100 nM strongly stimulated channel activity with multiple channel openings observed. P_o after activation (0.3–0.4) was comparable with that of wild-type CFTR (Dalemans et al., 1991; Haws et al., 1996) (Fig. 5B). Analysis of gating kinetics indicated that the increase in P_o was caused by a reduction in mean channel closed time (T_c) rather than an increase in T_o (Fig. 5B).

The possibility was evaluated that the PG or SF ΔF508 -CFTR potentiators might correct defective gating in other mutant CFTRs that cause CF in humans. Measurements were done in the “class III” mutants G551D and G1349D, which produce a severe gating defect without impairment in protein trafficking (Gregory et al., 1991). These mutations

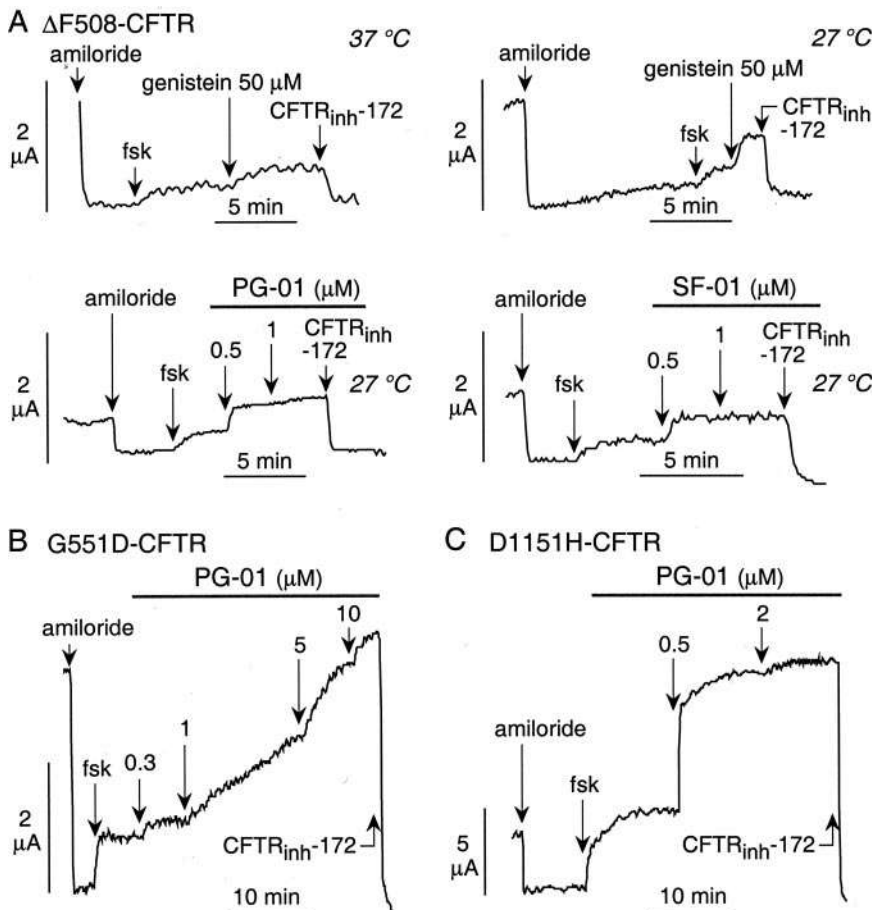


Fig. 7. Stimulation of Cl^- secretion in CF human airway epithelial cells. Transepithelial short-circuit Cl^- current measured in response to genistein and indicated ΔF508 -CFTR potentiators. A, nasal epithelial cells from a ΔF508 homozygous patient. Cells were incubated at 27°C for 24 h where indicated. B, G551D-CFTR cells. C, D1151H-CFTR cells.

affect the glycine residues in NBD1 and NBD2 that are highly conserved in ATP-binding cassette proteins (Hyde et al., 1990; Logan et al., 1994). The G551D and G1349D mutant CFTRs produced little Cl^- current after the addition of maximal forskolin (Fig. 6, A and B). Genistein, a known activator of G551D- and G1349D-CFTR, increased Cl^- current substantially, albeit at high micromolar concentrations (Fig. 6, A and B, top curves). PG-01 produced large currents in both G551D- and G1349D-CFTR-expressing cells as shown in Fig. 6, A and B (bottom curves) and summarized in Fig. 6, C and D. The currents were sensitive to CFTR_{inh}-172 and were not seen in nontransfected cells. In contrast, PG-01, SF-01, and the benzothienopyridine $\Delta F508_{\text{act}}$ -02 did not increase Cl^- currents in G551D- and G1349D-CFTR-expressing cells (data not shown).

The ability of PG-01 and SF-01 to correct defective CFTR channel gating in CF human airway epithelial cells was tested (Fig. 7). Human nasal epithelial cells from $\Delta F508$ homozygote subjects were cultured as polarized monolayers on permeable supports for transepithelial short-circuit current measurement. After blocking the epithelial Na^+ channel with amiloride, forskolin (20 μM) was applied, followed by genistein, PG-01, or SF-01. CFTR_{inh}-172 was applied at the end of each study to determine total CFTR-dependent current. Cells maintained at 37°C had little CFTR current, in agreement with the expected intracellular retention of $\Delta F508$ -CFTR. Low-temperature rescue by incubation at 27°C for 20 to 24 h produced greater $\Delta F508$ -

CFTR current, with significant activation by PG-01 and SF-01 at nanomolar concentrations (Fig. 7A). Stimulation by forskolin plus PG-01 or SF-01 was blocked by CFTR_{inh}-172. Genistein was comparably effective but at much higher concentrations. Primary cell cultures from subjects carrying CFTR mutations causing pure gating defects were also tested. For these studies, cells were cultured at 37°C. Nasal epithelial cells from a subject with the G551D mutation (Zegar-Moran et al., 2002) showed a large response to PG-01 after forskolin stimulation (Fig. 7B). Cells were also tested from a subject having D1152H and $\Delta F508$ CFTR mutations, with the former mutation affecting the second nucleotide-binding domain and causing a decrease in channel activity (Vankeerberghen et al., 1998). The D1152H/ $\Delta F508$ cells maintained at 37°C showed large CFTR currents in response to PG-01 (Fig. 7C).

To predict hepatic clearance of PG-01 and SF-03, in vitro incubations were done with rat hepatic microsomes for 1 h at 37°C in the absence (control) and presence of NADPH followed by LCMS analysis. SF-03 was chosen for these studies as the most potent of the SF compounds. Figure 8A (top, left and right) shows representative HPLC chromatograms, with PG-01 eluting at 7.85 min and its two major metabolites (M1 and M2) eluting at 7.16 and 6.88 min. Mass spectrometry identified the original compound, and M1 and M2 with m/z 456 ($\sim\text{PG-01} + \text{OH}$; $[\text{M} + 1]^+$) and 472 ($\sim\text{PG-01} + 2\text{OH}$; $[\text{M} + 1]^+$), respectively (Fig. 8A, top, middle). A minor metabolite was also detected at 7.43 min with m/z 428. Approximately

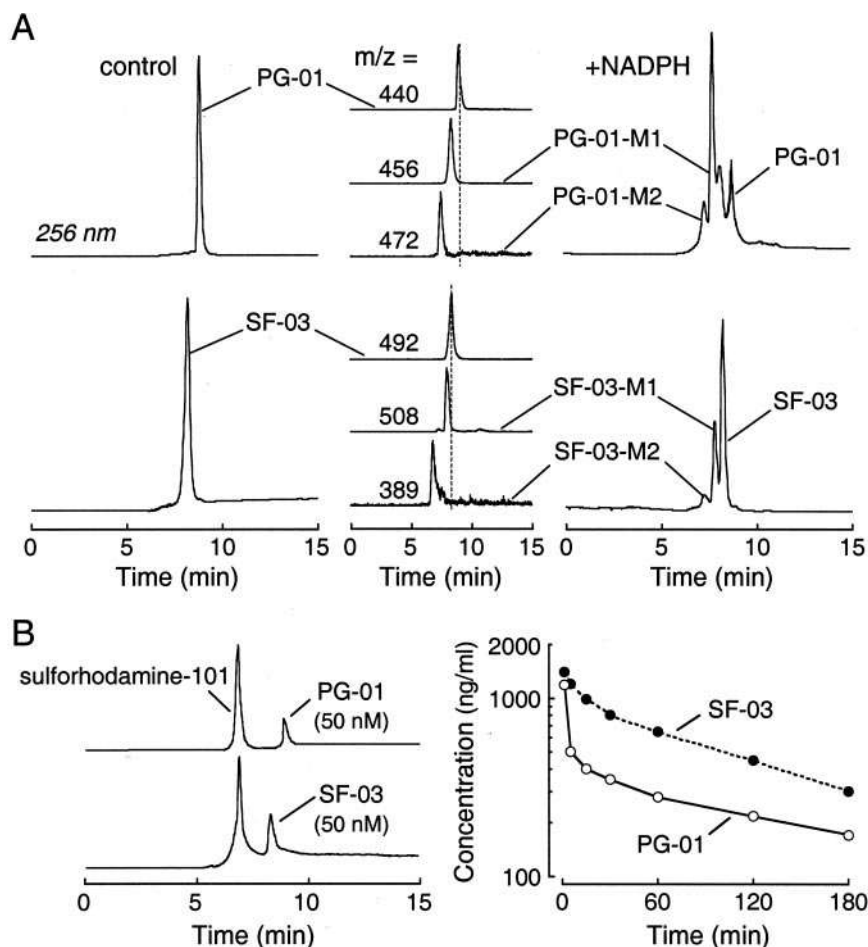


Fig. 8. Liquid chromatography/mass spectrometry analysis of microsomal metabolites of PG-01 and SF-03, and rat pharmacokinetics. A, microsomes were incubated with PG-01 or SF-03 (each 10 μM) in the absence (control) or presence of NADPH for 1 h at 37°C, and processed as described under *Materials and Methods*. HPLC chromatograms at 256 nm for control (left) and NADPH (right) samples, and corresponding ion current chromatograms for positive ion electrospray mass spectrometry for indicated m/z (middle). M1, metabolite 1; M2, metabolite 2. B, pharmacokinetic analysis. Left, HPLC chromatogram of PG-01 and SF-03 demonstrating assay sensitivity to greater than 50 nM. Right, pharmacokinetics of PG-01 (\circ) and SF-03 (\bullet) after 5 mg/kg intravenous bolus injection (mean \pm S.E., $n = 3-4$ rats).

90% of the PG-01 was metabolized after incubation with microsomes for 1 h in the presence of NADPH, and nonmetabolized PG-01 was not detectable after 2 h (data not shown). Figure 8A (bottom, left and right) shows the HPLC profile for SF-03 and its two major metabolites eluting at 7.44 min and 7.16/6.77 min, respectively, with corresponding molecular ion peaks (Fig. 8A, bottom, middle) at m/z 492 (SF-03, $[M + 1]^+$), 508 (\sim SF-03+OH, $[M + 1]^+$) and 389. SF-03 was \sim 35% degraded after a 1-h incubation with liver microsomes in the presence of NADPH.

Pharmacokinetic analysis of PG-01 and SF-03 in rats was done by serial measurements of plasma concentrations after single bolus infusions (5 mg/kg). Figure 8B (left) shows HPLC chromatograms for PG-01 and SF-03 (each at 50 nM added to control plasma and supplemented with sulforhodamine 101 as internal standard), demonstrating the sensitivity of the assay. PG-01 pharmacokinetics fitted a two-compartment model with half-times of <5 min and 130 min with volume of distribution ~ 4 L, whereas SF-03 clearance had elimination half-times of ~ 7 and 110 min with volume of distribution ~ 2 L (Fig. 8B, right).

Discussion

The purpose of this study was to identify new classes of drug-like compounds that strongly activate CF-causing mutant CFTRs. Our strategy was to carry out high-throughput screening for $\Delta F508$ -CFTR potentiators using a collection of 50,000 diverse, drug-like small molecules. The screening yielded two novel classes of $\Delta F508$ -CFTR potentiators having phenylglycine and sulfonamide scaffolds. Several rounds of optimization involving testing of analogs of each compound class produced $\Delta F508$ -CFTR potentiators that fully activated $\Delta F508$ -CFTR with potencies greater than 100 nM. Many active phenylglycine and sulfonamide analogs of widely differing activities were identified, which is an important prerequisite for the development of these compounds as drugs to treat CF. Analysis of phenylglycine properties revealed a number of favorable properties, including the ability to correct defective channel gating in several different CFTR mutants and synergy with cAMP agonists. The phenylglycine PG-01 was metabolized rapidly in hepatic microsomes, suggesting the possibility of aerosol delivery for CF therapy in which any absorbed compound would be inactivated rapidly by hepatic metabolism. The sulfonamides were relatively stable metabolically and did not correct defective gating in non- $\Delta F508$ CFTR mutants, although they did show synergy with cAMP agonists.

Measurement of transepithelial chloride current in FRT cells confirmed the correction of defective $\Delta F508$ -CFTR gating by the phenylglycine and sulfonamide compounds. In one protocol, cells were stimulated with maximal forskolin, followed by increasing concentrations of test compounds. Total current activated by forskolin plus potentiators was blocked by CFTR_{inh}-172. In a different protocol, a dose-response to forskolin was done with versus without prior potentiator addition. Little response to forskolin was seen in the absence of potentiator, and only at high forskolin concentrations. The addition of the potentiator first, which did not itself activate $\Delta F508$ -CFTR, restored substantial sensitivity to forskolin. Measurements of cellular cAMP concentrations indicated that the apparent synergy of the potentiators with forskolin

is not caused by cAMP elevation. We propose a direct interaction between the phenylglycine and sulfonamide potentiators with $\Delta F508$ -CFTR. The lack of effect of these compounds in the absence of cAMP-elevating agents and the apparent synergy with cAMP-elevating agents are favorable properties in that near-native CFTR regulation is recapitulated.

Cell-attached patch-clamp experiments were carried out to investigate the mechanism of channel activation. In the presence of forskolin alone, $\Delta F508$ -CFTR produced bursts of channel openings separated by long closures lasting for several seconds, resulting in reduced open-channel probability. The potentiators strongly increased channel activity, remarkably reducing the time spent in the closed state. The resulting open-channel probability was comparable with that of wild-type CFTR.

The phenylglycines corrected defective gating in a number of CF-causing CFTR mutants including $\Delta F508$, G551D, G1349D, and D1152H. G551D and G1349D affect critical glycine residues in nucleotide binding domains 1 and 2 of CFTR, respectively (Hyde et al., 1990), producing a severe gating defect (Gregory et al., 1991; Logan et al., 1994; Derand et al., 2002; Zegarra-Moran et al., 2002). Forskolin alone produced little activation of these mutant CFTRs even at high concentrations, whereas PG-01 after forskolin produced a >10 -fold elevation in current. The apparent K_d for PG-01 for G551D-CFTR activation was ~ 1 μ M, approximately 100-fold better than that of genistein. The potency for activation G1349D-CFTR by PG-01 was even better at ~ 40 nM. In contrast to $\Delta F508$, other cystic fibrosis mutations, of which more than 1000 have been identified, have a relatively very low frequency. The fraction of CF mutations that cause a pure gating defect (class III mutants) is unknown but is likely to be substantial. The phenylglycines may be useful in monodrug therapy for many of these mutations. Further studies are warranted to establish the molecular mechanism by which a small molecule is able to correct defective channel gating in quite different CFTR mutants.

Transepithelial current measurements on primary cultures of human airway epithelia indicated that the phenylglycine and sulfonamide potentiators identified here are also effective in a native epithelium. This finding is not unexpected because these compounds probably bind to mutant CFTRs directly, and so their activity should be cell-context-independent. The best phenylglycine was also effective on cells cultured from subjects with CF having G551D and D1152H CFTR mutations, supporting the possible use of this class of compounds for monotherapy of CF caused by some mutations. For treatment of CF caused by the $\Delta F508$ -CFTR mutation, the potentiators would probably need to be combined with compounds that correct defective $\Delta F508$ -CFTR cellular processing.

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(54) Title: COMPOUNDS, COMPOSITIONS AND METHODS COMPRISING PYRIDAZINE SULFONAMIDE DERIVATIVES

(57) Abstract: The present invention relates to compositions and methods for treating a disease in an animal, which disease is responsive to inhibiting of functional cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide by administering to a mammal in need thereof an effective amount of a compound defined herein (including those compounds set forth in Tables 1-3 or encompassed by formula I-III) or compositions thereof, thereby treating the disease. The present invention particularly, relates to a method of treating diarrhea and polycystic kidney disease.



WO 2010/123822 A1

**COMPOUNDS, COMPOSITIONS AND METHODS COMPRISING
PYRIDAZINE SULFONAMIDE DERIVATIVES**

CROSS REFERENCE TO RELATED APPLICATION

5 [0001] This application claims benefit under 35 U.S.C. §119(e) of U.S. Provisional Application 61/171,048, filed April 20, 2009, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

10 [0002] This application and invention disclose pyridazine sulfonamide-containing compounds that inhibit the transport of ions (*e.g.*, chloride ions) across cell membranes expressing the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CFTR inhibitory compounds and derivatives thereof, as well as compositions, pharmaceutical formulations and methods of use are described in more detail below.

BACKGROUND

15 [0003] Diarrhea is commonly caused by infection by a variety of bacteria, parasites and viruses and is a fundamental threat to regions lacking potable water. Preventing exposure to the pathogens responsible for diarrhea is the only way to avert infection. Unfortunately, this requires massive improvement in both sanitation and nutritional status in developing countries, which is unlikely to occur in the short term. Thus, it is a continuing threat to the
20 third world and especially the health of children who may lack a robust immune response. Second only to respiratory infection, diarrheal disease is responsible for approximately two million deaths in children under five years of age annually. Many who do survive have lasting health problems due to the effects of recurrent infections and malnutrition. Diarrheal diseases also are the major cause of childhood hospitalization, primarily for dehydration.
25 Each year in developing countries, roughly four billion episodes of acute diarrhea, or approximately 3.2 episodes per child, occur among children under five years of age. See, in general, Diarrheal Diseases Fact Sheet, available at www.oneworldhealth.org.

[0004] Diarrheal episodes can be either acute or persistent (lasting two weeks or more). Of all childhood infectious diseases, diarrheal diseases are thought to have the greatest effect
30 on growth, by reducing appetite, altering feeding patterns, and decreasing absorption of

nutrients. The number of diarrheal episodes in the first two years of life has been shown not only to affect growth but also fitness, cognitive function, and school performance.

[0005] The primary cause of death from diarrhea is dehydration. As dehydration worsens, symptoms progress from thirst, restlessness, decreased skin turgor and sunken eyes to
5 diminished consciousness, rapid and feeble pulse and low or undetectable blood pressure. Diarrhea also often arises as a result of coinfection with other diseases such as malaria and HIV and is frequently a comorbidity factor associated with deaths due to these diseases.

[0006] It is well established that the cystic fibrosis transmembrane conductance regulator (CFTR) protein plays a pivotal role in enterotoxin-mediated secretory diarrheal disease and
10 dehydration which occurs as a consequence of body fluid loss following electrolyte transport across the epithelial cells lining the gastrointestinal tract. Kunzelmann and Mall, (2002) *Physiological Rev.* **82**(1):245-289. CFTR is a 1480 amino acid protein that is a member of the ATP binding cassette (ABC) transporter family. The CFTR cAMP-activated Cl⁻ channel is expressed primarily in the apical or luminal surface of epithelial cells in
15 mammalian intestine, lungs, proximal tubules (and cortex and medulla) of kidney, pancreas, testes, sweat glands and cardiac tissue where it functions as the principal pathway for secretion of Cl⁻/HCO₃⁻ and Na⁺/H⁺. See Field *et al.* (1974) *N. Engl. J. Med.* **71**:3299-3303 and Field *et al.* (1989) *N. Eng. J. Med.* **321**:879-883.

[0007] In secretory diarrhea, intestinal colonization by pathogenic microorganisms alters
20 ion transport, disrupts tight cell junctions and activates an inflammatory response. Enterotoxins produced by Enterotoxigenic *Escherichia coli* (ETEC) and *Vibrio cholerae* bind to receptors on the luminal surface of enterocytes and generate intracellular second messengers that lead to upregulation of CFTR and secretion of negatively charged ions (e.g. chloride) across the intestinal epithelia which creates the driving force for sodium and water
25 secretion. Kunzelmann (2002) *supra*. Luminal CFTR therefore plays the central role in secretory diarrhea and the excessive loss of water which leads to severe dehydration and rapid progression to death if untreated. Blocking ion transport across luminal CFTR channels has been proposed as one way to treat secretory diarrhea and other disease etiologically related to ion transport across CFTR channels.

[0008] Mutations in CFTR protein, *e.g.*, $\Delta F508$, are responsible for cystic fibrosis (CF), one of the most common serious inherited diseases amongst Caucasians, affecting approximately 1 in 2,500 individuals. Pedemonte *et al.* (2005) *J. Clin. Invest.* **115**(9):2564-2571. In the United States and in the majority of European countries, the incidence of carriers of the CF gene is 1 in 20 to 1 in 30. CF can affect many organs including sweat glands (high sweat electrolyte with depletion in a hot environment), intestinal glands (meconium ileus), biliary tree (biliary cirrhosis), pancreas (CF patients can be pancreatic insufficient and may require enzyme supplements in the diet) and bronchial glands (chronic bronchopulmonary infection with emphysema). Hormones, such as a β -adrenergic agonist, or a toxin, such as cholera toxin, lead to an increase in cAMP, activation of cAMP-dependent protein kinase, and phosphorylation of the CFTR Cl^- channel, which causes the channel to open. An increase in cell Ca^{2+} can also activate different apical membrane channels. Phosphorylation by protein kinase C can either open or shut Cl^- channels in the apical membrane.

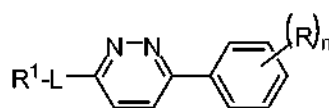
[0009] The transport of fluids mediated by CFTR also has been linked to Polycystic Kidney Disease (PKD). Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common genetic renal disorder occurring in 1:1000 individuals and is characterized by focal cyst formation in all tubular segments. Friedman, J. Cystic Diseases of the Kidney, in PRINCIPLES AND PRACTICE OF MEDICAL GENETICS (A. Emery and D. Rimoin, Eds.) pp. 1002-1010, Churchill Livingston, Edinburgh, U.K. (1983); Striker & Striker (1986) *Am. J. Nephrol.* **6**:161-164. Extrarenal manifestations include hepatic and pancreatic cysts as well as cardiovascular complications. Gabow & Grantham (1997) Polycystic Kidney Disease, in DISEASES OF THE KIDNEY (R. Schrier & C. Gottschalk, Eds.), pp. 521-560, Little Brown, Boston; Welling & Grantham (1996) Cystic Diseases of the Kidney, in RENAL PATHOLOGY (C. Tisch & B. Brenner, Eds.) pp:1828-1863, Lippincott, Philadelphia. Studies suggest that increased cAMP-mediated chloride secretion provides the electrochemical driving force, which mediates fluid secretion in cystic epithelia. Nakanishi *et al.* (2001) *J. Am. Soc. Nephrol.* **12**:719-725. PKD is a leading cause of end-stage renal failure and a common indication for dialysis or renal transplantation. PKD may arise sporadically as a developmental abnormality or may be acquired in adult life, but most forms are hereditary. Among the acquired forms, simple

cysts can develop in kidney as a consequence of aging, dialysis, drugs and hormones. Rapaport (2007) QJM **100**:1-9 and Wilson (2004) N. Eng. J. Med. **350**:151-164.

[0010] CFTR inhibitors have been discovered, although they have a weak potency and lack CFTR specificity. The oral hypoglycemic agent glibenclamide inhibits CFTR Cl⁻ conductance from the intracellular side by an open channel blocking mechanism (Sheppard & Robinson (1997) J. Physiol. **503**:333-346; Zhou *et al.* (2002) J. Gen. Physiol. **120**:647-662) at high micromolar concentrations where it affects Cl⁻ and other cation channels. Rabe *et al.* (1995) Br. J. Pharmacol. **110**:1280-1281 and Schultz *et al.* (1999) Physiol. Rev. **79**:S109-S144. Other non-selective anion transport inhibitors including diphenylamine-2-carboxylate (DPC), 5-nitro-2(3-phenylpropyl-amino)benzoate (NPPB), flufenamic acid and niflumic acid also inhibit CFTR by occluding the pore at an intracellular site. Dawson *et al.* (1999) Physiol. Rev. **79**:S47-S75; McCarty (2000) J. Exp. Biol. **203**:1947-1962, Cai *et al.* (2004) J. Cyst. Fibrosis **3**:141-147. Hence, high-affinity CFTR inhibitors can have clinical applications in the therapy of secretory diarrheas, cystic kidney disease, and other associated disorder reported to be mediated by functional CFTR.

SUMMARY OF THE INVENTION

[0011] This invention is directed to one or more of compounds, compositions and methods which are useful in treating diarrhea. In one embodiment, this invention provides a compound of formula I:



I

wherein

n is 1, 2, 3, 4, or 5;

L is a bond or a linker of 1 to 6 linear or branched covalently linked atoms;

R¹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted

cycloalkenyloxy, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, aryloxy and substituted aryloxy;

or R¹ and L are taken together with the atom to which they are bonded to form a heterocycle or substituted heterocycle; and

5 each R are independently selected from the group consisting of hydrogen, hydroxyl, alkyl, substituted alkyl, halo, amino, sulfonylamino, aminocarbonyl, alkoxy and substituted alkoxy, provided that at least one R is sulfonylamino or aminocarbonyl;

or a pharmaceutically acceptable salt, isomer, or tautomer thereof;

10 wherein said compound exhibits at least one of the following:

a) an IC₅₀ of less than 30 μM in the T84 assay;

b) a greater than 30% inhibition at 20 μM in the FRT assay; or

c) a greater than 35% inhibition at 50 μM in a T84 assay, provided that the compound does not have an IC₅₀ greater than 30 μM.

15 [0012] In one embodiment, the compounds of formula I exhibit a greater than 30% inhibition at 20 μM in the FRT assay described herein.

[0013] In another embodiment, the compounds of formula I exhibit an IC₅₀ of less than 30 μM when tested in the T84 assay described herein. In an alternative embodiment, the compounds of formula I exhibit at least 35% inhibition at 50 μM when tested in the T84
20 assay described herein, provided that the compound does not have an IC₅₀ greater than 30 μM.

[0014] In another embodiment, this invention provides a composition comprising a therapeutically effective amount of a compound of formula I as defined above.

[0015] In another embodiment, this invention provides a pharmaceutical composition
25 comprising a therapeutically effective amount of a compound as defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) and a pharmaceutically acceptable carrier.

[0016] Another aspect of this invention relates to a method for treating diarrhea in an animal in need thereof by administering to the animal an effective amount of one or more of

the compounds defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) or compositions comprising these compounds, thereby treating diarrhea.

5 [0017] Still another aspect of this invention relates to a method for treating polycystic kidney disease (PKD) in an animal in need thereof, by administering to the animal an effective amount of one or more of the compounds defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) or compositions comprising these compounds, thereby treating PKD.

10 [0018] Another aspect of the present invention relates to a method of treating a disease in an animal, which disease is responsive to the inhibition of functional CFTR protein by administering to an animal in need thereof an effective amount of a compound defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) or compositions comprising these compounds, thereby treating the disease.

15 [0019] Yet another aspect of the present invention relates to a method for inhibiting the transport of a halide ion across a mammalian cell membrane expressing functional CFTR protein comprising contacting the CFTR protein with an effective amount of compound defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) or compositions comprising these compounds, thereby inhibiting the transport of the halide ion by the CFTR protein.

20 **DETAILED DESCRIPTION OF THE INVENTION**

[0020] The invention relates to pyridazine sulfonamide-containing compounds that are CFTR inhibitors. The CFTR inhibitory compounds and derivatives thereof, as well as compositions, pharmaceutical formulations and methods of use, are described in more detail below.

25 [0021] Throughout this application, the various embodiments are only exemplary and should not be construed as descriptions of alternative species. Rather it should be noted that the descriptions of various embodiments provided herein may be of overlapping scope. The embodiments discussed

[0022] Also throughout this disclosure, various publications, patents and published patent specifications are referenced by an identifying citation. The disclosures of these publications, patents and published patent specifications are hereby incorporated by reference into the present disclosure in their entirety to more fully describe the state of the art to which this invention pertains.

A. Definitions

[0023] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, immunology, molecular biology, microbiology, cell biology and recombinant DNA, which are within the skill of the art. See, *e.g.*, Sambrook, Fritsch and Maniatis, MOLECULAR CLONING: A LABORATORY MANUAL, 2nd edition (1989); CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (F. M. Ausubel, *et al.* eds., (1987)); the series METHODS IN ENZYMOLOGY (Academic Press, Inc.); PCR 2: A PRACTICAL APPROACH (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995)), Harlow and Lane, eds. (1988) ANTIBODIES, A LABORATORY MANUAL, and ANIMAL CELL CULTURE (R.I. Freshney, ed. (1987)).

[0024] As used in the specification and claims, the singular form “a,” “an” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes a plurality of cells, including mixtures thereof.

[0025] As used herein, the term “comprising” is intended to mean that the compositions and methods include the recited elements, but not excluding others. “Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination. Thus, a composition consisting essentially of the elements as defined herein would not exclude trace contaminants from the isolation and purification method and pharmaceutically acceptable carriers, such as phosphate buffered saline, preservatives, and the like. “Consisting of” shall mean excluding more than trace elements of other ingredients. Embodiments defined by each of these transition terms are within the scope of this invention.

[0026] All numerical designations, *e.g.*, pH, temperature, time, concentration, and molecular weight, including ranges, are approximations which are varied (+) or (-) by

increments of 0.1. It is to be understood, although not always explicitly stated that all numerical designations are preceded by the term “about.” It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

5 [0027] The terms “polypeptide” and “protein” are synonymously used in their broadest sense to refer to a compound of two or more subunit amino acids, amino acid analogs, or peptidomimetics. The subunits may be linked by peptide bonds. In another embodiment, the subunit may be linked by other bonds, *e.g.*, ester, ether, etc. As used herein the term “amino acid” refers to either natural and/or unnatural or synthetic amino acids, including
10 glycine and both the D or L optical isomers, and amino acid analogs and peptidomimetics. A peptide of three or more amino acids is commonly called an oligopeptide if the peptide chain is short. If the peptide chain is long, the peptide is commonly called a polypeptide or a protein.

[0028] “Hybridization” refers to a reaction in which one or more polynucleotides react to
15 form a complex that is stabilized via hydrogen bonding between the bases of the nucleotide residues. The hydrogen bonding may occur by Watson-Crick base pairing, Hoogsteen binding, or in any other sequence-specific manner. The complex may comprise two strands forming a duplex structure, three or more strands forming a multi-stranded complex, a single self-hybridizing strand, or any combination of these. A hybridization reaction may
20 constitute a step in a more extensive process, such as the initiation of a PCR reaction, or the enzymatic cleavage of a polynucleotide by a ribozyme.

[0029] Hybridization reactions can be performed under conditions of different “stringency.” In general, a low stringency hybridization reaction is carried out at about 40 °C in 10 x SSC or a solution of equivalent ionic strength/temperature. A moderate stringency hybridization
25 is typically performed at about 50 °C in 6 x SSC, and a high stringency hybridization reaction is generally performed at about 60 °C in 1 x SSC.

[0030] When hybridization occurs in an antiparallel configuration between two single-stranded polynucleotides, the reaction is called “annealing” and those polynucleotides are described as “complementary.” A double-stranded polynucleotide can
30 be “complementary” or “homologous” to another polynucleotide, if hybridization can occur

between one of the strands of the first polynucleotide and the second. “Complementarity” or “homology” (the degree that one polynucleotide is complementary with another) is quantifiable in terms of the proportion of bases in opposing strands that are expected to form hydrogen bonding with each other, according to generally accepted base-pairing rules.

5 [0031] A polynucleotide or polynucleotide region (or a polypeptide or polypeptide region) has a certain percentage (for example, 80%, 85%, 90%, or 95%) of “sequence identity” to another sequence when aligned, that percentage of bases (or amino acids) are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those
10 described in CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (F.M. Ausubel *et al.*, eds., 1987) Supplement 30, section 7.7.18, Table 7.7.1. Preferably, default parameters are used for alignment. A preferred alignment program is BLAST, using default parameters. In particular, preferred programs are BLASTN and BLASTP, using the following default parameters: Genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10;
15 Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + SwissProtein + SPupdate + PIR. Details of these programs can be found at the following Internet address: <http://www.ncbi.nlm.nih.gov/cgi-bin/BLAST>.

[0032] A variety of sequence alignment software programs are available in the art.
20 Non-limiting examples of these programs are BLAST family programs including BLASTN, BLASTP, BLASTX, TBLASTN, and TBLASTX (BLAST is available from the worldwide web at ncbi.nlm.nih.gov/BLAST/), FastA, Compare, DotPlot, BestFit, GAP, FrameAlign, ClustalW, and Pileup. These programs are obtained commercially available in a comprehensive package of sequence analysis software such as GCG Inc.’s Wisconsin
25 Package. Other similar analysis and alignment programs can be purchased from various providers such as DNA Star’s MegAlign, or the alignment programs in GeneJockey. Alternatively, sequence analysis and alignment programs can be accessed through the world wide web at sites such as the CMS Molecular Biology Resource at sdsc.edu/ResTools/cmshp.html. Any sequence database that contains DNA or
30 protein sequences corresponding to a gene or a segment thereof can be used for sequence analysis. Commonly employed databases include but are not limited to GenBank, EMBL, DDBJ, PDB, SWISS-PROT, EST, STS, GSS, and HTGS.

[0033] Parameters for determining the extent of homology set forth by one or more of the aforementioned alignment programs are known. They include but are not limited to p value, percent sequence identity and the percent sequence similarity. P value is the probability that the alignment is produced by chance. For a single alignment, the p value can be calculated according to Karlin *et al.* (1990) PNAS **87**:2246. For multiple alignments, the p value can be calculated using a heuristic approach such as the one programmed in BLAST. Percent sequence identity is defined by the ratio of the number of nucleotide or amino acid matches between the query sequence and the known sequence when the two are optimally aligned. The percent sequence similarity is calculated in the same way as percent identity except one scores amino acids that are different but similar as positive when calculating the percent similarity. Thus, conservative changes that occur frequently without altering function, such as a change from one basic amino acid to another or a change from one hydrophobic amino acid to another are scored as if they were identical.

[0034] "Animal" of diagnosis or treatment refers to an animal such as a mammal, or a human, ovine, bovine, feline etc. Non-human animals subject to diagnosis or treatment include, for example, simians, murine, such as, rat, mice, canine, leporid, livestock, sport animals, and pets.

[0035] "Alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms and preferably 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH₃-), ethyl (CH₃CH₂-), n-propyl (CH₃CH₂CH₂-), isopropyl ((CH₃)₂CH-), n-butyl (CH₃CH₂CH₂CH₂-), isobutyl ((CH₃)₂CHCH₂-), sec-butyl ((CH₃)(CH₃CH₂)CH-), t-butyl ((CH₃)₃C-), n-pentyl (CH₃CH₂CH₂CH₂CH₂-), and neopentyl ((CH₃)₃CCH₂-).

[0036] "Alkenyl" refers to straight or branched hydrocarbyl groups having from 2 to 6 carbon atoms and preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1 to 2 sites of vinyl (>C=C<) unsaturation. Such groups are exemplified, for example, by vinyl, allyl, and but-3-en-1-yl. Included within this term are the *cis* and *trans* isomers or mixtures of these isomers.

[0037] "Alkynyl" refers to straight or branched monovalent hydrocarbyl groups having from 2 to 6 carbon atoms and preferably 2 to 3 carbon atoms and having at least 1 and

preferably from 1 to 2 sites of acetylenic ($-C\equiv C-$) unsaturation. Examples of such alkynyl groups include acetylenyl ($-C\equiv CH$), and propargyl ($-CH_2C\equiv CH$).

[0038] "Substituted alkyl" refers to an alkyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H , substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

[0039] "Substituted alkenyl" refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxyl, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H , substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and

substituted alkylthio, wherein said substituents are as defined herein and with the proviso that any hydroxyl or thiol substitution is not attached to a vinyl (unsaturated) carbon atom.

[0040] “Substituted alkynyl” refers to alkynyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO₃H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein and with the proviso that any hydroxyl or thiol substitution is not attached to an acetylenic carbon atom.

[0041] “Alkoxy” refers to the group -O-alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, sec-butoxy, and n-pentoxy.

[0042] “Substituted alkoxy” refers to the group -O-(substituted alkyl) wherein substituted alkyl is defined herein.

[0043] “Acyl” refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl,

heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. Acyl includes the “acetyl” group $\text{CH}_3\text{C(O)-}$.

[0044] “Acylamino” refers to the groups $-\text{NR}^{47}\text{C(O)alkyl}$, $-\text{NR}^{47}\text{C(O)substituted alkyl}$, $-\text{NR}^{47}\text{C(O)cycloalkyl}$, $-\text{NR}^{47}\text{C(O)substituted cycloalkyl}$, $-\text{NR}^{47}\text{C(O)cycloalkenyl}$, $-\text{NR}^{47}\text{C(O)substituted cycloalkenyl}$, $-\text{NR}^{47}\text{C(O)alkenyl}$, $-\text{NR}^{47}\text{C(O)substituted alkenyl}$, $-\text{NR}^{47}\text{C(O)alkynyl}$, $-\text{NR}^{47}\text{C(O)substituted alkynyl}$, $-\text{NR}^{47}\text{C(O)aryl}$, $-\text{NR}^{47}\text{C(O)substituted aryl}$, $-\text{NR}^{47}\text{C(O)heteroaryl}$, $-\text{NR}^{47}\text{C(O)substituted heteroaryl}$, $-\text{NR}^{47}\text{C(O)heterocyclic}$, and $-\text{NR}^{47}\text{C(O)substituted heterocyclic}$ wherein R^{47} is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0045] “Acyloxy” refers to the groups alkyl-C(O)O- , substituted alkyl-C(O)O- , alkenyl-C(O)O- , substituted alkenyl-C(O)O- , alkynyl-C(O)O- , substituted alkynyl-C(O)O- , aryl-C(O)O- , substituted aryl-C(O)O- , cycloalkyl-C(O)O- , substituted cycloalkyl-C(O)O- , $\text{cycloalkenyl-C(O)O-}$, substituted $\text{cycloalkenyl-C(O)O-}$, heteroaryl-C(O)O- , substituted heteroaryl-C(O)O- , $\text{heterocyclic-C(O)O-}$, and substituted $\text{heterocyclic-C(O)O-}$ wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0046] “Amino” refers to the group $-\text{NH}_2$.

[0047] “Substituted amino” refers to the group $-\text{NR}^{48}\text{R}^{49}$ where R^{48} and R^{49} are independently selected from the group consisting of hydrogen, acyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, $-\text{SO}_2\text{-alkyl}$, $-\text{SO}_2\text{-substituted alkyl}$, $-\text{SO}_2\text{-alkenyl}$, $-\text{SO}_2\text{-substituted alkenyl}$, $-\text{SO}_2\text{-cycloalkyl}$, $-\text{SO}_2\text{-substituted cycloalkyl}$, $-\text{SO}_2\text{-cycloalkenyl}$, $-\text{SO}_2\text{-substituted cycloalkenyl}$, $-\text{SO}_2\text{-aryl}$, $-\text{SO}_2\text{-substituted aryl}$, $-\text{SO}_2\text{-heteroaryl}$, $-\text{SO}_2\text{-substituted heteroaryl}$, $-\text{SO}_2\text{-heterocyclic}$, and $-\text{SO}_2\text{-substituted}$

heterocyclic and wherein R⁴⁸ and R⁴⁹ are optionally joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that R⁴⁸ and R⁴⁹ are both not hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. When R⁴⁸ is hydrogen and R⁴⁹ is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When R⁴⁸ and R⁴⁹ are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino. When referring to a monosubstituted amino, it is meant that either R⁴⁸ or R⁴⁹ is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R⁴⁸ nor R⁴⁹ are hydrogen.

[0048] "Aminocarbonyl" refers to the group -C(O)NR⁵⁰R⁵¹ where R⁵⁰ and R⁵¹ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, sulfonyl, and substituted sulfonyl and where R⁵⁰ and R⁵¹ are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0049] "Aminothiocabonyl" refers to the group -C(S)NR⁵⁰R⁵¹ where R⁵⁰ and R⁵¹ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R⁵⁰ and R⁵¹ are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0050] "Aminocarbonylamino" refers to the group $-NR^{47}C(O)NR^{50}R^{51}$ where R^{47} is hydrogen or alkyl and R^{50} and R^{51} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic, and where R^{50} and R^{51} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0051] "Aminothiocabonylamino" refers to the group $-NR^{47}C(S)NR^{50}R^{51}$ where R is hydrogen or alkyl and R^{50} and R^{51} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{50} and R^{51} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0052] "Aminocarbonyloxy" refers to the group $-O-C(O)NR^{50}R^{51}$ where R^{50} and R^{51} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{50} and R^{51} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0053] "Aminosulfonyl" refers to the group $-\text{SO}_2\text{NR}^{50}\text{R}^{51}$ where R^{50} and R^{51} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{50} and R^{51} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0054] "Aminosulfonyloxy" refers to the group $-\text{O}-\text{SO}_2\text{NR}^{50}\text{R}^{51}$ where R^{50} and R^{51} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{50} and R^{51} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0055] "Aminosulfonylamino" refers to the group $-\text{NR}^{47}\text{SO}_2\text{NR}^{50}\text{R}^{51}$ where R^{47} is hydrogen or alkyl and R^{50} and R^{51} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{50} and R^{51} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0056] "Amidino" refers to the group $-C(=NR^{52})NR^{50}R^{51}$ where R^{50} , R^{51} , and R^{52} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{50} and R^{51} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0057] "Aryl" or "Ar" refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl) which condensed rings may or may not be aromatic (*e.g.*, 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7-yl, and the like) provided that the point of attachment is at an aromatic carbon atom. Preferred aryl groups include phenyl and naphthyl.

[0058] "Substituted aryl" refers to aryl groups which are substituted with 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H , substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

[0059] "Aryloxy" refers to the group -O-aryl, where aryl is as defined herein, that includes, by way of example, phenoxy and naphthoxy.

[0060] "Substituted aryloxy" refers to the group -O-(substituted aryl) where substituted aryl is as defined herein.

5 [0061] "Arylthio" refers to the group -S-aryl, where aryl is as defined herein.

[0062] "Substituted arylthio" refers to the group -S-(substituted aryl), where substituted aryl is as defined herein.

[0063] "Carbonyl" refers to the divalent group -C(O)- which is equivalent to -C(=O)-.

[0064] "Carboxyl" or "carboxy" refers to -COOH or salts thereof.

10 [0065] "Carboxyl ester" or "carboxy ester" refers to the groups -C(O)O-alkyl, -C(O)O-substituted alkyl, -C(O)O-alkenyl, -C(O)O-substituted alkenyl, -C(O)O-alkynyl, -C(O)O-substituted alkynyl, -C(O)O-aryl, -C(O)O-substituted aryl, -C(O)O-cycloalkyl, -C(O)O-substituted cycloalkyl, -C(O)O-cycloalkenyl, -C(O)O-substituted cycloalkenyl, -C(O)O-heteroaryl, -C(O)O-substituted heteroaryl, -C(O)O-heterocyclic, and
15 -C(O)O-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0066] "(Carboxyl ester)amino" refers to the group -NR⁴⁷C(O)O-alkyl, -NR⁴⁷C(O)O-substituted alkyl, -NR⁴⁷C(O)O-alkenyl, -NR⁴⁷C(O)O-substituted alkenyl, -NR⁴⁷C(O)O-alkynyl, -NR⁴⁷C(O)O-substituted alkynyl, -NR⁴⁷C(O)O-aryl, -NR⁴⁷C(O)O-substituted aryl, -NR⁴⁷C(O)O-cycloalkyl, -NR⁴⁷C(O)O-substituted cycloalkyl, -NR⁴⁷C(O)O-cycloalkenyl, -NR⁴⁷C(O)O-substituted cycloalkenyl, -NR⁴⁷C(O)O-heteroaryl, -NR⁴⁷C(O)O-substituted heteroaryl, -NR⁴⁷C(O)O-heterocyclic, and
20 -NR⁴⁷C(O)O-substituted heterocyclic wherein R⁴⁷ is alkyl or hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined
25 herein.

[0067] “(Carboxyl ester)oxy” refers to the group -O-C(O)O-alkyl, -O-C(O)O-substituted alkyl, -O-C(O)O-alkenyl, -O-C(O)O-substituted alkenyl, -O-C(O)O-alkynyl, -O-C(O)O-substituted alkynyl, -O-C(O)O-aryl, -O-C(O)O-substituted aryl, -O-C(O)O-cycloalkyl, -O-C(O)O-substituted cycloalkyl, -O-C(O)O-cycloalkenyl, -O-C(O)O-substituted cycloalkenyl, -O-C(O)O-heteroaryl, -O-C(O)O-substituted heteroaryl, -O-C(O)O-heterocyclic, and -O-C(O)O-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0068] “Cyano” refers to the group -CN.

[0069] “Cycloalkyl” refers to cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple cyclic rings including fused, bridged, and spiro ring systems. Examples of suitable cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl.

[0070] “Cycloalkenyl” refers to non-aromatic cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple cyclic rings and having at least one $>C=C<$ ring unsaturation and preferably from 1 to 2 sites of $>C=C<$ ring unsaturation.

[0071] “Substituted cycloalkyl” and “substituted cycloalkenyl” refers to a cycloalkyl or cycloalkenyl group having from 1 to 5 or preferably 1 to 3 substituents selected from the group consisting of oxo, thioxo, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted

heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO₃H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio,
 5 wherein said substituents are as defined herein.

[0072] "Cycloalkyloxy" refers to -O-cycloalkyl.

[0073] "Substituted cycloalkyloxy refers to -O-(substituted cycloalkyl).

[0074] "Cycloalkylthio" refers to -S-cycloalkyl.

[0075] "Substituted cycloalkylthio" refers to -S-(substituted cycloalkyl).

10 [0076] "Cycloalkenyloxy" refers to -O-cycloalkenyl.

[0077] "Substituted cycloalkenyloxy" refers to -O-(substituted cycloalkenyl).

[0078] "Cycloalkenylthio" refers to -S-cycloalkenyl.

[0079] "Substituted cycloalkenylthio" refers to -S-(substituted cycloalkenyl).

[0080] "Guanidino" refers to the group -NHC(=NH)NH₂.

15 [0081] "Substituted guanidino" refers to -NR⁵³C(=NR⁵³)N(R⁵³)₂ where each R⁵³ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclic, and substituted heterocyclic and two R⁵³ groups attached to a common guanidino nitrogen atom are optionally joined together with the nitrogen bound thereto to
 20 form a heterocyclic or substituted heterocyclic group, provided that at least one R⁵³ is not hydrogen, and wherein said substituents are as defined herein.

[0082] "Halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

[0083] "Hydroxy" or "hydroxyl" refers to the group -OH.

[0084] "Heteroaryl" refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4
 25 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the

ring. Such heteroaryl groups can have a single ring (*e.g.*, pyridinyl or furyl) or multiple condensed rings (*e.g.*, indolizinyl or benzothienyl) wherein the condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for the N-oxide (N→O), sulfinyl, or sulfonyl moieties. Preferred heteroaryls include pyridinyl, pyrrolyl, indolyl, thiophenyl, and furanyl.

[0085] “Substituted heteroaryl” refers to heteroaryl groups that are substituted with from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of the same group of substituents defined for substituted aryl.

[0086] “Heteroaryloxy” refers to -O-heteroaryl.

[0087] “Substituted heteroaryloxy” refers to the group -O-(substituted heteroaryl).

[0088] “Heteroarylthio” refers to the group -S-heteroaryl.

[0089] “Substituted heteroarylthio” refers to the group -S-(substituted heteroaryl).

[0090] “Heterocycle” or “heterocyclic” or “heterocycloalkyl” or “heterocyclyl” refers to a saturated or partially saturated, but not aromatic, group having from 1 to 10 ring carbon atoms and from 1 to 4 ring heteroatoms selected from the group consisting of nitrogen, sulfur, or oxygen. Heterocycle encompasses single ring or multiple condensed rings, including fused bridged and spiro ring systems. In fused ring systems, one or more the rings can be cycloalkyl, aryl, or heteroaryl provided that the point of attachment is through a non-aromatic ring. In one embodiment, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for the N-oxide, sulfinyl, or sulfonyl moieties.

[0091] “Substituted heterocyclic” or “substituted heterocycloalkyl” or “substituted heterocyclyl” refers to heterocyclyl groups that are substituted with from 1 to 5 or preferably 1 to 3 of the same substituents as defined for substituted cycloalkyl.

[0092] “Heterocyclyloxy” refers to the group -O-heterocyclyl.

[0093] “Substituted heterocyclyloxy” refers to the group -O-(substituted heterocyclyl).

[0094] "Heterocyclylthio" refers to the group -S-heterocycyl.

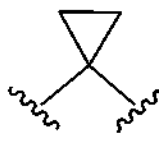
[0095] "Substituted heterocyclylthio" refers to the group -S-(substituted heterocycyl).

[0096] Examples of heterocycle and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, oxadiazole, pyridine, pyrazine, pyrimidine, isoxazole, indolizine, isindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), 1,1-dioxothiomorpholinyl, piperidinyl, pyrrolidine, and tetrahydrofuranyl.

[0097] "Nitro" refers to the group -NO₂.

[0098] "Oxo" refers to the atom (=O) or (-O⁻).

[0099] "Spirocycloalkyl" and "spiro ring systems" refers to divalent cyclic groups from 3 to 10 carbon atoms having a cycloalkyl or heterocycloalkyl ring with a spiro union (the union formed by a single atom which is the only common member of the rings) as exemplified by the following structure:



[0100] "Sulfonyl" refers to the divalent group -S(O)₂-.

[0101] "Substituted sulfonyl" refers to the group -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-cycloalkenyl, -SO₂-substituted cycloalkenyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic, -SO₂-amino, and -SO₂-substituted amino, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl,

cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. Substituted sulfonyl includes groups such as methyl-SO₂-, phenyl-SO₂-, and 4-methylphenyl-SO₂-.

[0102] “Substituted sulfonyloxy” refers to the group -OSO₂-alkyl, -OSO₂-substituted alkyl, -OSO₂-alkenyl, -OSO₂-substituted alkenyl, -OSO₂-cycloalkyl, -OSO₂-substituted cycloalkyl, -OSO₂-cycloalkenyl, -OSO₂-substituted cycloalkenyl, -OSO₂-aryl, -OSO₂-substituted aryl, -OSO₂-heteroaryl, -OSO₂-substituted heteroaryl, -OSO₂-heterocyclic, -OSO₂-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0103] “Sulfonylamino” refers to the group -NR⁵⁰SO₂R⁵¹, wherein R⁵⁰ and R⁵¹ independently are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, amino, and substituted amino, and where R⁵⁰ and R⁵¹ are optionally joined together with the atoms bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0104] “Thioacyl” refers to the groups H-C(S)-, alkyl-C(S)-, substituted alkyl-C(S)-, alkenyl-C(S)-, substituted alkenyl-C(S)-, alkynyl-C(S)-, substituted alkynyl-C(S)-, cycloalkyl-C(S)-, substituted cycloalkyl-C(S)-, cycloalkenyl-C(S)-, substituted cycloalkenyl-C(S)-, aryl-C(S)-, substituted aryl-C(S)-, heteroaryl-C(S)-, substituted heteroaryl-C(S)-, heterocyclic-C(S)-, and substituted heterocyclic-C(S)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0105] "Thiol" refers to the group -SH.

[0106] "Thiocarbonyl" refers to the divalent group -C(S)- which is equivalent to -C(=S)-.

[0107] "Thioxo" refers to the atom (=S).

[0108] "Alkylthio" refers to the group -S-alkyl wherein alkyl is as defined herein.

5 [0109] "Substituted alkylthio" refers to the group -S-(substituted alkyl) wherein substituted alkyl is as defined herein.

[0110] "Isomer" refers to tautomerism, conformational isomerism, geometric isomerism, stereoisomerism and/or optical isomerism. For example, the compounds and prodrugs of the invention may include one or more chiral centers and/or double bonds and as a
10 consequence may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers, diastereomers, and mixtures thereof, such as racemic mixtures. As another example, the compounds and prodrugs of the invention may exist in several tautomeric forms, including the enol form, the keto form, and mixtures thereof.

[0111] "Stereoisomer" or "stereoisomers" refer to compounds that differ in the chirality of
15 one or more stereocenters. Stereoisomers include enantiomers and diastereomers.

[0112] "Tautomer" refer to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- moiety and a ring =N- moiety such as oxadiazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

20 [0113] "Prodrug" refers to art recognized modifications to one or more functional groups which functional groups are metabolized *in vivo* to provide a compound of this invention or an active metabolite thereof. Such functional groups are well known in the art including acyl or thioacyl groups for hydroxyl and/or amino substitution, conversion of one or more hydroxyl groups to the mono-, di- and tri-phosphate wherein optionally one or more of the
25 pendent hydroxyl groups of the mono-, di- and tri-phosphate have been converted to an alkoxy, a substituted alkoxy, an aryloxy or a substituted aryloxy group, and the like.

[0114] "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound, which salts are derived from a variety of organic and inorganic counter ions well

known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, and tetraalkylammonium; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, and oxalate (see Stahl and Wermuth, eds.,
5 "HANDBOOK OF PHARMACEUTICALLY ACCEPTABLE SALTS," (2002), Verlag Helvetica Chimica Acta, Zürich, Switzerland), for an extensive discussion of pharmaceutical salts, their selection, preparation, and use.

[0115] Generally, pharmaceutically acceptable salts are those salts that retain substantially one or more of the desired pharmacological activities of the parent compound and which are
10 suitable for administration to humans. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids or organic acids. Inorganic acids suitable for forming pharmaceutically acceptable acid addition salts include, by way of example and not limitation, hydrohalide acids (*e.g.*, hydrochloric acid, hydrobromic acid, hydroiodic acid, etc.), sulfuric acid, nitric acid, phosphoric acid, and the like.

[0116] Organic acids suitable for forming pharmaceutically acceptable acid addition salts include, by way of example and not limitation, acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, oxalic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, palmitic acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid,
20 mandelic acid, alkylsulfonic acids (*e.g.*, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, etc.), arylsulfonic acids (*e.g.*, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, etc.), 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary
25 butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

[0117] Pharmaceutically acceptable salts also include salts formed when an acidic proton present in the parent compound is either replaced by a metal ion (*e.g.*, an alkali metal ion, an alkaline earth metal ion, or an aluminum ion) or coordinates with an organic base (*e.g.*,
30 ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, piperidine, dimethylamine, diethylamine, triethylamine, and ammonia).

[0118] Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent “arylalkyloxycarbonyl” refers to the group (aryl)-(alkyl)-O-C(O)-.

5 [0119] It is understood that in all substituted groups defined above, polymers or other compounds arrived at by defining substituents with further substituents to themselves (*e.g.*, substituted aryl having a substituted aryl group or another group as a substituent which is itself substituted with a substituted aryl group or another group, which is further substituted by a substituted aryl group or another group etc.) are not intended for inclusion herein. In
10 such cases, the maximum number of such substitutions is four. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to -substituted aryl-(substituted aryl)-substituted aryl-(substituted aryl).

[0120] Similarly, it is understood that the above definitions are not intended to include impermissible substitution patterns (*e.g.*, methyl substituted with 5 fluoro groups). Such
15 impermissible substitution patterns are well known to the skilled artisan.

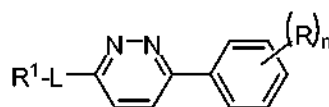
[0121] An “effective amount” is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages. Such delivery is dependent on a number of variables including the time period for which the individual dosage unit is to be used, the bioavailability of the therapeutic agent,
20 the route of administration, etc. It is understood, however, that specific dose levels of the therapeutic agents of the present invention for any particular subject depends upon a variety of factors including the activity of the specific compound employed, bioavailability of the compound, the route of administration, the age of the animal and its body weight, general health, sex, the diet of the animal, the time of administration, the rate of excretion, the drug
25 combination, and the severity of the particular disorder being treated and form of administration. Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from *in vitro* and/or *in vivo* tests initially can provide useful guidance on the proper doses for patient administration. Studies in animal models generally may be used for guidance regarding effective dosages for
30 treatment of diseases such as diarrhea and PKD. In general, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the

concentrations found to be effective *in vitro*. Thus, where a compound is found to demonstrate *in vitro* activity, for example as noted in the Tables discussed below one can extrapolate to an effective dosage for administration *in vivo*. These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks. Consistent with this definition and as used herein, the term “therapeutically effective amount” is an amount sufficient to treat a specified disorder or disease or alternatively to obtain a pharmacological response such as inhibiting function CFTR.

[0122] As used herein, “treating” or “treatment” of a disease in a patient refers to (1) preventing the symptoms or disease from occurring in an animal that is predisposed or does not yet display symptoms of the disease; (2) inhibiting the disease or arresting its development; or (3) ameliorating or causing regression of the disease or the symptoms of the disease. As understood in the art, “treatment” is an approach for obtaining beneficial or desired results, including clinical results. For the purposes of this invention, beneficial or desired results can include one or more, but are not limited to, alleviation or amelioration of one or more symptoms, diminishment of extent of a condition (including a disease), stabilized (i.e., not worsening) state of a condition (including disease), delay or slowing of condition (including disease), progression, amelioration or palliation of the condition (including disease), states and remission (whether partial or total), whether detectable or undetectable. Preferred are compounds that are potent and can be administered locally at very low doses, thus minimizing systemic adverse effects.

B. Compounds of the invention

[0123] The present invention relates to pyridazine sulfonamide-containing compounds which are CFTR inhibitors. In one aspect, the invention relates to a compound of formula I:



I

wherein

n is 1, 2, 3, 4, or 5;

L is a bond or a linker of 1 to 6 linear or branched covalently linked atoms;

R¹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, aryloxy and substituted aryloxy;

or R¹ and L are taken together with the atom to which they are bonded to form a heterocycle or substituted heterocycle; and

each R are independently selected from the group consisting of hydrogen, hydroxyl, alkyl, substituted alkyl, halo, amino, sulfonylamino, aminocarbonyl, alkoxy and substituted alkoxy, provided that at least one R is sulfonylamino or aminocarbonyl;

or a pharmaceutically acceptable salt, isomer, or tautomer thereof;

wherein said compound exhibits at least one of the following:

- a) an IC₅₀ of less than 30 μM in the T84 assay;
- b) a greater than 30% inhibition at 20 μM in the FRT assay; or
- c) a greater than 35% inhibition at 50 μM in a T84 assay, provided that the compound does not have an IC₅₀ greater than 30 μM.

[0124] In a particular aspect, the invention relates to a compound of formula I, wherein said compound exhibits an IC₅₀ of less than 30 μM in the T84 assay.

[0125] In another aspect, the invention relates to a compound of formula I, wherein said compound exhibits a greater than 30% inhibition at 20 μM in the FRT assay.

[0126] In another aspect, the invention relates to a compound of formula I, wherein said compound exhibits a greater than 35% inhibition at 50 μM in a T84 assay, provided that the compound does not have an IC₅₀ greater than 30 μM.

[0127] In some embodiments, R is hydrogen, hydroxyl, bromo, chloro, methoxy, amino, -NH-S(O)₂-R², or -C(O)NH-S(O)₂-R² where R² is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino.

[0128] In some embodiments, R is $-\text{NH}-\text{S}(\text{O})_2-\text{R}^2$, where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino. In some embodiments, substituted aryl is substituted with a substituent selected from the group consisting of halo, alkyl, alkoxy, halo, cyano, amino, substituted amino, heterocycle, and substituted heterocycle. In some
5 embodiments, substituted alkyl is substituted with a halo or aryl.

[0129] In some embodiments, R is $-\text{C}(\text{O})\text{NH}-\text{S}(\text{O})_2-\text{R}^2$, where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino. In some embodiments, substituted aryl is substituted with a group selected from the group consisting of alkyl, alkoxy, halo, cyano, amino, substituted amino, heterocycle, and substituted heterocycle. In some embodiments, substituted alkyl is substituted with a halo or aryl.
10

[0130] In some embodiments, R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl.

[0131] In some embodiments, R^1 and L are taken together with the atom to which they are bonded to form a heterocycle or substituted heterocycle.
15

[0132] In some embodiments, R^1 is substituted alkyl substituted with aryl or substituted aryl.

[0133] In some embodiments, R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl.
20

[0134] In some embodiments, R^1 is substituted alkyl substituted with a substituent selected from the group consisting of phenyl, 4-chlorophenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, and 3-trifluoromethylphenyl.

[0135] In some embodiments, L is selected from the group consisting of alkylene, substituted alkylene, $-\text{O}-$, $-\text{NR}^3-$, $-\text{S}-$, $-\text{NR}^3\text{C}(\text{O})-$, and $-\text{C}(\text{OH})\text{R}^3-$; where
25

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy,

cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, aryloxy and substituted aryloxy;

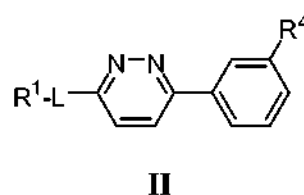
or R^1 and R^3 are taken together with the atom to which they are bonded to form a heterocycle or substituted heterocycle.

[0136] In some embodiments, L is selected from the group consisting of $-O-$, $-NR^3-$, and $-NR^3C(O)-$, where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl.

[0137] In some embodiments, L is $-O-$ or $-N(CH_2CH_3)-$.

[0138] In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3.

[0139] In one aspect, there is provided a compound of formula II:



wherein

L is $-O-$, $-NR^3-$, and $-NR^3C(O)-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl;

R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, aryloxy and substituted aryloxy;

or R^1 and L are taken together with the atom to which they are bonded to form a heterocycle or substituted heterocycle; and

R^4 is sulfonylamino or aminocarbonyl;

or a pharmaceutically acceptable salt, isomer, or tautomer thereof;

wherein said compound exhibits at least one of the following:

- a) an IC_{50} of less than 30 μM in the T84 assay;
- b) a greater than 30% inhibition at 20 μM in the FRT assay; or
- c) a greater than 35% inhibition at 50 μM in a T84 assay, provided that the compound does not have an IC_{50} greater than 30 μM .

5 [0140] Some embodiments of the above noted aspect are as provided below. It is to be understood that any combination of the below noted embodiments is within the scope of the invention.

[0141] In some embodiments of the above noted aspect, L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl.

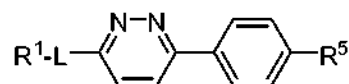
10 [0142] In some embodiments, R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl.

[0143] In some embodiments, R^4 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino.

15 [0144] In some embodiments, there is provided a compound of formula II wherein L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl; R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl; and R^4 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino.

20 [0145] In some embodiments, there is provided a compound of formula II wherein L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl; R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl; and R^4 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl; substituted alkyl substituted with halo or aryl; aryl; substituted aryl substituted with halo, alkyl, alkoxy, cyano, or acylamino; heteroaryl; substituted heteroaryl substituted with heterocycle; amino; and substituted amino substituted with alkyl.

[0146] In another aspect, there is provided a compound of formula III:



III

wherein

5 L is $-O-$, $-NR^3-$, and $-NR^3C(O)-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl;

R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, aryloxy and substituted aryloxy;

10 or R^1 and L are taken together with the atom to which they are bonded to form a heterocycle or substituted heterocycle; and

R^5 is sulfonylamino or aminocarbonyl;

or a pharmaceutically acceptable salt, isomer, or tautomer thereof;

wherein said compound exhibits at least one of the following:

- a) an IC_{50} of less than 30 μM in the T84 assay;
- 20 b) a greater than 30% inhibition at 20 μM in the FRT assay; or
- c) a greater than 35% inhibition at 50 μM in a T84 assay, provided that the compound does not have an IC_{50} greater than 30 μM .

[0147] Some embodiments of the above noted aspect are as provided below. It is to be understood that any combination of the below noted embodiments is within the scope of the invention.

[0148] In some embodiments, L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl.

[0149] In some embodiments, R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl.

[0150] In some embodiments, R^5 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino.

5 [0151] In some embodiments, L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl; R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl; and R^5 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, and substituted aryl.

10 [0152] In some embodiments, L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl; R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl; and R^5 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl; substituted alkyl substituted with halo; aryl; substituted aryl substituted with halo or alkyl.

15 [0153] In some embodiments, the invention relates to a compound of formula I, II, or III or compounds set forth in Tables 1-3 wherein said compound exhibits an IC_{50} of less than about 30 μM ; or less than about 25 μM ; or less than about 20 μM ; or less than about 15 μM ; or less than about 10 μM ; or less than about 5 μM ; or less than about 3 μM ; or less than about 2 μM ; or less than about 1 μM ; or less than about 0.5 μM ; or about 0.1 μM , in the T84 assay.

20 [0154] In some embodiments, the invention relates to a compound of formula I, II, or III or compounds set forth in Tables 1-3 wherein said compound exhibits an IC_{50} of between about 20-30 μM or between about 15-30 μM , or between about 1-15 μM ; or between about 0.5-1 μM , or between about 1-10 μM , or between about 25-30 μM , or between about 5-15 μM , in the T84 assay.

25 [0155] In another aspect, the invention relates to a compound of formula I, II, or III or compounds set forth in Tables 1-3 wherein said compound exhibits a greater than 30% inhibition at 20 μM in the FRT assay.

[0156] In some embodiments, the invention relates to a compound of formula I, II, or III or compounds set forth in Tables 1-3, wherein said compound exhibits greater than about 30% inhibition at 20 μM ; or greater than about 35% inhibition at 20 μM ; or greater than

about 40% inhibition at 20 μ M; or greater than about 45% inhibition at 20 μ M; or greater than about 50% inhibition at 20 μ M; or greater than about 60% inhibition at 20 μ M; or greater than about 70% inhibition at 20 μ M; or greater than about 80% inhibition at 20 μ M; or greater than about 90% inhibition at 20 μ M; or about 99% inhibition at 20 μ M, in the FRT assay.

[0157] In some embodiments, the invention relates to a compound of formula I, II, or III or compounds set forth in Tables 1-3, wherein said compound exhibits between about 30-50% inhibition at 20 μ M, or between about 40-60% inhibition at 20 μ M, or between about 30-40% inhibition at 20 μ M, or between about 50-70% inhibition at 20 μ M, or between about 70-90% inhibition at 20 μ M, or between about 80-90% inhibition at 20 μ M, or between about 90-99% inhibition at 20 μ M, in the FRT assay.

[0158] In another aspect, the invention relates to a compound of formula I, II, or III or compounds set forth in Tables 1-3 wherein said compound exhibits a greater than 35% inhibition at 50 μ M in a T84 assay, provided that the compound does not have an IC_{50} greater than 30 μ M.

[0159] In some embodiments, the invention relates to a compound of formula I, II, or III or compounds set forth in Tables 1-3, wherein said compound exhibits a greater than about 35% inhibition at 50 μ M; or greater than about 40% inhibition at 50 μ M; or greater than about 45% inhibition at 50 μ M; or greater than about 50% inhibition at 50 μ M; or greater than about 60% inhibition at 50 μ M; or greater than about 70% inhibition at 50 μ M; or greater than about 80% inhibition at 50 μ M; or greater than about 90% inhibition at 50 μ M; or about 99% inhibition at 50 μ M, in a T84 assay, provided that the compound does not have an IC_{50} greater than 30 μ M.

[0160] In some embodiments, the invention relates to a compound of formula I, II, or III or compounds set forth in Tables 1-3, wherein said compound exhibits between about 35-40% inhibition at 50 μ M, or between about 40-50% inhibition at 50 μ M, or between about 50-60% inhibition at 50 μ M, or between about 60-70% inhibition at 50 μ M, or between about 70-80% inhibition at 50 μ M, or between about 80-90% inhibition at 50 μ M, or

between about 90-99% inhibition at 50 μ M, in a T84 assay, provided that the compound does not have an IC_{50} greater than 30 μ M.

[0161] In some embodiments, there is provided a compound selected from the group consisting of:

- 5 N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)methanesulfonamide;
- N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-1,1,1-
- trifluoromethanesulfonamide;
- N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-4-cyanobenzenesulfonamide;
- N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-6-morpholinopyridine-3-
- 10 sulfonamide;
- N-(4-(N-(3-(6-(4-chlorophenethoxy)pyridazin-3-
- yl)phenyl)sulfamoyl)phenyl)acetamide;
- 4-(6-(4-chlorophenethoxy)pyridazin-3-yl)-2-methoxyphenol;
- N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)dimethylaminosulfonamide;
- 15 N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)methanesulfonamide;
- N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-4-methylbenzenesulfonamide;
- N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-3-bromobenzenesulfonamide;
- N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-1,1,1-
- trifluoromethanesulfonamide;
- 20 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(4-methoxyphenylsulfonyl)benzamide;
- 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(4-fluorophenylsulfonyl)benzamide;
- 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(ethylsulfonyl)benzamide;
- N-(4-tert-butylphenylsulfonyl)-3-(6-(4-chlorophenethoxy)pyridazin-3-yl)benzamide;
- 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(3,4-
- 25 difluorophenylsulfonyl)benzamide;
- N-(3-(6-(benzylamino)pyridazin-3-yl)phenyl)-4-methylbenzenesulfonamide;
- N-(benzylsulfonyl)-3-(6-(4-chlorophenethoxy)pyridazin-3-yl)benzamide;

- 4-tert-butyl-N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)benzenesulfonamide;
- 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(3,4-difluorophenylsulfonyl)benzamide;
- 5 N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-2,2,2-trifluoroethanesulfonamide;
- 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(2,4-difluorophenylsulfonyl)benzamide;
- 10 N-(4-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
- 4-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-tosylbenzamide;
- Benzyl-{6-[3-(1,1-dioxo-isothiazolidin-2-yl)-phenyl]-pyridazin-3-yl}-ethylamine;
- and
- 15 N-(4-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-2-methylpropane-1-sulfonamide;
- or a pharmaceutically acceptable salt, isomer, or tautomer thereof.

[0162] In a certain aspect, there is provided a composition comprising a compound as defined herein and a carrier.

20 [0163] It will be appreciated by one of skill in the art that the embodiments summarized above may be used together in any suitable combination to generate additional embodiments not expressly recited above, and that such embodiments are considered to be part of the present invention.

25 [0164] Those of skill in the art will appreciate that the compounds described herein may include functional groups that can be masked with progroups to create prodrugs. Such prodrugs are usually, but need not be, pharmacologically inactive until converted into their active drug form. The compounds described in this invention may include promoieties that are hydrolyzable or otherwise cleavable under conditions of use. For example, ester groups commonly undergo acid-catalyzed hydrolysis to yield the parent hydroxyl group when exposed to the acidic conditions of the stomach or base-catalyzed hydrolysis when exposed

to the basic conditions of the intestine or blood. Thus, when administered to a subject orally, compounds that include ester moieties can be considered prodrugs of their corresponding hydroxyl, regardless of whether the ester form is pharmacologically active.

[0165] Prodrugs designed to cleave chemically in the stomach to the active compounds can employ progroups including such esters. Alternatively, the progroups can be designed to metabolize in the presence of enzymes such as esterases, amidases, lipolases, and phosphatases, including ATPases and kinase, etc. Progroups including linkages capable of metabolizing *in vivo* are well known and include, by way of example and not limitation, ethers, thioethers, silylethers, silylthioethers, esters, thioesters, carbonates, thiocarbonates, carbamates, thiocarbamates, ureas, thioureas, and carboxamides.

[0166] In the prodrugs, any available functional moiety can be masked with a progroup to yield a prodrug. Functional groups within the compounds of the invention that can be masked with progroups include, but are not limited to, amines (primary and secondary), hydroxyls, sulfanyls (thiols), and carboxyls. A wide variety of progroups suitable for masking functional groups in active compounds to yield prodrugs are well-known in the art. For example, a hydroxyl functional group can be masked as a sulfonate, ester, or carbonate promoiety, which can be hydrolyzed *in vivo* to provide the hydroxyl group. An amino functional group can be masked as an amide, carbamate, imine, urea, phosphenyl, phosphoryl, or sulfenyl promoiety, which can be hydrolyzed *in vivo* to provide the amino group. A carboxyl group can be masked as an ester (including silyl esters and thioesters), amide, or oxadiazolepromoiety, which can be hydrolyzed *in vivo* to provide the carboxyl group. Other specific examples of suitable progroups and their respective promoieties will be apparent to those of skill in the art. All of these progroups, alone or in combinations, can be included in the prodrugs.

[0167] As noted above, the identity of the progroup is not critical, provided that it can be metabolized under the desired conditions of use, for example, under the acidic conditions found in the stomach and/or by enzymes found *in vivo*, to yield a biologically active group, *e.g.*, the compounds as described herein. Thus, skilled artisans will appreciate that the progroup can comprise virtually any known or later-discovered hydroxyl, amine or thiol protecting group. Non-limiting examples of suitable protecting groups can be found, for

example, in PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, Greene & Wuts, 2nd Ed., John Wiley & Sons, New York, 1991.

[0168] Additionally, the identity of the progroup(s) can also be selected so as to impart the prodrug with desirable characteristics. For example, lipophilic groups can be used to decrease water solubility and hydrophilic groups can be used to increase water solubility. In this way, prodrugs specifically tailored for selected modes of administration can be obtained. The progroup can also be designed to impart the prodrug with other properties, such as, for example, improved passive intestinal absorption, improved transport-mediated intestinal absorption, protection against fast metabolism (slow-release prodrugs), tissue-selective delivery, passive enrichment in target tissues, and targeting-specific transporters. Groups capable of imparting prodrugs with these characteristics are well-known and are described, for example, in Ettmayer *et al.* (2004), J. Med. Chem. **47(10)**:2393-2404. All of the various groups described in these references can be utilized in the prodrugs described herein.

[0169] As noted above, progroup(s) may also be selected to increase the water solubility of the prodrug as compared to the active drug. Thus, the progroup(s) may include or can be a group(s) suitable for imparting drug molecules with improved water solubility. Such groups are well-known and include, by way of example and not limitation, hydrophilic groups such as alkyl, aryl, and arylalkyl, or cycloheteroalkyl groups substituted with one or more of an amine, alcohol, a carboxylic acid, a phosphorous acid, a sulfoxide, a sugar, an amino acid, a thiol, a polyol, an ether, a thioether, and a quaternary amine salt. Numerous references teach the use and synthesis of prodrugs, including, for example, Ettmayer *et al.*, *supra* and Bungeard *et al.* (1989) J. Med. Chem. **32(12)**: 2503-2507.

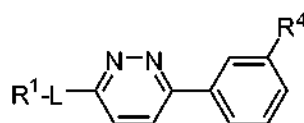
[0170] One of ordinary skill in the art will appreciate that many of the compounds of the invention and prodrugs thereof, may exhibit the phenomena of tautomerism, conformational isomerism, geometric isomerism, and/or optical isomerism. For example, the compounds and prodrugs of the invention may include one or more chiral centers and/or double bonds and as a consequence may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers, diastereomers, and mixtures thereof, such as racemic mixtures. As another example, the compounds and prodrugs of the invention may exist in several tautomeric forms, including the enol form, the keto form, and mixtures thereof. As

the various compound names, formulae and compound drawings within the specification and claims can represent only one of the possible tautomeric, conformational isomeric, optical isomeric, or geometric isomeric forms, it should be understood that the invention encompasses any tautomeric, conformational isomeric, optical isomeric, and/or geometric isomeric forms of the compounds or prodrugs having one or more of the utilities described herein, as well as mixtures of these various different isomeric forms.

[0171] Depending upon the nature of the various substituents, the compounds and prodrugs of the invention can be in the form of salts. Such salts include pharmaceutically acceptable salts, salts suitable for veterinary uses, etc. Such salts can be derived from acids or bases, as is well-known in the art. In one embodiment, the salt is a pharmaceutically acceptable salt.

[0172] In one embodiment, this invention provides a compound, isomer, tautomer, prodrug, or pharmaceutically acceptable salt thereof, selected from **Table 1**.

Table 1

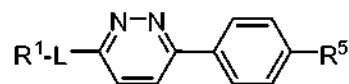


II

Cmpd. No.	R ¹	L	R ⁴
1	4-chlorophenethoxy	-O-	-NHSO ₂ CH ₃
2	4-chlorophenethoxy	-O-	-NHSO ₂ CF ₃
3	4-chlorophenethoxy	-O-	
4	4-chlorophenethoxy	-O-	
5	4-chlorophenethoxy	-O-	
6	benzyl	-N(CH ₂ CH ₃)-	
7	benzyl	-N(CH ₂ CH ₃)-	-NHSO ₂ CH ₃
8	benzyl	-N(CH ₂ CH ₃)-	

Cmpd. No.	R ¹	L	R ⁴
9	benzyl	-N(CH ₂ CH ₃)-	
10	benzyl	-N(CH ₂ CH ₃)-	-NHSO ₂ CF ₃
11	4-chlorophenethoxy	-O-	
12	4-chlorophenethoxy	-O-	
13	4-chlorophenethoxy	-O-	
14	4-chlorophenethoxy	-O-	
15	4-chlorophenethoxy	-O-	
16	benzyl	-NH-	
17	4-chlorophenethoxy	-O-	
18	4-chlorophenethoxy	-O-	
19	4-chlorophenethoxy	-O-	
20	4-chlorophenethoxy	-O-	
21	4-chlorophenethoxy	-O-	

Table 2



III

Cmpd. No.	R ¹	L	R ⁵
22	4-chlorophenethoxy	-O-	
23	4-chlorophenethoxy	-O-	
24	4-chlorophenethoxy	-O-	

5

Table 3

Cmpd. No.	Structure	Compound Name
1		N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)methanesulfonamide
2		N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide
3		N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-4-cyanobenzenesulfonamide
4		N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-6-morpholinopyridine-3-sulfonamide

Cmpd No.	Structure	Compound Name
5		N-(4-(N-(3-(6-(4-chlorophenoxy)pyridazin-3-yl)phenyl)sulfamoyl)phenyl)acetamide
6		N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)dimethylaminosulfonamide
7		N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)methanesulfonamide
8		N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-4-methylbenzenesulfonamide
9		N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-3-bromobenzenesulfonamide
10		N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide
11		3-(6-(4-chlorophenoxy)pyridazin-3-yl)-N-(4-methoxyphenyl)sulfonylbenzamide
12		3-(6-(4-chlorophenoxy)pyridazin-3-yl)-N-(4-fluorophenyl)sulfonylbenzamide
13		3-(6-(4-chlorophenoxy)pyridazin-3-yl)-N-(ethylsulfonyl)benzamide

Cmpd No.	Structure	Compound Name
14		N-(4-tert-butylphenylsulfonyl)-3-(6-(4-chlorophenethoxy)pyridazin-3-yl)benzamide
15		3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(3,4-difluorophenylsulfonyl)benzamide
16		N-(3-(6-(benzylamino)pyridazin-3-yl)phenyl)-4-methylbenzenesulfonamide
17		N-(benzylsulfonyl)-3-(6-(4-chlorophenethoxy)pyridazin-3-yl)benzamide
18		4-tert-butyl-N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)benzenesulfonamide
19		3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(3,4-difluorophenylsulfonyl)benzamide
20		N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-2,2,2-trifluoroethanesulfonamide

Cmpd No.	Structure	Compound Name
21		3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(2,4-difluorophenylsulfonyl)benzamide
22		N-(4-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide
23		4-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-tosylbenzamide
24		N-(4-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-2-methylpropane-1-sulfonamide
25		4-(6-(4-chlorophenethoxy)pyridazin-3-yl)-2-methoxyphenol
26		Benzyl-{6-[3-(1,1-dioxo-isothiazolidin-2-yl)phenyl]-pyridazin-3-yl}-ethylamine

C. Methods of the invention

[0173] The compounds disclosed herein are useful in the treatment of a condition, disorder or disease or symptom of such condition, disorder, or disease, where the condition, disorder or disease is responsive to inhibition of functional CFTR. Such diseases or conditions include, but are not limited to the various forms of diarrhea, PKD and male infertility. The methods include administration of an effective amount of a compound defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) or compositions thereof, thereby treating the disease. In one aspect, the compounds of the invention treat these diseases by inhibiting ion transport, *e.g.* HCO_3^- or halide ion, *e.g.*, chloride ion, transport by CFTR.

[0174] In one aspect, the compounds and compositions are administered or delivered to treat diarrhea and associated symptoms in an animal in need of such treatment. The term “animal” is used broadly to include mammals such as a human patient or other farm animals in need of such treatment. In one aspect, the animal is an infant (i.e., less than 2 years old, or alternatively, less than one year old, or alternatively, less than 6 months old, or alternatively, less than 3 months old, or alternatively, less than 2 months old, or alternatively, less than 1 one month old, or alternatively, less than 2 weeks old), a newborn (e.g., less than one week old, or alternatively, less than one day old), a pediatric patient (e.g., less than 18 years old or alternatively less than 16 years old) or yet further, a geriatric patient (e.g., greater than 65 years old).

[0175] Since CFTR function has been associated with a wide spectrum of diseases (including secretory diarrhea, polycystic kidney disease (PKD), cardiac arrhythmia, disorders associated with neovascularization, male infertility, chronic obstructive pulmonary disorders, pancreatic insufficiency, bacterial pulmonary conditions, and an abnormally concentrated sudoriparous secretion, chronic idiopathic pancreatitis, sinusitis, allergic bronchopulmonary aspergillosis (ABPA), asthma, primary sclerosing cholangitis, congenital bilateral absence of the vas deferens (CBAVD), hydrosalpinx, liver disease, bile duct injury, mucoviscidosis, etc.), administration of an effective amount of a compound of this invention will treat such diseases when administered to an animal such as a human patient in need thereof. Accordingly, in one aspect the invention relates to a method of treating a disease in an animal, where the disease is responsive to inhibition of functional CFTR and is selected from the group consisting of secretory diarrhea, polycystic kidney disease (PKD), cardiac arrhythmia and disorders associated with neovascularization, by administering an effective amount of a compound defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) or compositions thereof, thereby treating the disease. Additional examples of diseases responsive to inhibiting of functional CFTR polypeptide that can be treated by the compounds of the invention include, but are not limited to, chronic idiopathic pancreatitis, sinusitis, allergic bronchopulmonary aspergillosis (ABPA), asthma, primary sclerosing cholangitis, congenital bilateral absence of the vas deferens (CBAVD), hydrosalpinx, liver disease, bile duct injury, and mucoviscidosis.

[0176] In one aspect, the compounds of the invention are used in the treatment of the conditions associated with aberrantly increased intestinal secretion, particularly acute aberrantly increased intestinal secretion. Such intestinal secretion can result in intestinal inflammatory disorders and diarrhea, particularly secretory diarrhea. In another aspect, the invention relates to a treatment of diarrhea by administering an effective amount of the compound defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) or compositions thereof. In a further embodiment, the invention relates to treatment of secretory diarrhea by administering an effective amount of the compound defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) or compositions thereof. In a yet further aspect, the invention relates to the treatment of diarrhea by administering an effective amount of the compound defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) or compositions thereof, where the diarrhea is for example, infectious diarrhea, inflammatory diarrhea or diarrhea associated with chemotherapy. In one embodiment, the invention relates to a treatment of secretory diarrhea which involves use of compounds of the invention to inhibit the CFTR chloride channel.

[0177] As used herein, "diarrhea" intends a medical syndrome which is characterized by the primary symptom of diarrhea (or scours in animals) and secondary clinical symptoms that may result from a secretory imbalance and without regard to the underlying cause and therefore includes exudative (inflammatory), decreased absorption (osmotic, anatomic derangement, and motility disorders) and secretory. As noted previously, all forms of diarrhea have a secretory component. Symptoms include, but are not limited to impaired colonic absorption, ulcerative colitis, shigellosis, and amebiasis. Osmotic diarrhea can occur as a result of digestive abnormalities such as lactose intolerance. Anatomic derangement results in a decreased absorption surface caused by such procedures as subtotal colectomy and gastrocolic fistula. Motility disorders result from decreased contact time resulting from such diseases as hyperthyroidism and irritable bowel syndrome. Secretory diarrhea is characterized by the hypersecretion of fluid and electrolytes from the cells of the intestinal wall. In classical form, the hypersecretion is due to changes which are independent of the permeability, absorptive capacity and exogenously generated osmotic gradients within the intestine. However, all forms of diarrhea can manifest a secretory component.

[0178] The compounds and compositions of this invention can also treat PKD and associated diseases or disorders such as Autosomal Dominant Polycystic Kidney Disease (ADPKD), Autosomal Recessive Polycystic Kidney Disease and Acquired Cystic Kidney Disease. The major manifestation of PKD is the progressive cystic dilation of renal tubules which ultimately leads to renal failure in half of affected individuals. U.S. Patent No. 5,891,628 and Gabow, P. A. (1990) Am. J. Kidney Dis. 16:403-413. PKD-associated renal cysts may enlarge to contain several liters of fluid and the kidneys usually enlarge progressively causing pain. Other abnormalities such as hematuria, renal and urinary infection, renal tumors, salt and water imbalance and hypertension frequently result from the renal defect. Cystic abnormalities in other organs, including the liver, pancreas, spleen and ovaries are commonly found in PKD. Massive liver enlargement occasionally causes portal hypertension and hepatic failure. Cardiac valve abnormalities and an increased frequency of subarachnoid and other intracranial hemorrhage have also been observed in PKD. U.S. Patent No. 5,891,628. Biochemical abnormalities which have been observed have involved protein sorting, the distribution of cell membrane markers within renal epithelial cells, extracellular matrix, ion transport, epithelial cell turnover, and epithelial cell proliferation. The most carefully documented of these findings are abnormalities in the composition of tubular epithelial cells, and a reversal of the normal polarized distribution of cell membrane proteins, such as the Na⁺/K⁺ ATPase. Carone, F.A. *et al.* (1994) Lab. Inv. 70:437-448.

[0179] Diarrhea amenable to treatment using the compounds of the invention can result from exposure to a variety of pathogens or agents including, without limitation, *cholera* toxin (*Vibrio cholera*), *E. coli* (particularly enterotoxigenic (ETEC)), *Salmonella*, *e.g.* *Cryptosporidiosis*, diarrheal viruses (*e.g.*, rotavirus)), food poisoning, or toxin exposure that results in increased intestinal secretion mediated by CFTR.

[0180] Other diarrheas that can be treated by the compounds of the invention include diarrhea associated with AIDS (*e.g.*, AIDS-related diarrhea), diarrheas caused by anti-AIDS medications such as protease inhibitors and inflammatory gastrointestinal disorders, such as ulcerative colitis, inflammatory bowel disease (IBD), Crohn's disease, chemotherapy, and the like. It has been reported that intestinal inflammation modulates the expression of three major mediators of intestinal salt transport and may contribute to diarrhea in ulcerative

colitis both by increasing transepithelial Cl^- secretion and by inhibiting the epithelial NaCl absorption. See, e.g., Lohi *et al.* (2002) *Am. J. Physiol. Gastrointest. Liver Physiol* **283**(3):G567-75).

[0181] In one embodiment, this invention provides use of a compound of formula I, II, or III or compounds set forth in Tables 1-3 or a composition comprising a compound of formula I, II, or III or compounds set forth in Tables 1-3, for treating diarrhea in an animal in need thereof, comprising administering to the animal an effective amount of a compound of formula I, II, or III, or compounds set forth in Tables 1-3 or a composition comprising a compound of formula I, II, or III, or compounds set forth in Tables 1-3, thereby treating diarrhea.

[0182] In another embodiment, this invention provides use of a compound of formula I, II, or III or compounds set forth in Tables 1-3 or a composition comprising a compound of formula I, II, or III or compounds set forth in Tables 1-3, for treating polycystic kidney disease (PKD) in an animal in need thereof, comprising administering to the animal an effective amount of a compound of formula I, II, or III, or compounds set forth in Tables 1-3 or a composition comprising a compound of formula I, II, or III, or compounds set forth in Tables 1-3, thereby treating PKD.

[0183] In another embodiment, this invention provides use of a compound of formula I, II, or III or compounds set forth in Tables 1-3, or a composition comprising a compound of formula I, II, or III or compounds set forth in Tables 1-3, for treating a disease in an animal, which disease is responsive to inhibiting of functional cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide, comprising administering to an animal in need thereof an effective amount of a compound of formula I, II, or III, or compounds set forth in Tables 1-3 or a composition comprising a compound of formula I, II, or III, or compounds set forth in Tables 1-3, thereby treating the disease.

[0184] In another embodiment, this invention provides use of a compound of formula I, II, or III or compounds set forth in Tables 1-3, or a composition comprising a compound of formula I, II, or III or compounds set forth in Tables 1-3, for inhibiting the transport of a halide ion across a mammalian cell membrane expressing functional cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide, comprising contacting the

CFTR polypeptide with an effective amount of a compound of formula I, II, or III, or compounds set forth in Tables 1-3 or a composition comprising a compound of formula I, II, or III, or compounds set forth in Tables 1-3, thereby inhibiting the transport of the halide ion.

5 [0185] In another embodiment, this invention provides use of a compound of formula I, II, or III or compounds set forth in Tables 1-3, or a composition comprising a compound of formula I, II, or III or compounds set forth in Tables 1-3, in the manufacture of a medicament for treating diarrhea.

10 [0186] In another embodiment, this invention provides use of a compound of formula I, II, or III or compounds set forth in Tables 1-3 or a composition comprising a compound of formula I, II, or III or compounds set forth in Tables 1-3, in the manufacture of a medicament for treating polycystic kidney disease (PKD) in an animal in need thereof.

15 [0187] In another embodiment, this invention provides use of a compound of formula I, II, or III or compounds set forth in Tables 1-3 or a composition comprising a compound of formula I, II, or III or compounds set forth in Tables 1-3, in the manufacture of a medicament for treating a disease in an animal, which disease is responsive to inhibiting of functional cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide.

20 [0188] In another embodiment, this invention provides use of a compound of formula I, II, or III or compounds set forth in Tables 1-3 or a composition comprising a compound of formula I, II, or III or compounds set forth in Tables 1-3, in the manufacture of a medicament for inhibiting the transport of a halide ion across a mammalian cell membrane expressing functional cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide.

25 [0189] The compounds and compositions can be administered alone or combined with other suitable therapy such as Oral Rehydration Therapy (ORT), supportive renal therapy, administration of an antiviral, vaccine, or other compound to treat the underlying infection or by administering an effective amount of an oral glucose-electrolyte solution to the animal. In another aspect, the compounds or compositions are co-administered with micronutrients, *e.g.*, zinc, iron, and vitamin A. The therapies may be administered
30 simultaneously or concurrently. Administration is by any appropriate route and varies with

the disease or disorder to be treated and the age and general health of the animal or human patient.

[0190] The compounds of the invention can be administered on a mucosal surface of the gastrointestinal tract (*e.g.*, by an enteral route, such as oral, intrainestinal, intraluminally, rectal as a suppository, and the like) or to a mucosal surface of the oral or nasal cavities (*e.g.*, intranasal, buccal, sublingual, and the like). In one embodiment, the compounds disclosed herein are administered in a pharmaceutical formulation suitable for oral administration, intraluminally or intraperitoneal administration. In another embodiment, the compounds disclosed herein are administered in a pharmaceutical formulation suitable for sustained release.

[0191] The compounds of the invention can also find further use as male infertility drugs, by inhibition of CFTR activity in the testes.

[0192] In one aspect, the compound is administered in a sustained release formulation which comprises the compound and an effective amount of a pharmaceutically-acceptable polymer. Such sustained release formulations provide a composition having a modified pharmacokinetic profile that is suitable for treatment as described herein. In one aspect of the invention, the sustained release formulation provides decreased C_{max} and increased T_{max} without altering bioavailability of the drug.

[0193] In one aspect, the compound is admixed with about 0.2 % to about 5.0 % w/v solution of a pharmaceutically-acceptable polymer. In other embodiments, the amount of pharmaceutically-acceptable polymer is between about 0.25% and about 5.0 %; between about 1% and about 4.5%; between about 2.0% and about 4.0 %; between about 2.5% and about 3.5%; or alternatively about 0.2%; about 0.25%; about 0.3%; about 0.35%; about 0.4%; about 0.45%; about 0.5%, about 1.0%, about 2.0%, about 3.0%, or about 4.0%, of the polymer.

[0194] The therapeutic and prophylactic methods of this invention are useful to treat human patients in need of such treatment. However, the methods are not to be limited only to human patient but rather can be practiced and are intended to treat any animal in need thereof. Such animals will include, but not be limited to farm animals and pets such as

cows, pigs and horses, sheep, goats, cats and dogs. Diarrhea, also known as scours, is a major cause of death in these animals.

[0195] Diarrhea in animals can result from any major transition, such as weaning or physical movement. Just as with human patients, one form of diarrhea is the result of a bacterial or viral infection and generally occurs within the first few hours of the animal's life. Infections with rotavirus and coronavirus are common in newborn calves and pigs. Rotavirus infection often occurs within 12 hours of birth. Symptoms of rotaviral infection include excretion of watery feces, dehydration and weakness. Coronavirus which causes a more severe illness in the newborn animals, has a higher mortality rate than rotaviral infection. Often, however, a young animal may be infected with more than one virus or with a combination of viral and bacterial microorganisms at one time. This dramatically increases the severity of the disease.

[0196] Yet another aspect of the present invention relates to a method for inhibiting the transport of a halide ion across a mammalian cell membrane expressing functional CFTR protein by contacting the cell expressing functional CFTR with an effective amount of the compound defined herein (including those compounds set forth in Tables 1-3 or encompassed by formulas I-III) or compositions thereof, thereby inhibiting the transport of the halide ion. As used herein, the term "functional CFTR" intends the full length wild type CFTR protein, a functional equivalent, or a biologically active fragment thereof. CFTR has been isolated, cloned and recombinantly expressed in a variety of cell types, which include but are not limited to Fischer rat thyroid (FRT) epithelial cells, Human colonic T84 cells, intestinal crypt cells, colonic epithelial cells, mouse fibroblast cells, bronchial epithelial, tracheobronchial epithelial, sero/mucous epithelial cells, kidney cells. Such cells are known to those skilled in the art and described, for example in Galletta *et al.* (2001) J. Biol. Chem. **276**(23):19723-19728; Sheppard *et al.* (1994) Am. J. Physiol. **266** (Lung Cell. Mol. Physiol. **10**):L405-L413; Chao *et al.* (1989) Biophys. J. **56**:1071-1081 and Chao *et al.* (1990) J. Membrane Biol. **113**:193-202. CFTR-expressing cell lines also are available from the American Type Culture Collection (ATCC). The open reading frame and polypeptide sequence of wild-type CFTR has been previously described in U.S. Patent Nos. 6,984,487; 6,902,907; 6,730,777; and 6,573,073. The delta 508 mutant is specifically (see U.S. Patent Nos. 7,160,729 and 5,240,846) excluded as an equivalent polynucleotide or polypeptide.

Equivalents of function CFTR include, but are not limited to polynucleotides that have the same or similar activity to transport ions across the cell membrane. At the sequence level, equivalent sequences are at least 90 % homologous (as determined under default parameters) to wild-type CFTR or those which hybridize under stringent conditions to the complement of these coding sequences. Biologically active functional fragments are those having contiguous identity to wild-type CFTR but contain less than 1480 amino acids. Functional fragments have been described. See U.S. Patent Nos. 5,639,661 and 5,958,893.

[0197] The methods can be practiced *in vivo* in an acceptable animal model to confirm *in vitro* efficacy or to treat the disease or condition as described above.

[0198] Equivalent polynucleotides also include polynucleotides that are greater than 75%, or 80%, or more than 90%, or more than 95% homologous to wild-type CFTR and as further isolated and identified using sequence homology searches. Sequence homology is determined using a sequence alignment program run under default parameters and correcting for ambiguities in the sequence data, changes in nucleotide sequence that do not alter the amino acid sequence because of degeneracy of the genetic code, conservative amino acid substitutions and corresponding changes in nucleotide sequence, and variations in the lengths of the aligned sequences due to splicing variants or small deletions or insertions between sequences that do not affect function.

[0199] In one embodiment, the halide ion is at least one of I^- , Cl^- , or Br^- . In one preferred embodiment, the halide ion is Cl^- . In one embodiment, the functional CFTR is wild-type full length CFTR. In one embodiment, the mammalian cell is an epithelial cell or a kidney cell. In one preferred embodiment, the mammalian cell is an intestinal epithelial cell or a colon epithelial cell.

[0200] When used to treat or prevent the diseases responsive to inhibiting of functional CFTR, the compounds of the present invention can be administered singly, as mixtures of one or more compounds of the invention, or in mixture or combination with other agents useful for treating such diseases and/or the symptoms associated with such diseases. The compounds of the present invention may also be administered in mixture or in combination with agents useful to treat other disorders or maladies, such as steroids, membrane stabilizers, 5-lipoxygenase (5LO) inhibitors, leukotriene synthesis and receptor inhibitors,

inhibitors of IgE isotype switching or IgE synthesis, IgG isotype switching or IgG synthesis, β -agonists, tryptase inhibitors, aspirin, cyclooxygenase (COX) inhibitors, methotrexate, anti-TNF drugs, retuxin, PD4 inhibitors, p38 inhibitors, PDE4 inhibitors, and antihistamines, to name a few. The compounds of the invention can be administered *per se*
5 in the form of prodrugs or as pharmaceutical compositions, comprising an active compound or prodrug.

[0201] The method can be practiced *in vitro* or *in vivo*. When practiced *in vitro*, the method can be used to screen for compounds, compositions and methods that possess the same or similar activity. Activity is determined using the methods described below or others known
10 to those of skill in the art and described in Verkmann and Galietta (2006) Progress in Respiratory Research, Vol. 34, pages 93-101.

[0202] For example, Human colonic T84 cells can be acquired from the European Collection of Cell Cultures (ECACC) and grown in standard culture conditions as described by the supplier. On the day before assay 25,000 T84 cells per well are plated into standard
15 black walled, clear bottom 384-well assay plates in standard growth medium consisting of DMEM:F12 with 10% FBS and incubated overnight. On the day of the assay the plates are washed using a standard assay buffer (HBSS with 10 mM Hepes) and incubated for 15 minutes in serum free cell culture medium before the addition of a commercially available membrane potential sensitive fluorescent dye (FLIPR Red membrane potential dye,
20 Molecular Devices Corporation). T84 cells are incubated with the FLIPR Red membrane potential dye for 45 minutes in the presence and absence of test compound before being transferred to a commercially available fluorescence imaging plate reader (FLIPR384, Molecular Devices Corporation). Fluorescence levels are monitored continuously every second for 150 seconds; after an initial 10 second baseline, CFTR channel activity is
25 stimulated through the addition of 10 μ M forskolin in the presence of 100 μ M of the phosphodiesterase inhibitor iso-butyl-methylxanthine (IBMX). Addition of the forskolin leads to the activation of intracellular adenylyl cyclase 1, elevating cAMP levels and results in the phosphorylation and opening of CFTR anion channels. CFTR channel opening causes chloride ion efflux and subsequent depolarization of the cells, which is measured by
30 an increase in fluorescence. CFTR inhibitor compounds prevent cell depolarization and the associated increase in fluorescence.

[0203] For the purpose of illustration only, Fisher Rat Thyroid (FRT) cells stably co-expressing wildtype human CFTR and a reporter protein such as green fluorescent protein (GFP) or a mutant such as the yellow fluorescent protein-based $\text{Cl}^{31}/\text{I}^-$ halide sensor *e.g.* YFP-HI48Q can be cultured on 96-well plates as described in Gruenert (2004), *supra* or Ma
5 *et al.* (2002) *J. Clin. Invest.* **110**:1651-1658. Following a 48 hour incubation confluent FRT-CFTR-YFP-HI48Q cells in 96-well plates are washed three times with phosphate buffered saline (PBS) and then CFTR halide conductance is activated by incubation for 5 minutes with a cocktail containing 5 μM , forskolin, 25 μM apigenin and 100 μM IBMX. Test compounds at a final concentration of 10 μM and 20 μM are added five minutes prior
10 to assay of iodide influx in which cells are exposed to a 100 mM inwardly-directed iodide gradient. Baseline YFP fluorescence is recorded for two seconds followed by 12 seconds of continuous recording of fluorescence after rapid addition of the I^- containing solution. To create a I^- gradient. Initial rates of I^- influx can be computed from the time course of decreasing fluorescence after the I^- gradient as known to those skilled in the art and
15 described in Yang *et al.* (2002) *J. Biol. Chem.*: 35079-35085.

[0204] Activity of the CFTR channel can also be measured directly using electrophysiological methods. An example protocol for measuring CFTR current is described as whole cell patch clamp method. As an illustration, recordings are conducted at room temperature ($\sim 21^\circ\text{C}$) using a HEKA EPC-10 amplifier. Electrodes are fabricated from
20 1.7 mm capillary glass with resistances between 2 and 3 $\text{M}\Omega$ using a Sutter P-97 puller. For recording the CFTR channels, the extracellular solution can contain (in mM) 150 NaCl, 1 CaCl_2 , 1 MgCl_2 , 10 glucose, 10 mannitol, and 10 TES (pH 7.4), and the intracellular (pipette) solution can contain 120 CsCl, MgCl_2 , 10 TEA-Cl, 0.5 EGTA, 1 Mg-ATP and 10 HEPES (pH 7.3).

25 [0205] The CFTR channels are activated by forskoin (5 μM) in the extracellular solution. The cells are held at a potential of 0 mV and currents are recorded by a voltage ramp protocol from -120 mV to +80 mV over 500 ms every 10 seconds. No leak subtraction was employed. Compounds are superfused to individual cells using a Biologic MEV-9/EVH-9 rapid perfusion system.

30 [0206] Other *in vitro* methods for inhibitory activity have been described in the art, *e.g.*, U.S. Patent Publication No. 2005/0239740 (paragraphs [0184] and [0185]). For PKD,

therapeutic activity is determined using art recognized methods as described, for example in U.S. Patent Publications Nos.: 2006/0088828; 2006/0079515 and 2003/0008288.

[0207] For *in vivo* confirmatory studies for treatment of diarrhea, mice (CD1 strain, 25-35 g) are deprived of food prior to surgery and can be anaesthetized with any suitable agent such as intraperitoneal ketamine (40 mg/kg) and xylazine (8 mg/kg). Body temperature should be maintained at 36-38° C using a heating pad. A small abdominal incision is made and 3 closed intestinal (ileal and/or duodenum/jejunum) loops (length 15-30 mm) proximal to the cecum are isolated by sutures. Loops are injected with 100 µL of PBS or PBS containing cholera toxin (1µg) with or without test compound at appropriate doses. The abdominal incision is closed with suture and mice are allowed to recover from anesthesia. Approximately four to six hours later, the mice are anesthetized, intestinal loops are removed, and loop length and weight are measured to quantify net fluid secretion to be measured as g/cm of loop.

[0208] For *in vivo* confirmatory studies of PKD therapeutica activity, the Han:SPRD rat is well characterized and can be used as a model of ADPKD. Cowley B. *Et al.* (1993) *Kidney Int.* **49**:522-534; Gretz N. *Et al.* (1996) *Nephrol. Dial. Transplant* **11**:46-51; Kaspareit-Rittinghausen J. *Et al.* (1990) *Transpl. Proc.* **22**:2582-2583; and Schafer K. *et al.* (1994) *Kidney Int.* **46**:134-152. Using this model, varying amount of the compounds or compositions are administered to the animals and therapeutic effect is noted.

D. Pharmaceutical formulations and administration

[0209] The compounds or isomers, prodrug, tautomer, or pharmaceutically acceptable salts thereof, of the present invention can be formulated in the pharmaceutical compositions *per se*, or in the form of a hydrate, solvate, N-oxide, or pharmaceutically acceptable salt, as described herein. Typically, such salts are more soluble in aqueous solutions than the corresponding free acids and bases, but salts having lower solubility than the corresponding free acids and bases may also be formed. The present invention includes within its scope solvates of the compounds and salts thereof, for example, hydrates. The compounds may have one or more asymmetric centers and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

[0210] In one embodiment, this invention provides a pharmaceutical composition comprising a compound provided herein and a pharmaceutically acceptable carrier. In another embodiment, this invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein and a pharmaceutically acceptable carrier. In one embodiment, this invention provides a pharmaceutical formulation comprising a compound selected from the compounds of the invention or isomers, hydrates, tautomer, or pharmaceutically acceptable salts thereof and at least one pharmaceutically acceptable excipient, diluent, preservative, stabilizer, or mixture thereof.

[0211] In one embodiment, the methods can be practiced as a therapeutic approach towards the treatment of the conditions described herein. Thus, in a specific embodiment, the compounds of the invention can be used to treat the conditions described herein in animal subjects, including humans. The methods generally comprise administering to the subject an amount of a compound of the invention, or a salt, prodrug, hydrate, or N-oxide thereof, effective to treat the condition.

[0212] In some embodiments, the subject is a non-human mammal, including, but not limited to, bovine, horse, feline, canine, rodent, or primate. In another embodiment, the subject is a human.

[0213] The compounds of the invention can be provided in a variety of formulations and dosages. It is to be understood that reference to the compound of the invention, or "active" in discussions of formulations is also intended to include, where appropriate as known to those of skill in the art, formulation of the prodrugs of the compounds.

[0214] In one embodiment, the compounds are provided as non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts such as those formed with hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl, or substituted alkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically

acceptable salts thereof may include metal salts such as alkali metal salts, *e.g.*, sodium or potassium salts; and alkaline earth metal salts, *e.g.*, calcium or magnesium salts.

[0215] The pharmaceutically acceptable salts of the present invention can be formed by conventional means, such as by reacting the free base form of the product with one or more
5 equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble or in a solvent such as water which is removed in vacuo, by freeze drying, or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

[0216] Pharmaceutical compositions comprising the compounds described herein (or prodrugs thereof) can be manufactured by means of conventional mixing, dissolving,
10 granulating, dragee-making levigating, emulsifying, encapsulating, entrapping, or lyophilization processes. The compositions can be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients, or auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically.

[0217] The compounds of the invention can be administered by oral, parenteral (*e.g.*,
15 intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray nasal, vaginal, rectal, sublingual, urethral (*e.g.*, urethral suppository) or topical routes of administration (*e.g.*, gel, ointment, cream, aerosol, etc.) and can be formulated, alone or together, in suitable dosage unit
20 formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, excipients, and vehicles appropriate for each route of administration.

[0218] The pharmaceutical compositions for the administration of the compounds can be conveniently presented in dosage unit form and can be prepared by any of the methods well known in the art of pharmacy. The pharmaceutical compositions can be, for example,
25 prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier, a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired therapeutic effect. For example, pharmaceutical compositions of the invention may take a form suitable for
30 virtually any mode of administration, including, for example, topical, ocular, oral, buccal,

systemic, nasal, injection, transdermal, rectal, and vaginal, or a form suitable for administration by inhalation or insufflation.

[0219] For topical administration, the compound(s) or prodrug(s) can be formulated as solutions, gels, ointments, creams, suspensions, etc., as is well-known in the art.

- 5 [0220] Systemic formulations include those designed for administration by injection (*e.g.*, subcutaneous, intravenous, intramuscular, intrathecal, or intraperitoneal injection) as well as those designed for transdermal, transmucosal, oral, or pulmonary administration.

- [0221] Useful injectable preparations include sterile suspensions, solutions, or emulsions of the active compound(s) in aqueous or oily vehicles. The compositions may also contain
10 formulating agents, such as suspending, stabilizing, and/or dispersing agents. The formulations for injection can be presented in unit dosage form, *e.g.*, in ampules or in multidose containers, and may contain added preservatives.

- [0222] Alternatively, the injectable formulation can be provided in powder form for reconstitution with a suitable vehicle, including but not limited to sterile pyrogen free water,
15 buffer, and dextrose solution, before use. To this end, the active compound(s) can be dried by any art-known technique, such as lyophilization, and reconstituted prior to use.

[0223] For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are known in the art.

- [0224] For oral administration, the pharmaceutical compositions may take the form of, for
20 example, lozenges, tablets, or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinised maize starch, polyvinylpyrrolidone, or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose, or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc, or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or
25 wetting agents (*e.g.*, sodium lauryl sulfate). The tablets can be coated by methods well known in the art with, for example, sugars, films, or enteric coatings. Additionally, the pharmaceutical compositions containing the 2,4-substituted pyrimidinediamine as active ingredient or prodrug thereof in a form suitable for oral use may also include, for example,

troches, lozenges, aqueous, or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

[0225] Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, 5 flavoring agents, coloring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient (including drug and/or prodrug) in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients can be for 10 example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents (*e.g.*, corn starch or alginic acid); binding agents (*e.g.* starch, gelatin, or acacia); and lubricating agents (*e.g.*, magnesium stearate, stearic acid, or talc). The tablets can be left uncoated or they can be coated by known techniques to delay disintegration and absorption in the gastrointestinal 15 tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions.

[0226] Liquid preparations for oral administration may take the form of, for example, 20 elixirs, solutions, syrups, or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives, or hydrogenated edible fats); 25 emulsifying agents (*e.g.*, lecithin, or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol, cremophoreTM, or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, preservatives, flavoring, coloring, and sweetening agents as appropriate.

[0227] Preparations for oral administration can be suitably formulated to give controlled 30 release or sustained release of the active compound, as is well known. The sustained release formulations of this invention are preferably in the form of a compressed tablet comprising

an intimate mixture of compound of the invention and a partially neutralized pH-dependent binder that controls the rate of compound dissolution in aqueous media across the range of pH in the stomach (typically approximately 2) and in the intestine (typically approximately about 5.5).

5 [0228] To provide for a sustained release of compounds of the invention, one or more pH-dependent binders can be chosen to control the dissolution profile of the sustained release formulation so that the formulation releases compound slowly and continuously as the formulation is passed through the stomach and gastrointestinal tract. Accordingly, the pH-dependent binders suitable for use in this invention are those which inhibit rapid release of
10 drug from a tablet during its residence in the stomach (where the pH is below about 4.5), and which promotes the release of a therapeutic amount of the compound of the invention from the dosage form in the lower gastrointestinal tract (where the pH is generally greater than about 4.5). Many materials known in the pharmaceutical art as enteric binders and coating agents have a desired pH dissolution properties. The examples include phthalic acid
15 derivatives such as the phthalic acid derivatives of vinyl polymers and copolymers, hydroxyalkylcelluloses, alkylcelluloses, cellulose acetates, hydroxyalkylcellulose acetates, cellulose ethers, alkylcellulose acetates, and the partial esters thereof, and polymers and copolymers of lower alkyl acrylic acids and lower alkyl acrylates, and the partial esters thereof. One or more pH-dependent binders present in the sustained release formulation of
20 the invention are in an amount ranging from about 1 to about 20 wt %, more preferably from about 5 to about 12 wt % and most preferably about 10 wt %.

[0229] One or more pH-independent binders may be used in oral sustained release formulation of the invention. The pH-independent binders can be present in the formulation of this invention in an amount ranging from about 1 to about 10 wt %, and preferably in
25 amount ranging from about 1 to about 3 wt % and most preferably about 2 wt %.

[0230] The sustained release formulation of the invention may also contain pharmaceutical excipients intimately admixed with the compound and the pH-dependent binder. Pharmaceutically acceptable excipients may include, for example, pH-independent binders or film-forming agents such as hydroxypropyl methylcellulose, hydroxypropyl cellulose,
30 methylcellulose, polyvinylpyrrolidone, neutral poly(meth)acrylate esters, starch, gelatin, sugars, carboxymethylcellulose, and the like. Other useful pharmaceutical excipients

include diluents such as lactose, mannitol, dry starch, microcrystalline cellulose and the like; surface active agents such as polyoxyethylene sorbitan esters, sorbitan esters and the like; and coloring agents and flavoring agents. Lubricants (such as talc and magnesium stearate) and other tableting aids can also be optionally present.

- 5 [0231] The sustained release formulations of this invention have a compound of this invention in the range of about 50% by weight to about 95% or more by weight, and preferably between about 70% to about 90% by weight; a pH-dependent binder content of between 5% and 40%, preferably between 5% and 25%, and more preferably between 5% and 15%; with the remainder of the dosage form comprising pH-independent binders,
10 fillers, and other optional excipients.

[0232] For buccal administration, the compositions may take the form of tablets or lozenges formulated in the conventional manner.

- [0233] For rectal and vaginal routes of administration, the active compound(s) can be formulated as solutions (for retention enemas), suppositories, or ointments containing
15 conventional suppository bases such as cocoa butter or other glycerides.

- [0234] For nasal administration or administration by inhalation or insufflation, the active compound(s) or prodrug(s) can be conveniently delivered in the form of an aerosol spray from pressurized packs or a nebulizer with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, fluorocarbons,
20 carbon dioxide, or other suitable gas). In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges for use in an inhaler or insufflator (for example, capsules and cartridges comprised of gelatin) can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

- 25 [0235] The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent. Among the
30 acceptable vehicles and solvents that can be employed are water, Ringer's solution, and

isotonic sodium chloride solution. The compounds may also be administered in the form of suppositories for rectal or urethral administration of the drug.

[0236] For topical use, creams, ointments, jellies, gels, solutions, suspensions, etc., containing the compounds of the invention, can be employed. In some embodiments, the compounds of the invention can be formulated for topical administration with polyethylene glycol (PEG). These formulations may optionally comprise additional pharmaceutically acceptable ingredients such as diluents, stabilizers, and/or adjuvants.

[0237] Included among the devices which can be used to administer compounds of the invention, are those well-known in the art, such as metered dose inhalers, liquid nebulizers, dry powder inhalers, sprayers, thermal vaporizers, and the like. Other suitable technology for administration of particular compounds of the invention, includes electrohydrodynamic aerosolizers. As those skilled in the art will recognize, the formulation of compounds, the quantity of the formulation delivered, and the duration of administration of a single dose depend on the type of inhalation device employed as well as other factors. For some aerosol delivery systems, such as nebulizers, the frequency of administration and length of time for which the system is activated will depend mainly on the concentration of compounds in the aerosol. For example, shorter periods of administration can be used at higher concentrations of compounds in the nebulizer solution. Devices such as metered dose inhalers can produce higher aerosol concentrations and can be operated for shorter periods to deliver the desired amount of compounds in some embodiments. Devices such as dry powder inhalers deliver active agent until a given charge of agent is expelled from the device. In this type of inhaler, the amount of compounds in a given quantity of the powder determines the dose delivered in a single administration.

[0238] Formulations of compounds of the invention for administration from a dry powder inhaler may typically include a finely divided dry powder containing compounds, but the powder can also include a bulking agent, buffer, carrier, excipient, another additive, or the like. Additives can be included in a dry powder formulation of compounds of the invention, for example, to dilute the powder as required for delivery from the particular powder inhaler, to facilitate processing of the formulation, to provide advantageous powder properties to the formulation, to facilitate dispersion of the powder from the inhalation device, to stabilize to the formulation (e.g., antioxidants or buffers), to provide taste to the

formulation, or the like. Typical additives include mono-, di-, and polysaccharides; sugar alcohols and other polyols, such as, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol, starch, or combinations thereof; surfactants, such as sorbitols, diphosphatidyl choline, or lecithin; and the like.

5 [0239] For prolonged delivery, the compound(s) or prodrug(s) of the invention can be formulated as a depot preparation for administration by implantation or intramuscular injection. The active ingredient can be formulated with suitable polymeric or hydrophobic materials (*e.g.*, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives (*e.g.*, as a sparingly soluble salt). Alternatively, transdermal delivery
10 systems manufactured as an adhesive disc or patch which slowly releases the active compound(s) for percutaneous absorption can be used. To this end, permeation enhancers can be used to facilitate transdermal penetration of the active compound(s). Suitable transdermal patches are described in, for example, U.S. Patent No. 5,407,713.; U.S. Patent No. 5,352,456; U.S. Patent No. 5,332,213; U.S. Patent No. 5,336,168; U.S. Patent No.
15 5,290,561; U.S. Patent No. 5,254,346; U.S. Patent No. 5,164,189; U.S. Patent No. 5,163,899; U.S. Patent No. 5,088,977; U.S. Patent No. 5,087,240; U.S. Patent No. 5,008,110; and U.S. Patent No. 4,921,475.

[0240] Alternatively, other pharmaceutical delivery systems can be employed. Liposomes and emulsions are well-known examples of delivery vehicles that can be used to deliver
20 active compound(s) or prodrug(s). Certain organic solvents such as dimethylsulfoxide (DMSO) may also be employed, although usually at the cost of greater toxicity.

[0241] The pharmaceutical compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active compound(s). The pack may, for example, comprise metal or plastic foil, such as a blister
25 pack. The pack or dispenser device can be accompanied by instructions for administration.

[0242] The compound(s) or prodrug(s) described herein, or compositions thereof, will generally be used in an amount effective to achieve the intended result, for example, in an amount effective to treat or prevent the particular condition being treated. The compound(s) can be administered therapeutically to achieve therapeutic benefit or prophylactically to
30 achieve prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of

the underlying disorder being treated and/or eradication or amelioration of one or more of the symptoms associated with the underlying disorder such that the patient reports an improvement in feeling or condition, notwithstanding that the patient may still be afflicted with the underlying disorder. For example, administration of a compound to a patient
5 suffering from an diarrhea provides therapeutic benefit not only when the diarrhea is eradicated or ameliorated, but also when the patient reports a decrease in the severity or duration of the symptoms associated with the diarrhea. Therapeutic benefit also includes halting or slowing the progression of the disease, regardless of whether improvement is realized.

10 [0243] The amount of compound administered will depend upon a variety of factors, including, for example, the particular condition being treated, the mode of administration, the severity of the condition being treated, the age and weight of the patient, the bioavailability of the particular active compound. Determination of an effective dosage is well within the capabilities of those skilled in the art. As known by those of skill in the art,
15 the preferred dosage of compounds of the invention will also depend on the age, weight, general health, and severity of the condition of the individual being treated. Dosage may also need to be tailored to the sex of the individual and/or the lung capacity of the individual, where administered by inhalation. Dosage, and frequency of administration of the compounds or prodrugs thereof, will also depend on whether the compounds are
20 formulated for treatment of acute episodes of a condition or for the prophylactic treatment of a disorder. A skilled practitioner will be able to determine the optimal dose for a particular individual.

[0244] For prophylactic administration, the compound can be administered to a patient at risk of developing one of the previously described conditions. For example, if it is
25 unknown whether a patient is allergic to a particular drug, the compound can be administered prior to administration of the drug to avoid or ameliorate an allergic response to the drug. Alternatively, prophylactic administration can be applied to avoid the onset of symptoms in a patient diagnosed with the underlying disorder.

[0245] Effective dosages can be estimated initially from *in vitro* assays. For example, an
30 initial dosage for use in animals can be formulated to achieve a circulating blood or serum concentration of active compound that is at or above an IC_{50} of the particular compound as

measured in as *in vitro* assay. Calculating dosages to achieve such circulating blood or serum concentrations taking into account the bioavailability of the particular compound is well within the capabilities of skilled artisans. For guidance, the reader is referred to Fingl & Woodbury, "General Principles," GOODMAN AND GILMAN'S THE
5 PHARMACEUTICAL BASIS OF THERAPEUTICS, Chapter 1, pp. 1-46, latest edition, Pergamagon Press, and the references cited therein.

[0246] Initial dosages can also be estimated from *in vivo* data, such as animal models. Animal models useful for testing the efficacy of compounds to treat or prevent the various diseases described above are well-known in the art. Ordinarily skilled artisans can routinely
10 adapt such information to determine dosages suitable for human administration.

[0247] Dosage amounts will typically be in the range of from about 0.0001 or 0.001 or 0.01 mg/kg/day to about 100 mg/kg/day, but can be higher or lower, depending upon, among other factors, the activity of the compound, its bioavailability, the mode of administration, and various factors discussed above. Dosage amount and interval can be adjusted
15 individually to provide plasma levels of the compound(s) which are sufficient to maintain therapeutic or prophylactic effect. For example, the compounds can be administered once per week, several times per week (*e.g.*, every other day), once per day, or multiple times per day, depending upon, among other things, the mode of administration, the specific indication being treated, and the judgment of the prescribing physician. In cases of local
20 administration or selective uptake, such as local topical administration, the effective local concentration of active compound(s) may not be related to plasma concentration. Skilled artisans will be able to optimize effective local dosages without undue experimentation.

[0248] Preferably, the compound(s) will provide therapeutic or prophylactic benefit without causing substantial toxicity. Toxicity of the compound(s) can be determined using standard
25 pharmaceutical procedures. The dose ratio between toxic and therapeutic (or prophylactic) effect is the therapeutic index. Compounds(s) that exhibit high therapeutic indices are preferred.

[0249] The foregoing disclosure pertaining to the dosage requirements for the compounds of the invention is pertinent to dosages required for prodrugs, with the realization, apparent
30 to the skilled artisan, that the amount of prodrug(s) administered will also depend upon a

variety of factors, including, for example, the bioavailability of the particular prodrug(s) and the conversion rate and efficiency into active drug compound under the selected route of administration. Determination of an effective dosage of prodrug(s) for a particular use and mode of administration is well within the capabilities of those skilled in the art.

5 [0250] Also provided are kits for administration of the compounds of the invention, prodrug thereof, or pharmaceutical formulations comprising the compound that may include a dosage amount of at least one compound or a composition comprising at least one compound, as disclosed herein. Kits may further comprise suitable packaging and/or instructions for use of the compound. Kits may also comprise a means for the delivery of
10 the at least one compound or compositions comprising at least one compound of the invention, such as an inhaler, spray dispenser (*e.g.*, nasal spray), syringe for injection, or pressure pack for capsules, tablets, suppositories, or other device as described herein.

[0251] Other types of kits provide the compound and reagents to prepare a composition for administration. The composition can be in a dry or lyophilized form or in a solution,
15 particularly a sterile solution. When the composition is in a dry form, the reagent may comprise a pharmaceutically acceptable diluent for preparing a liquid formulation. The kit may contain a device for administration or for dispensing the compositions, including, but not limited to, syringe, pipette, transdermal patch, or inhalant.

[0252] The kits may include other therapeutic compounds for use in conjunction with the
20 compounds described herein. These compounds can be provided in a separate form or mixed with the compounds of the present invention. The kits will include appropriate instructions for preparation and administration of the composition, side effects of the compositions, and any other relevant information. The instructions can be in any suitable format, including, but not limited to, printed matter, videotape, computer readable disk, or
25 optical disc.

[0253] In one embodiment, this invention provides a kit comprising a compound selected from the compounds of the invention or a prodrug thereof, packaging, and instructions for use.

[0254] In another embodiment, this invention provides a kit comprising the pharmaceutical
30 formulation comprising a compound selected from the compounds of the invention or a

prodrug thereof and at least one pharmaceutically acceptable excipient, diluent, preservative, stabilizer, or mixture thereof, packaging, and instructions for use. In another embodiment, kits for treating an individual who suffers from or is susceptible to the conditions described herein are provided, comprising a container comprising a dosage
5 amount of a compound of this invention or composition, as disclosed herein, and instructions for use. The container can be any of those known in the art and appropriate for storage and delivery of oral, intravenous, topical, rectal, urethral, or inhaled formulations.

[0255] Kits may also be provided that contain sufficient dosages of the compounds or composition to provide effective treatment for an individual for an extended period, such as
10 a week, 2 weeks, 3, weeks, 4 weeks, 6 weeks, or 8 weeks or more.

E. General synthesis of the compounds of the invention

[0256] The compounds and prodrugs of the invention can be synthesized *via* a variety of different synthetic routes using commercially available starting materials and/or starting materials prepared by conventional synthetic methods. It will also be appreciated by those
15 skilled in the art that in the process described below, the functional groups of intermediate compounds may need to be protected by suitable protecting groups.

[0257] The exact identity of any protecting group(s) used will depend upon the identity of the functional group being protected, and will be apparent to those of skill in the art. Guidance for selecting appropriate protecting groups, as well as synthetic strategies for their
20 attachment and removal, can be found, for example, in Greene & Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, 3d Edition, John Wiley & Sons, Inc., New York (1999) and the references cited therein. Examples of functional groups include hydroxyl, amino, mercapto and carboxylic acid.

[0258] Thus, "protecting group" refers to a group of atoms that, when attached to a reactive
25 functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group can be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, as mentioned above, and, additionally, in Harrison *et al.*, COMPENDIUM OF SYNTHETIC ORGANIC METHODS, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative
30 amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl,

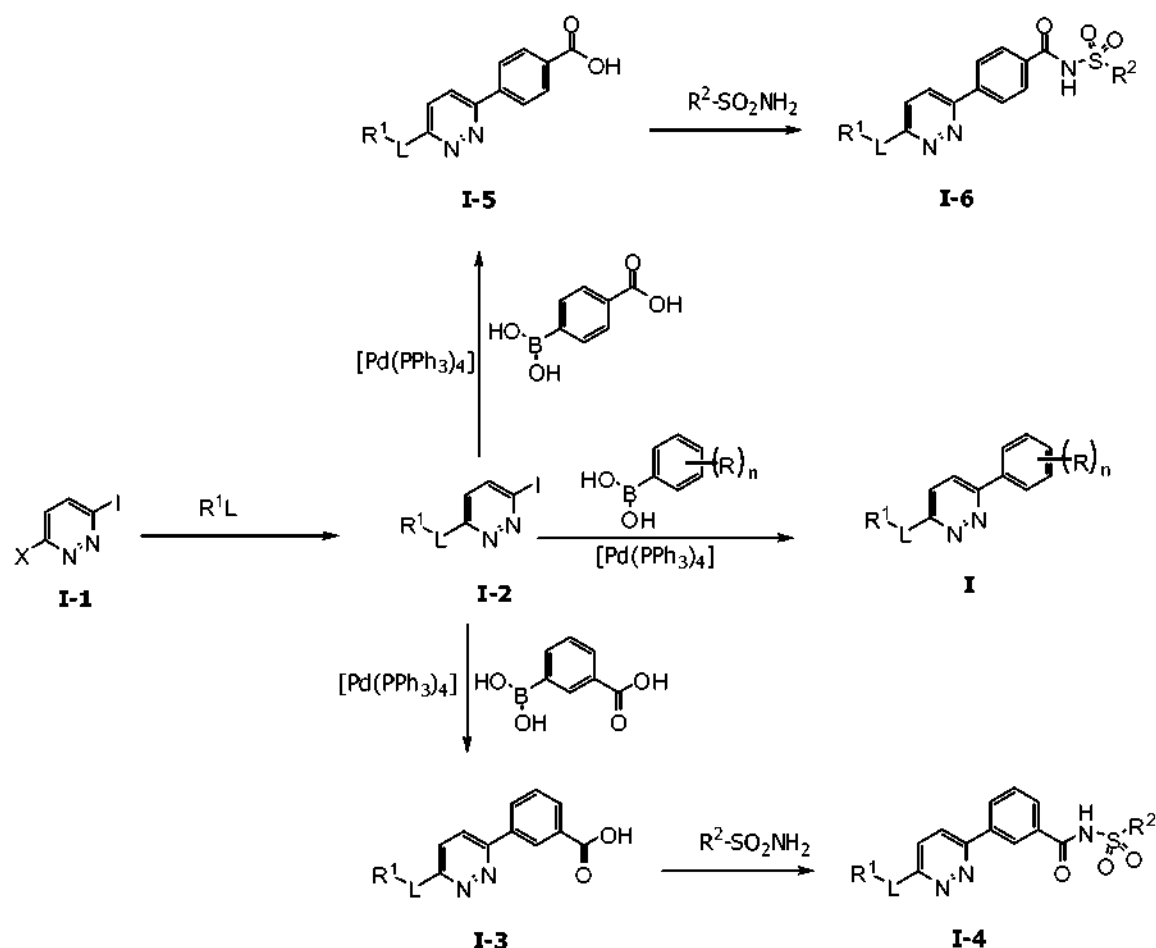
benzyl, benzyloxycarbonyl ("CBZ"), *tert*-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("Fmoc"), nitro-veratryloxycarbonyl ("NVOC"), and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated to form acetate and benzoate esters or alkylated to form benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (*e.g.*, TMS or TIPPS groups), aryl silyl ethers (*e.g.*, triphenylsilyl ether), mixed alkyl and aryl substituted silyl ethers, and allyl ethers.

[0259] The following reaction Schemes illustrate methods to make compounds of the invention. It is understood that one of ordinary skill in the art would be able to make the compounds of the invention by similar methods or by methods known to one skilled in the art. In general, starting components may be obtained from sources such as Aldrich, or synthesized according to sources known to those of ordinary skill in the art (see, *e.g.*, Smith and March, MARCH'S ADVANCED ORGANIC CHEMISTRY: REACTIONS, MECHANISMS, AND STRUCTURE, 5th edition (Wiley Interscience, New York)). Moreover, the various substituted groups (*e.g.*, R¹, R², R³, R⁴, R⁵, R⁶, *p* etc.) of the compounds of the invention may be attached to the starting components, intermediate components, and/or final products according to methods known to those of ordinary skill in the art.

[0260] A variety of exemplary synthetic routes that can be used to synthesize the compounds of the invention are described in Scheme I below. Specifically, compounds of formula I can be synthesized using the methods disclosed hereinbelow. These methods can be routinely adapted to synthesize the compounds and prodrugs described herein.

[0261] In one exemplary embodiment, various compounds of formula I can be synthesized from pyridazines **I-1** as illustrated in Scheme I, below:

Scheme I



[0262] In Scheme I, the substituents n, L, R, R^1 , and R^2 are as defined herein and X is halo. The starting halo substituted pyridazine **I-1** can be purchased from commercial sources or prepared using standard techniques of organic chemistry. Typically, halo substituted pyridazine **I-1** is reacted with a substituted alkyl, an alcohol, an amine or a thiol (R^1L) under suitable conditions to result in pyridazine **I-2**. For example, R^1L is treated with sodium hydride in the presence of a suitable solvent, such as tetrahydrofuran, at around freezing temperature. The resulting reaction mixture is then treated with **I-1** (when L is OH or SH and X is Cl) to result in **I-2**. The pyridazine **I-2** is then treated with substituted phenyl boronic acid hydrochloride in the presence of tetrakis(triphenylphosphine)palladium(0) and a suitable solvent, such as ethanol, to give compounds of formula I.

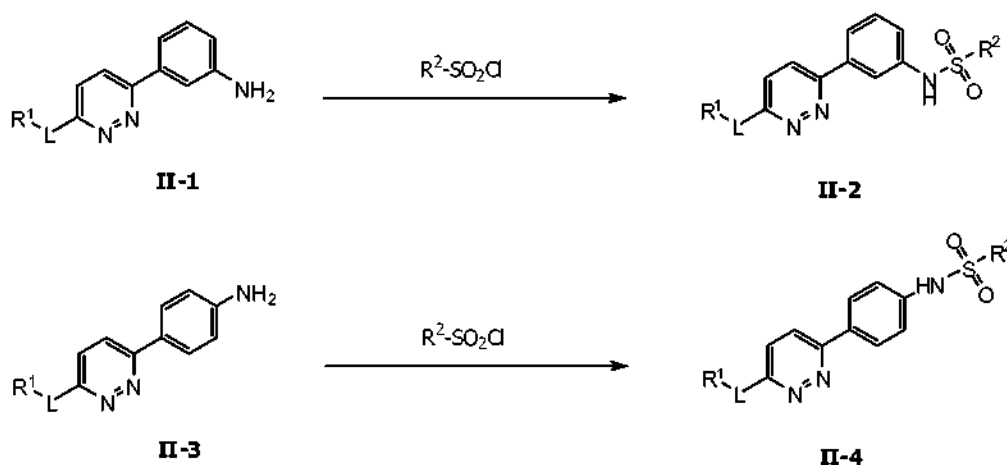
[0263] Similarly, when L is substituted amine and X is I, then **I-1** is treated with R^1L at reflux temperature to result in **I-2**. The pyridazine **I-2** is then treated with substituted phenyl boronic acid in the presence of polymer-bound

tetrakis(triphenylphosphine)palladium(0) and a suitable solvent, such as ethanol, to give compounds of formula I.

[0264] Alternatively, pyridazine I-2 can be treated with 3-carboxyphenylboronic acid in the presence of tetrakis(triphenylphosphine)palladium(0) and a suitable solvent, such as ethanol, to give pyridazine I-3 or I-5 (Scheme I). The pyridazine I-3 or I-5 is then treated with an appropriate benzene sulfonamide in the presence of a coupling agent, such as *N*-cyclohexylcarbodiimide-*N'*-methyl polystyrene HL, and a base, such as 4-(dimethylamino)pyridine (DMAP) to give pyridazine I-4 or I-6.

[0265] Substituent R in phenyl boronic acid may be a sulfonamide or may be converted into a sulfonamide as shown in Scheme II. For example, when R is an amine in the compounds of formula I (pyridazine II-1 or II-3), it can be treated with a substituted sulfonyl chloride or sulfonyl anhydride in the presence of a base, such as anhydrous pyridine, to result in a sulfonamide II-2 or II-4.

Scheme II



[0266] Skilled artisans will recognize that in some instances, compounds I-1 may include functional groups that require protection during synthesis. The exact identity of any protecting group(s) used will depend upon the identity of the functional group being protected, and will be apparent to those of skill in the art. Guidance for selecting appropriate protecting groups, as well as synthetic strategies for their attachment and removal, can be found, for example, in Greene & Wuts, PROTECTIVE GROUPS IN

ORGANIC SYNTHESIS, 3d Edition, John Wiley & Sons, Inc., New York (1999) and the references cited therein (hereinafter "Greene & Wuts").

[0267] The following examples are intended to illustrate the various embodiments of this invention.

5

EXAMPLES

[0268] The invention is further understood by reference to the following examples, which are intended to be purely exemplary of the invention. The present invention is not limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention only. Any methods that are functionally equivalent are within the scope of the invention. Various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications fall within the scope of the appended claims.

10

[0269] In the examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

15

APCI	=	atmospheric pressure chemical ionization
ATP	=	adenosine tri-phosphate
br	=	broad
d	=	doublet
CH ₂ Cl ₂	=	dichloromethane
DMEM	=	Dulbecco's modified eagle's medium
DMSO	=	dimethylsulfoxide
EGTA	=	ethylene glycol tetraacetic acid
EtOH	=	ethanol
EtOAc	=	ethyl acetate
FBS	=	fetal bovine serum
g	=	gram
h	=	hour
LC	=	liquid chromatography
LCMS	=	liquid chromatography mass spectrometry
m	=	multiplet
m/z	=	mass/Charge
Me	=	methyl
MeOH	=	methanol
mg	=	milligram
MHz	=	megahertz
min	=	minute

mL	=	milliliter
mm	=	millimeter
mM	=	milimolar
mmol	=	millimole
ms	=	millisecond
MS	=	mass spectrum
mV	=	millivolt
MΩ	=	megaohm
N	=	normal
Na ₂ CO ₃	=	sodium carbonate
NaH	=	sodium hydride
NaOH	=	sodium hydroxide
nM	=	nanomolar
nm	=	nanometer
NMR	=	nuclear magnetic resonance
Pd(PPh ₃) ₄	=	tetrakis(triphenylphosphine)palladium(0)
ppm	=	parts per million
q	=	quartet
rt	=	room temperature
Rt	=	retention time
s	=	singlet
SSC	=	standard saline citrate
t	=	triplet
TEA	=	triethylamine
THF	=	tetrahydrofuran
UV	=	ultraviolet
v/v	=	volume/volume
μg	=	microgram
μL	=	microliter
μm	=	micrometer
μM	=	micromolar

General Synthetic Methods.

[0270] Unless otherwise stated, all chemicals were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on Bruker 400MHz spectrometers. Chemical shifts are reported in parts per million downfield from the internal standard Me₄Si (0.0 ppm) for CDCl₃ solutions. For DMSO-d₆ solutions, calibration was done on the solvent peak at 2.49 ppm.

Standard acidic LC-MS conditions: (10cm _esci_formic or 10cm _apci_formic):

[0271] A Phenomenex Luna 5μm C18 (2), 100 x 4.6 mm (plus guard cartridge) column using an acetonitrile (far UV grade) with 0.1% (v/v) formic acid: Water (high purity via

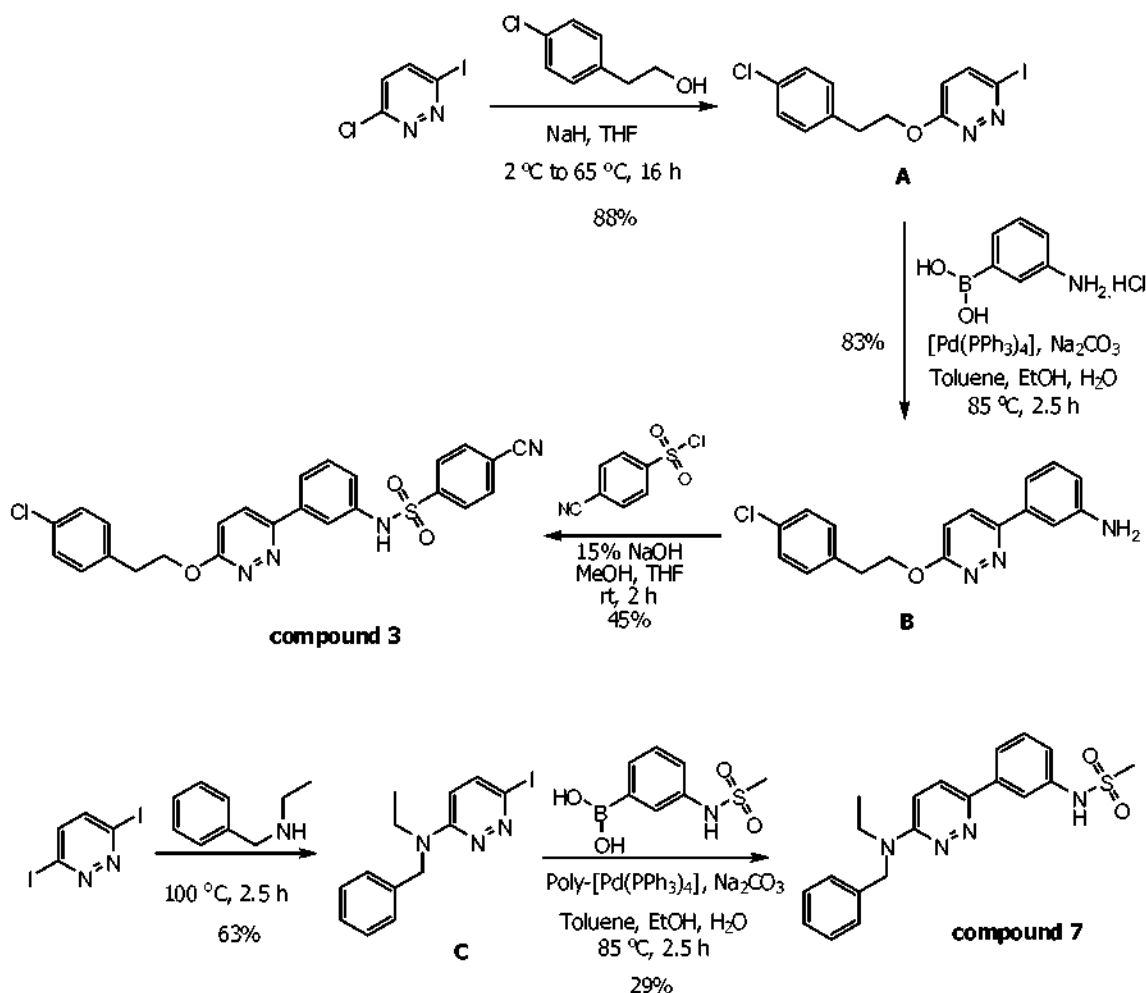
Elga UHQ unit) with 0.1% formic acid gradient was used. The flow rate was 2 mL/min. UV detection was done using a Waters diode array detector (start range 210 nm, end range 400 nm, range interval 4.0 nm). Mass detection was *via* a single quadrapole LCMS instrument. Ionization is either ESCiTM or APCI dependent on compound types. The
5 gradient used ran from 95% of aqueous solvent at time 0.00 min to 5% of aqueous solvent at 3.50 min. This percentage was then held for a further 2 min.

Standard basic LC-MS conditions: (10cm_esci_bicarb or 10cm_apci_bicarb):

[0272] A Waters Xterra MS 5 μ m C18 , 100 x 4.6 mm (plus guard cartridge) column using an acetonitrile (far UV grade):water (high purity via Elga UHQ unit) with 10 mM
10 ammonium bicarbonate (ammonium hydrogen carbonate) gradient was used. The flow rate was 2 mL/min. UV detection was done using a Waters diode array detector (start range 210 nm, end range 400 nm, range interval 4.0 nm). Mass detection was *via* a single quadrapole LCMS instrument. Ionization is either ESCiTM or APCI dependent on compound types. The
15 gradient used ran from 95% of aqueous solvent at time 0.00 min to 5% of aqueous solvent at 3.50 min. This percentage was then held for a further 2 min.

Example 1

Preparation of *N*-(3-(6-(4-Chlorophenethoxy)pyridazin-3-yl)phenyl)-4-cyanobenzenesulfonamide (Compound 3) and *N*-(3-(6-(Benzyl(ethyl)amino)pyridazin-3-yl)phenyl)methanesulfonamide (Compound 7)



5

Step 1: 3-(4-Chlorophenethoxy)-6-iodopyridazine (Compound A)

[0273] To a stirred mixture of 60% sodium hydride in mineral oil (0.96 g, 25.0 mmol) in anhydrous THF (30 mL) under nitrogen, cooled in an ice-water bath at 2 °C, was added 4-chlorophenethyl alcohol (3.10 mL, 22.9 mmol) drop-wise. After 30 min 3-chloro-6-iodopyridazine (5.00 g, 20.8 mmol) was added as a solution in THF (70 mL). The cooling bath was removed and stirring was continued at room temperature for 0.5 h then at 60 °C for 1.5 h. The mixture was cooled to room temperature and solvent removed *in vacuo*. The residue was partitioned between ethyl acetate (250 mL) and water (150 mL). The combined organic layer was washed with an aqueous solution of sodium chloride (150 mL) and dried

15

via hydrophobic frit. The resulting solution was concentrated to give a yellow solid. The residue was triturated (Et₂O/isohehexane 1:10, 75 mL) and filtered to give 6.53 g (88%) of the *title compound* as a white solid; ¹H NMR δ (ppm)(DMSO-d₆): 3.11 (2 H, t, J = 6.58 Hz), 4.64 (2 H, t, J = 6.58 Hz), 7.01 (1 H, d, J = 9.14 Hz), 7.32-7.42 (4 H, m), 7.99 (1 H, d, J = 9.14 Hz).

Step 2: 3-(6-(4-Chlorophenethoxy)pyridazin-3-yl)aniline (Compound B)

[0274] To a stirred mixture of 3-(4-chlorophenethoxy)-6-iodopyridazine (1.00 g, 2.78 mmol), 3-aminophenylboronic acid hydrochloride (0.53 g, 3.06 mmol), anhydrous sodium carbonate (1.15 g, 8.34 mmol) in degassed toluene (20 mL), absolute ethanol (20 mL) and water (2 mL) under nitrogen, was added tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.28 mmol). The mixture was stirred at room temperature under nitrogen for 15 minutes before heating at 80 °C for 3 h. The mixture was cooled to room temperature and solvent removed *in vacuo*. The residue was partitioned between ethyl acetate (100 mL) and water (150 mL). The combined organic layer was washed with an aqueous solution of sodium chloride (100 mL), dried (MgSO₄) and filtered. The resulting solution was concentrated to give a yellow residue. The residue was triturated (EtOAc/isohehexane 1:9, 80 mL) and filtered to give 0.82 g (83%) of the *title compound* as an orange solid. ¹H NMR δ (ppm)(DMSO-d₆): 3.16 (2 H, t, J = 6.74 Hz), 4.71 (2 H, t, J = 6.74 Hz), 5.29 (2 H, s), 6.67-6.72 (1 H, m), 7.11-7.20 (2 H, m), 7.25 (1 H, d, J = 9.26 Hz), 7.32 (1 H, s), 7.41 (4 H, s), 8.01 (1 H, d, J = 9.26 Hz).

Step 3: N-(3-(6-(4-Chlorophenethoxy)pyridazin-3-yl)phenyl)-4-cyanobenzenesulfonamide (Compound 3)

[0275] To a stirred solution of 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)aniline (33 mg, 0.10 mmol) in anhydrous dichloromethane (3 mL) and anhydrous pyridine (27 μL, 0.35 mmol) under nitrogen, cooled in an ice-water bath at 2 °C, was added 4-cyanobenzene-1-sulfonyl chloride (24.0 mg, 0.14 mmol). The cooling bath was then removed and stirring was continued at room temperature for 16 h. The reaction mixture was quenched with water (3 mL) and the organic layer dried *via* hydrophobic frit. Solvent was removed *in vacuo* and the residue purified by reverse phase preparative HPLC to give 22 mg (45%) of the *title compound* as a cream solid. ¹H NMR δ (ppm)(DMSO-d₆): 3.16 (2 H, t, J = 6.69

Hz), 4.73 (2 H, t, J = 6.70 Hz), 7.20-7.31 (2 H, m), 7.37-7.49 (5 H, m), 7.74 (1 H, d, J = 7.87 Hz), 7.90-8.00 (3 H, m), 8.04-8.09 (3 H, m), 10.78 (1 H, s). LCMS (10cm_ESI_formic) t_R 3.99 min; m/z 491/493 $[M+H]^+$.

Step 1: N-Benzyl-N-ethyl-6-iodopyridazin-3-amine (Compound C)

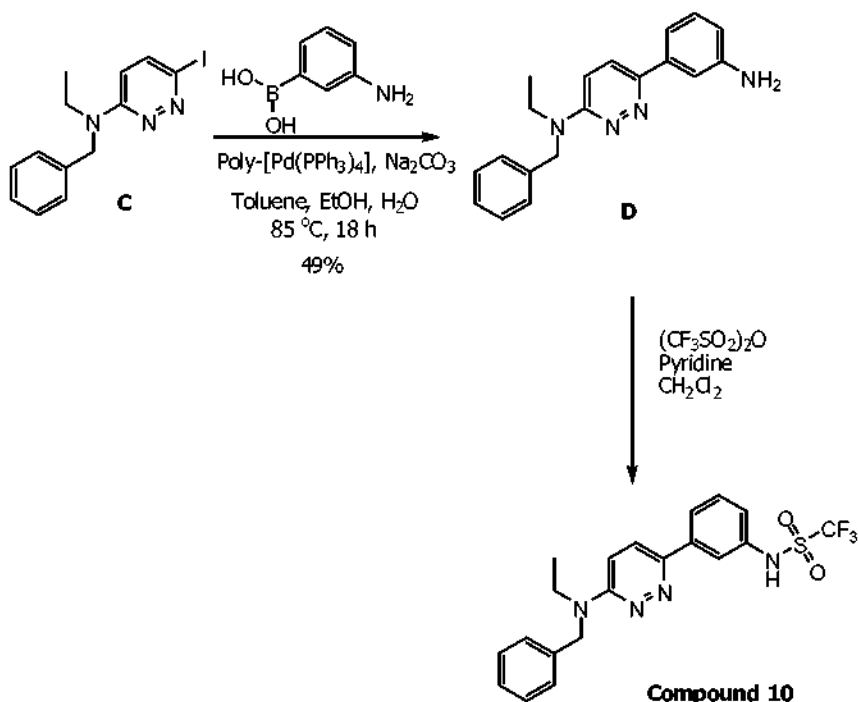
- 5 [0276] To a stirred solution of *N*-benzylethanamine (9 mL) was added 3,6-diiodopyridazine (1.50 g, 4.52 mmol). The reaction was then heated to 100 °C for 3 h. The reaction mixture was cooled to room temperature and the solution was partitioned between ethyl acetate (75 mL) and a saturated aqueous solution of citric acid (100 mL). The organic layer was washed with further saturated aqueous citric acid (2 x 75 mL), an aqueous solution of sodium chloride (100 mL), dried (MgSO₄) and filtered. Solvent was removed *in vacuo* to give an orange oil which was directly purified by flash chromatography (silica gel, 20% EtOAc/isohexane) to give 850 mg (63%) of the *title compound* as a pale brown solid. ¹H NMR δ (ppm)(DMSO-d₆): 1.14 (3 H, t, J = 6.98 Hz), 3.62 (2 H, q, J = 6.98 Hz), 4.80 (2 H, s), 6.86 (1 H, d, J = 9.49 Hz), 7.23-7.39 (5 H, m), 7.66 (1 H, d, J = 9.49 Hz).
- 10

15 **Step 2: N-(3-(6-(Benzyl(ethyl)amino)pyridazin-3-yl)phenyl)methanesulfonamide (Compound 7)**

- [0277] To a stirred mixture of *N*-benzyl-*N*-ethyl-6-iodopyridazin-3-amine (85 mg, 0.25 mmol), 3-(methylsulfonamido)phenylboronic acid (60.2 mg, 0.28 mmol), anhydrous sodium carbonate (0.12 g, 0.83 mmol) in degassed toluene (2 mL), absolute ethanol (2 mL) and water (0.2 mL) under nitrogen, was added polymer-bound tetrakis(triphenylphosphine)palladium(0) (75 mg, 0.03 mmol, 0.5-0.9 mmol/g loading). The mixture was stirred at room temperature under nitrogen for 15 minutes before heating at 90 °C for 3 h. The mixture was cooled to room temperature and solvent removed *in vacuo*. The residue obtained was submitted for reverse phase preparative HPLC to give 26.5 mg (29%) of the *title compound* as a yellow solid. ¹H NMR δ (ppm)(DMSO-d₆): 1.20 (3 H, t, J = 6.88 Hz), 3.05 (3 H, s), 3.66-3.77 (3 H, m), 4.91 (2 H, s), 7.15 (1 H, d, J = 9.60 Hz), 7.25-7.40 (6 H, m), 7.46 (1 H, t, J = 7.87 Hz), 7.71 (1 H, d, J = 7.78 Hz), 7.85 (1 H, d, J = 9.59 Hz), 7.95 (1 H, s). LCMS (10cm_ESI_bicarb) t_R 3.13 min; m/z 383 $[M+H]^+$.
- 20
- 25

Example 2

Preparation of *N*-(3-(6-(Benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide (Compound 10)



5 Step 1: 6-(3-Aminophenyl)-*N*-benzyl-*N*-ethylpyridazin-3-amine (Compound D)

[0278] To a stirred mixture of *N*-benzyl-*N*-ethyl-6-iodopyridazin-3-amine (100 mg, 0.29 mmol), 3-aminophenylboronic acid (55.3 mg, 0.32 mmol), potassium carbonate (0.12 g, 0.83 mmol) in degassed toluene (2 mL), absolute ethanol (2 mL) and water (0.2 mL) under nitrogen, was added polymer-bound tetrakis(triphenylphosphine)palladium(0) (75 mg, 0.03 mmol, 0.5-0.9 mmol/g loading). The mixture was stirred at room temperature under nitrogen for 15 minutes before heating at 90 °C for 18 h. The mixture was cooled to room temperature and solvent removed *in vacuo*. The residue was purified by column chromatography (eluent 9:1 to 2:1, hexane: ethyl acetate) to give 52mg (49%) of the *title compound* as a pale yellow solid. Used crude in next step with no further purification

15 Step 2: *N*-(3-(6-(Benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide (Compound 10)

[0279] To a stirred solution of 6-(3-aminophenyl)-*N*-benzyl-*N*-ethylpyridazin-3-amine (50mg, 0.164 mmol) and pyridine (30μL) in dichloromethane (4 mL) was added, dropwise, a solution of triflic anhydride (30 μL, 0.180 mmol) in dichloromethane (1 mL). After 1.5h,

the reaction mixture was washed with 0.5M HCl (3 x 5mL) then passed through a hydrophobic frit. The crude solution was then concentrated *in vacuo* & the residue purified by preparative HPLC. This gave the target compound as a white solid (36mg): ¹H NMR δ (ppm)(DMSO-d₆): 1.17 (3 H, t, J = 7.02 Hz), 3.70 (2 H, q, J = 7.02 Hz), 4.90 (2 H, s), 7.17-7.38 (7 H, m), 7.51 (1 H, t, J = 7.94 Hz), 7.83 (1 H, d, J = 7.89 Hz), 7.88-8.02 (2 H, m), 12.1 (1 H, s); LCMS (10cm_ESI_Bicarb_CH3CN) *t*_R 2.83 min; *m/z* 437 [M+H]⁺

[0280] Following the procedures set forth in the above examples, but employing a different boronic acid derivative, the following compounds in Table 4 were prepared:

Table 4

No.	Compound Name	¹ H NMR data	LCMS data
1	N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)methanesulfonamide	¹ H NMR δ (ppm)(DMSO-d ₆): 3.08 (3 H, s), 3.16 (2 H, t, J = 6.69 Hz), 4.74 (2 H, t, J = 6.70 Hz), 7.31 (1 H, d, J = 9.26 Hz), 7.36 (1 H, dd, J = 8.10, 2.12 Hz), 7.41 (4 H, s), 7.52 (1 H, t, J = 7.92 Hz), 7.77 (1 H, d, J = 7.83 Hz), 8.00 (1 H, s), 8.12 (1 H, d, J = 9.28 Hz), 9.85 (1 H, s).	LCMS (10cm_ESI_for mic) <i>Rt</i> 3.65 min; <i>m/z</i> 404/406 [M+H] ⁺
2	N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide	¹ H NMR δ (ppm)(DMSO-d ₆): 3.17 (2 H, t, J = 6.69 Hz), 4.75 (2 H, t, J = 6.70 Hz), 7.33 (1 H, d, J = 9.28 Hz), 7.35-7.45 (5 H, m), 7.60 (1 H, t, J = 7.94 Hz), 7.95 (1 H, d, J = 7.90 Hz), 8.07 (1 H, s), 8.18 (1 H, d, J = 9.31 Hz), 12.20 (1H, s)	LCMS (10cm_ESI_for mic) <i>Rt</i> 4.21 min; <i>m/z</i> 458/460 [M+H] ⁺
4	N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-6-morpholinopyridine-3-sulfonamide	¹ H NMR δ (ppm)(DMSO-d ₆): 3.16 (2 H, t, J = 6.70 Hz), 3.55-3.60 (4 H, m), 3.62-3.67 (4 H, m), 4.74 (2 H, t, J = 6.70 Hz), 6.91 (1 H, d, J = 9.23 Hz), 7.23-7.33 (2 H, m), 7.39-7.47 (5 H, m), 7.69 (1 H, d, J = 7.84 Hz), 7.81 (1 H, dd, J = 9.19, 2.59 Hz), 7.93 (1 H, t, J = 1.91 Hz), 8.07 (1 H, d, J = 9.30 Hz), 8.45 (1 H, d, J = 2.56 Hz), 10.35 (1 H, s).	LCMS (10cm_ESI_for mic) <i>Rt</i> 3.91 min; <i>m/z</i> 552/554 [M+H] ⁺

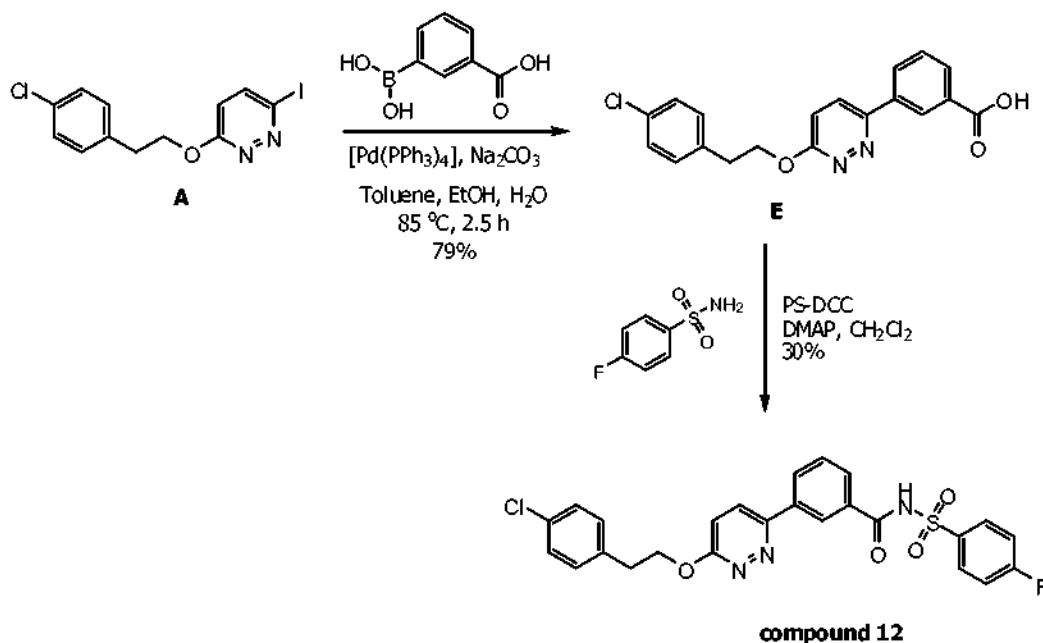
No.	Compound Name	¹ H NMR data	LCMS data
5	N-(4-(N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)sulfamoyl)phenyl)acetamide	¹ H NMR δ (ppm)(DMSO-d ₆): 2.07 (3 H, s), 2.11 (1 H, s), 3.16 (2 H, t, J = 6.69 Hz), 4.73 (2 H, t, J = 6.70 Hz), 7.19-7.31 (2 H, m), 7.35-7.44 (5 H, m), 7.65-7.80 (5 H, m), 8.04 (1 H, d, J = 9.31 Hz), 10.30 (1 H, s), 10.29-10.66 (1 H, m).	LCMS (10cm_ESI_for mic) Rt 3.68 min; m/z 523/525 [M+H] ⁺
6	N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)dimethylaminosulfonamide	¹ H NMR δ (ppm)(DMSO-d ₆): 1.20 (3 H, t, J = 6.95 Hz), 2.75 (6 H, s), 3.68-3.76 (2 H, m), 4.91 (2 H, s), 7.14 (1 H, d, J = 9.63 Hz), 7.25-7.45 (7 H, m), 7.64 (1 H, d, J = 7.84 Hz), 7.82 (1 H, d, J = 9.62 Hz), 7.95 (1 H, t, J = 1.89 Hz), 9.95 (1 H, s).	LCMS (10cm_ESI_bic arb) Rt 3.32 min; m/z 412 [M+H] ⁺
8	N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-4-methylbenzenesulfonamide	¹ H NMR δ (ppm)(DMSO-d ₆): 1.19 (3 H, t, J = 6.92 Hz), 2.35 (3 H, s), 3.71 (2 H, q, J = 6.98 Hz), 4.90 (2 H, s), 7.09-7.19 (2 H, m), 7.26-7.40 (8 H, m), 7.60 (1 H, d, J = 7.82 Hz), 7.66-7.79 (3 H, m), 7.85 (1 H, s), 10.33 (1 H, s).	LCMS (10cm_ESI_For mic_CH3CN) Rt 3.39 min; m/z 459 [M+H] ⁺
9	N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-3-bromobenzenesulfonamide	¹ H NMR δ (ppm)(DMSO-d ₆): 1.25 (3 H, t, J = 6.93 Hz), 3.77 (2 H, q, J = 7.00 Hz), 4.96 (2 H, s), 7.16-7.26 (2 H, m), 7.30-7.48 (6 H, m), 7.60 (1 H, t, J = 7.93 Hz), 7.72 (1 H, d, J = 7.86 Hz), 7.80-7.95 (4 H, m), 8.00 (1 H, t, J = 1.89 Hz), 10.60 (1 H, s).	LCMS (10cm_ESI_For mic_CH3CN) Rt 3.61 min; m/z 523/525 [M+H] ⁺
16	N-(3-(6-(benzylamino)pyridazin-3-yl)phenyl)-4-methylbenzenesulfonamide	¹ H NMR δ (ppm)(DMSO-d ₆): 2.30 (3 H, s), 4.61 (2 H, d, J = 5.86 Hz), 6.92 (1 H, d, J = 9.36 Hz), 7.11 (1 H, dd, J = 8.00, 2.17 Hz), 7.20-7.39 (8 H, m), 7.53 (2 H, t, J = 7.25 Hz), 7.63-7.69 (3 H, m), 7.77 (1 H, t, J = 1.92 Hz), 10.33 (1 H, s).	LCMS (10cm_ESI_Bic arb_CH3CN) Rt 3.38 min; m/z 431 [M+H] ⁺

No.	Compound Name	¹ H NMR data	LCMS data
18	4-tert-butyl-N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)benzenesulfonamide	¹ H NMR δ (ppm)(DMSO-d ₆): 1.22 (9 H, s), 3.11 (2 H, t, J = 6.68 Hz), 4.68 (2 H, t, J = 6.69 Hz), 7.20-7.25 (2 H, m), 7.32-7.39 (5 H, m), 7.55 (2 H, d, J = 8.45 Hz), 7.63 (1 H, d, J = 7.83 Hz), 7.72 (2 H, d, J = 8.43 Hz), 7.87 (1 H, t, J = 1.85 Hz), 7.99 (1 H, d, J = 9.30 Hz), 10.45 (1 H, s).	LCMS (25cm_Bicarb_Slow_XBRIDG E_HPLC_CH3CN) Rt 23.76 min; m/z 522 [M+H] ⁺
20	N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-2,2,2-trifluoroethanesulfonamide	¹ H NMR δ (ppm)(DMSO-d ₆): 3.12 (2 H, t, J = 6.69 Hz), 4.53 (2 H, q, J = 9.86 Hz), 4.70 (2 H, t, J = 6.68 Hz), 7.22-7.39 (7 H, m), 7.43-7.51 (1 H, m), 7.76 (1 H, d, J = 7.83 Hz), 7.92 (1 H, d, J = 2.02 Hz), 8.08 (1 H, dd, J = 9.30, 5.94 Hz). NH not observed	LCMS (10cm_ESI_Fo r mic_CH3CN) Rt 3.93 min; m/z 472 [M+H] ⁺

Example 3

Preparation of 3-(6-(4-Chlorophenethoxy)pyridazin-3-yl)-N-(4-fluorophenylsulfonyl) benzamide (Compound 12)

5



Step 1: 3-(6-(4-Chlorophenethoxy)pyridazin-3-yl)benzoic acid (Compound E)

[0281] To a stirred mixture of 3-(4-chlorophenethoxy)-6-iodopyridazine (1.00 g, 2.78 mmol), 3-carboxyphenylboronic acid (0.51 g, 3.06 mmol), anhydrous sodium carbonate (1.15 g, 8.34 mmol) in degassed toluene (20 mL), absolute ethanol (20 mL) and water (2 mL) under nitrogen, was added tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.28 mmol). The mixture was stirred at room temperature under nitrogen for 15 minutes before heating at 80 °C for 3 h. The mixture was cooled to room temperature and solvent removed *in vacuo*. The residue was partitioned between dichloromethane (30 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The aqueous layer was washed successively with dichloromethane (3 x 30 mL), and then acidified to pH 1 (10 M HCl, 5 mL). The precipitated solid was solubilised with ethyl acetate (75 mL), washed with an aqueous solution of sodium chloride (100 mL), dried (MgSO₄) and filtered. The resulting solution was concentrated to give a yellow solid, which was triturated (EtOAc/isohexane 1:9, 25 mL) and filtered to give 0.82 g (79%) of the *title compound* as a cream solid. ¹H NMR δ (ppm)(DMSO-d₆): 3.17 (2 H, t, J = 6.65 Hz), 4.75 (2 H, t, J = 6.65 Hz), 7.23-7.50 (4 H, m), 7.44-7.51 (1 H, m), 7.58-7.68 (1 H, m), 7.65-7.74 (1 H, m), 7.93-8.10 (1 H, m), 8.23-8.37 (1 H, m), 8.67 (1 H, s), 13.18 (1 H, s).

Step 2: 3-(6-(4-Chlorophenethoxy)pyridazin-3-yl)-N-(4-fluorophenylsulfonyl)benzamide (Compound 12)

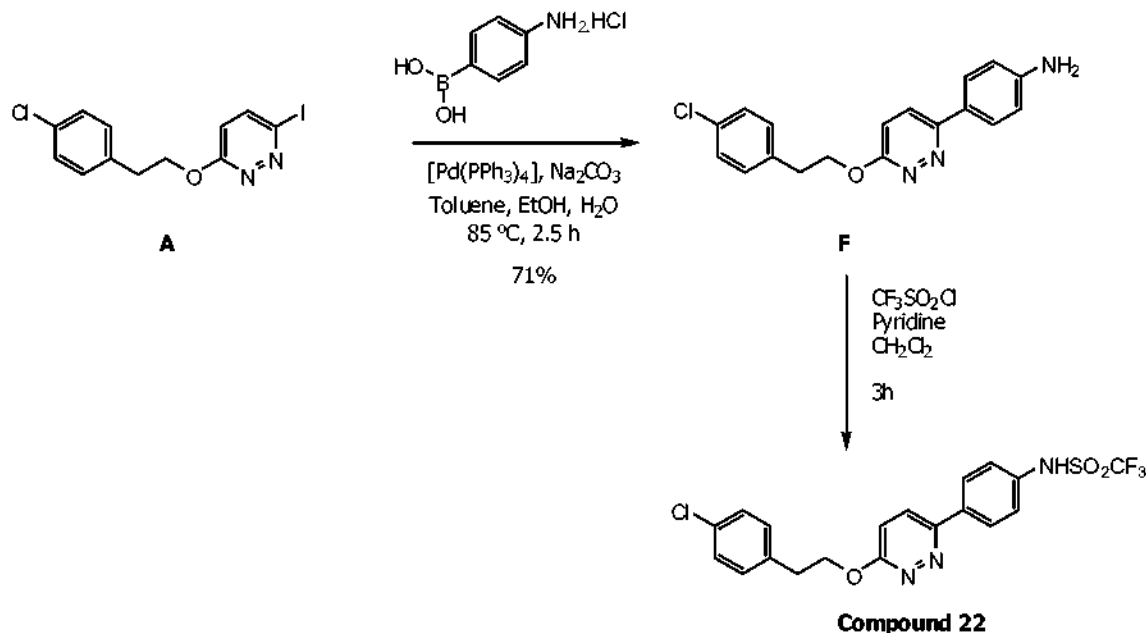
[0282] To a stirred solution of 3-(6-(4-chlorophenethoxy)pyridazin-3-yl) benzoic acid (30 mg, 0.12 mmol), 4-(dimethylamino)pyridine (16.9 mg, 0.14 mmol) and 4-fluorobenzenesulfonamide (24.2 mg, 0.14 mmol) in anhydrous dichloromethane (5 mL), was added *N*-cyclohexylcarbodiimide-*N'*-methyl polystyrene HL (0.10 g, 200 – 400 mesh). The reaction mixture was then stirred at room temperature for 3 h. Upon completion the organic layer was filtered *via* hydrophobic frit. Solvent was removed *in vacuo* and the residue submitted for reverse phase preparative HPLC to give 18 mg (30%) of the *title compound* as a white solid. ¹H NMR δ (ppm)(DMSO-d₆): 3.14 (2 H, t, J = 6.68 Hz), 4.72 (2 H, t, J = 6.68 Hz), 7.35 (1 H, d, J = 9.28 Hz), 7.39 (4 H, s), 7.50 (2 H, t, J = 8.77 Hz), 7.65 (1 H, t, J = 7.82 Hz), 7.95 (1 H, d, J = 7.86 Hz), 8.07-8.13 (2 H, m), 8.26 (1 H, d, J = 9.28 Hz), 8.34 (1 H, d, J = 7.86 Hz), 8.57 (1 H, t, J = 1.77 Hz), 1 x NH peak not observed. LCMS (10cm_ESCI_Bicarb) *t*_R 3.25 min; *m/z* 512/514 [M+H]⁺.

[0283] Following the procedure set forth in the above example, but employing a different sulfonamide derivative, the following compounds in Table 5 were prepared:

Table 5

No.	Compound Name	¹ H NMR data	LCMS data
11	3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(4-methoxyphenylsulfonyl)benzamide	¹ H NMR δ (ppm)(DMSO- d_6): 3.18 (2 H, t, J = 6.68 Hz), 3.89 (3 H, s), 4.75 (2 H, t, J = 6.68 Hz), 7.19 (2 H, d, J = 8.71 Hz), 7.38 (1 H, d, J = 9.29 Hz), 7.42 (3 H, s), 7.67 (1 H, t, J = 7.81 Hz), 7.94-8.02 (4 H, m), 8.29 (1 H, d, J = 9.29 Hz), 8.36 (1 H, d, J = 7.81 Hz), 8.59 (1 H, s), 12.61 (1 H, s).	LCMS (10cm_ESCI_Bicarb_MeCN) Rt 3.18 min; m/z 524/526 [M+H] ⁺
13	3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(ethylsulfonyl)benzamide	¹ H NMR δ (ppm)(DMSO- d_6): 1.31 (3 H, t, J = 7.33 Hz), 3.18 (2 H, t, J = 6.66 Hz), 3.58 (2 H, q, J = 7.33 Hz), 4.76 (2 H, t, J = 6.66 Hz), 7.39 (1 H, d, J = 9.31 Hz), 7.42 (4 H, s), 7.73 (1 H, t, J = 7.80 Hz), 8.07 (1 H, d, J = 7.80 Hz), 8.31 (1 H, d, J = 9.31 Hz), 8.40 (1 H, d, J = 7.80 Hz), 8.66 (1 H, s), 12.24 (1 H, s).	LCMS (10cm_ESCI_Bicarb_MeCN) Rt 2.98 min; m/z 446/448 [M+H] ⁺
14	N-(4-tert-butylphenylsulfonyl)-3-(6-(4-chlorophenethoxy)pyridazin-3-yl)benzamide	¹ H NMR δ (ppm)(DMSO- d_6): 1.30 (9 H, s), 3.12 (2 H, t, J = 6.68 Hz), 4.71 (2 H, t, J = 6.68 Hz), 7.29-7.38 (5 H, m), 7.59-7.68 (3 H, m), 7.91-7.96 (3 H, m), 8.25 (1 H, d, J = 9.30 Hz), 8.32 (1 H, d, J = 7.88 Hz), 8.56 (1 H, t, J = 1.77 Hz). NH not observed	LCMS (10cm_ESI_Formic_CH3CN) Rt 4.41 min; m/z 550 [M+H] ⁺
15	3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(3,4-difluorophenylsulfonyl)benzamide	¹ H NMR δ (ppm)(DMSO- d_6): 3.17 (2 H, t, J = 6.68 Hz), 4.75 (2 H, t, J = 6.68 Hz), 7.37 (1 H, d, J = 9.30 Hz), 7.42 (4 H, s), 7.68 (1 H, t, J = 7.82 Hz), 7.71-7.80 (1 H, m), 7.90-7.94 (1 H, m), 7.96-8.01 (1 H, m), 8.05-8.13 (1 H, m), 8.29 (1 H, d, J = 9.30 Hz), 8.32-8.37 (1 H, m), 8.61 (1 H, s)	LCMS (10cm_ESI_Bicarb_CH3CN) Rt 2.97 min; m/z 530/532 [M+H] ⁺

No.	Compound Name	¹ H NMR data	LCMS data
17	N-(benzylsulfonyl)-3-(6-(4-chlorophenethoxy)pyridazin-3-yl)benzamide	¹ H NMR δ (ppm)(DMSO-d ₆): 3.13 (2 H, t, J = 6.67 Hz), 4.71 (2 H, t, J = 6.67 Hz), 4.86 (2 H, s), 7.29-7.40 (10 H, m), 7.67 (1 H, t, J = 7.80 Hz), 8.00 (1 H, d, J = 7.84 Hz), 8.21 (1 H, d, J = 9.31 Hz), 8.34 (1 H, d, J = 7.86 Hz), 8.54 (1 H, s), 12.16 (1 H, s).	LCMS (10cm_ESI_Bicarb_CH3CN) Rt 4.05 min; m/z 508 [M+H] ⁺
19	3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(3,4-difluorophenylsulfonyl)benzamide	¹ H NMR δ (ppm)(DMSO-d ₆): 3.12 (2 H, t, J = 6.68 Hz), 4.70 (2 H, t, J = 6.66 Hz), 7.29-7.39 (5 H, m), 7.63 (1 H, t, J = 7.82 Hz), 7.72 (1 H, q, J = 8.87 Hz), 7.88 (1 H, s), 7.95 (1 H, d, J = 7.85 Hz), 8.01-8.07 (1 H, m), 8.24 (1 H, d, J = 9.30 Hz), 8.31 (1 H, d, J = 7.81 Hz), 8.57 (1 H, s). NH not observed	LCMS (25cm_Bicarb_Slow_XBRIDGE_HP LC_CH3CN) Rt 17.56 min; m/z 530 [M+H] ⁺
21	3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(2,4-difluorophenylsulfonyl)benzamide	¹ H NMR δ (ppm)(DMSO-d ₆): 3.09-3.16 (2 H, m), 4.71 (2 H, t, J = 6.67 Hz), 7.29-7.39 (4 H, m), 7.63 (2 H, m), 7.95 (1 H, d, J = 7.73 Hz), 8.08 (1 H, d, J = 8.31 Hz), 8.24 (1 H, d, J = 9.28 Hz), 8.31 (1 H, d, J = 7.79 Hz), 8.58 (1 H, s). NH not observed	LCMS (10cm_ESI_Bicarb_CH3CN) Rt 2.91 min; m/z 530 [M+H] ⁺

Example 4**Preparation of *N*-(4-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide (Compound 22)****5 Step 1: 4-(6-(4-Chlorophenethoxy)pyridazin-3-yl)aniline (Compound F)**

[0284] To a stirred mixture of 3-(4-chlorophenethoxy)-6-iodopyridazine (1.00 g, 2.78 mmol), 3-aminophenylboronic acid hydrochloride (0.53 g, 3.06 mmol), anhydrous sodium carbonate (1.15 g, 8.34 mmol) in degassed toluene (20 mL), absolute ethanol (20 mL) and water (2 mL) under nitrogen, was added tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.28 mmol). The mixture was stirred at room temperature under nitrogen for 15 minutes before heating at 80 °C for 3 h. The mixture was cooled to room temperature and solvent removed *in vacuo*. The residue was partitioned between ethyl acetate (100 mL) and water (150 mL). The combined organic layer was washed with an aqueous solution of sodium chloride (100 mL), dried (MgSO₄) and filtered. The resulting solution was concentrated to give a yellow residue. The residue was purified by column chromatography (EtOAc/isohexane 1:4) to give 0.72 g (71%) of the *title compound* as an orange solid. Used directly in subsequent step without further purification.

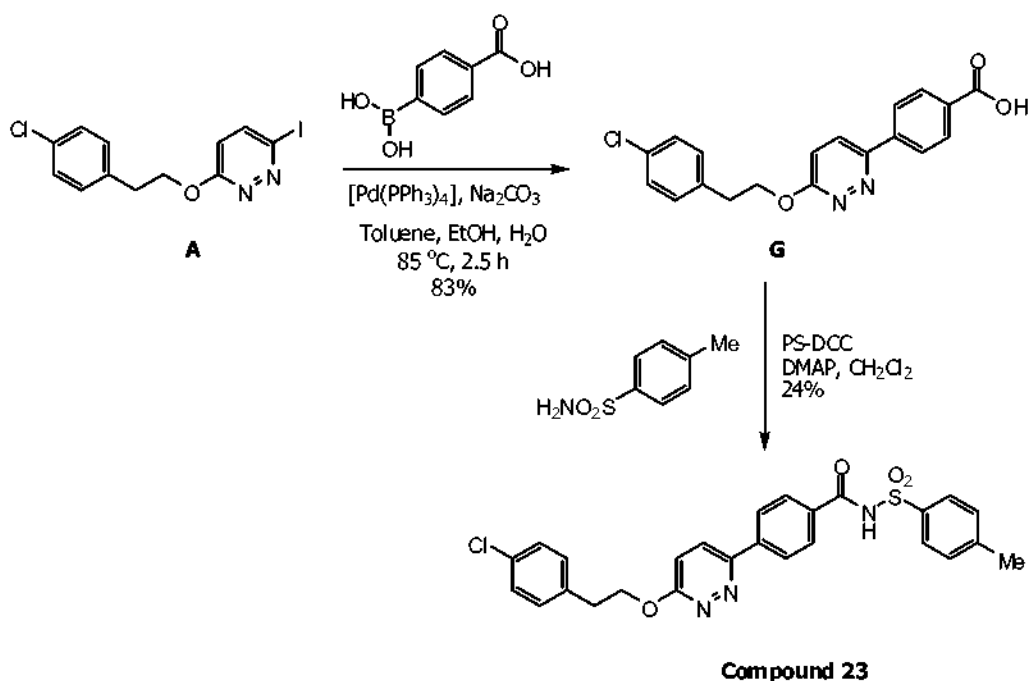
Step 2: *N*-(4-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide (Compound 22)

[0285] To a stirred solution of 4-(6-(4-chlorophenethoxy)pyridazin-3-yl)aniline (60 mg, 0.184 mmol) in dichloromethane (2 mL) and pyridine (50 μL) was added trifluoromethane

sulfonyl chloride. The result mixture was stirred for 3 h, at which point water (5 mL) was added. The resulting mixture was filtered through a hydrophobic frit and purified by preparative HPLC. This gave the target compound as a colorless solid: ^1H NMR δ (ppm)(DMSO- d_6): 3.08-3.18 (2 H, m), 4.69 (2 H, t, J = 6.68 Hz), 7.27 (1 H, d, J = 9.28 Hz),
 5 7.34-7.42 (5 H, m), 8.05-8.17 (4 H, m): LCMS (10cm_ESI_Bicarb_ CH_3CN) t_R 3.02 min; m/z 458 $[\text{M}+\text{H}]^+$

Example 5

Preparation of 4-(6-(4-chlorophenethoxy)pyridazin-3-yl)-*N*-tosylbenzamide (Compound 23)



Step 1: 4-(6-(4-Chlorophenethoxy)pyridazin-3-yl)benzoic acid (Compound G)

[0286] To a stirred mixture of 3-(4-chlorophenethoxy)-6-iodopyridazine (0.90 g, 2.50 mmol), 4-carboxyphenylboronic acid (0.415 g, 2.55 mmol), anhydrous potassium carbonate (1.03 g, 7.5 mmol) in degassed toluene (20 mL), absolute ethanol (20 mL) and water (2 mL)
 15 under nitrogen, was added tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.28 mmol). The mixture was stirred at room temperature under nitrogen for 15 minutes before heating at 80 °C for 3 h. The mixture was cooled to room temperature and solvent removed *in vacuo*. The residue was partitioned between dichloromethane (30 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The aqueous layer was washed
 20 successively with dichloromethane (3 x 30 mL), and then acidified to pH 1 (10 M HCl, 5

mL). The precipitated solid was solubilised with ethyl acetate (75 mL), washed with an aqueous solution of sodium chloride (100 mL), dried (MgSO₄) and filtered. The resulting solution was concentrated to give a yellow solid, which was purified by column chromatography (EtOAc: hexane 4:1) to give 0.78 g (83%) of the *title compound* as a cream solid.

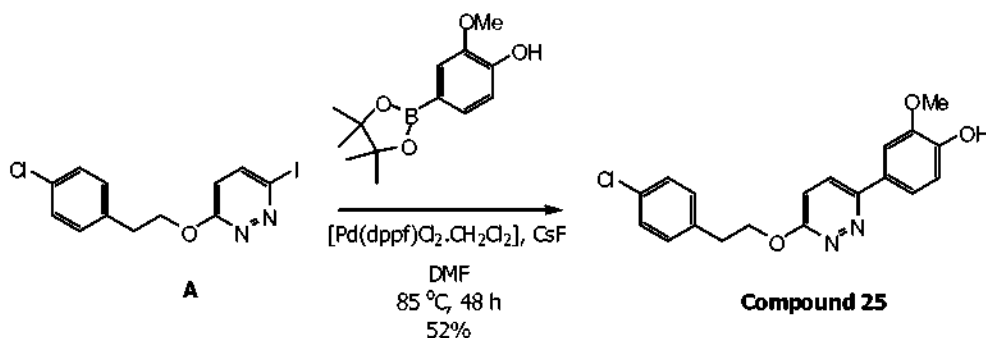
Step 2: 4-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-tosylbenzamide (Compound 23)

[0287] To a stirred solution of 4-(6-(4-chlorophenethoxy)pyridazin-3-yl) benzoic acid (30 mg, 0.12 mmol), 4-(dimethylamino)pyridine (16.9 mg, 0.14 mmol) and toluene-4-sulfonamide (23.6 mg, 0.14 mmol) in anhydrous dichloromethane (5 mL), was added *N*-cyclohexylcarbodiimide-*N'*-methyl polystyrene HL (0.10 g, 200 - 400 mesh). The reaction mixture was then stirred at room temperature for 3 h. Upon completion the organic layer was filtered *via* hydrophobic frit. Solvent was removed *in vacuo* and the residue submitted for reverse phase preparative HPLC to give 14 mg (24%) of the *title compound* as a white solid. ¹H NMR δ (ppm)(DMSO-d₆): 2.31 (3 H, s), 3.00-3.11 (2 H, m), 4.64 (2 H, t, J = 6.69 Hz), 7.22 (1 H, d, J = 9.29 Hz), 7.26-7.33 (5 H, m), 7.78 (2 H, d, J = 8.03 Hz), 7.92 (2 H, d, J = 8.32 Hz), 8.06 (2 H, d, J = 8.24 Hz), 8.15 (2 H, d, J = 9.32 Hz). NH not observed; LCMS (10cm_ESI_Bicarb_CH₃CN) *t*_R 2.92 min; *m/z* 508 [M+H]⁺

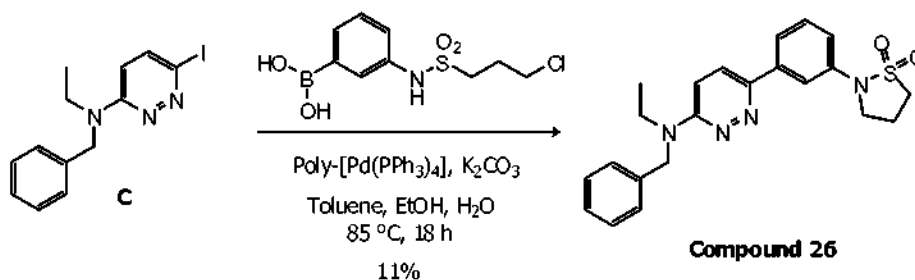
[0288] Following the procedures set forth in the above examples, but employing a different sulfonamide derivative, the following compounds in Table 6 were prepared:

Table 6

No.	Compound Name	¹ H NMR data	LCMS data
24	N-(4-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-2-methylpropane-1-sulfonamide	¹ H NMR δ (ppm)(DMSO-d ₆): 0.99 (6 H, d, J = 6.72 Hz), 2.14 (1 H, dt, J = 13.26, 6.63 Hz), 3.03 (2 H, d, J = 6.39 Hz), 3.11 (2 H, t, J = 6.68 Hz), 4.68 (2 H, t, J = 6.68 Hz), 7.20-7.34 (3 H, m), 7.36 (3 H, s), 8.02 (2 H, d, J = 8.51 Hz), 8.09 (1 H, d, J = 9.30 Hz). NH not observed	LCMS (10cm_ESI_Bicarb_CH ₃ CN) <i>R</i> _t 3.9 min; <i>m/z</i> 446 [M+H] ⁺

Example 6**Synthesis of 4-(6-(4-Chlorophenethoxy)pyridazin-3-yl)benzoic acid (Compound 25)**

[0289] To a stirred mixture of 3-(4-chlorophenethoxy)-6-iodopyridazine (40 mg, 0.111 mmol), 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (33.5 mg, 0.111 mmol), aqueous caesium fluoride (37 μL , 1.5M solution) in degassed DMF (1 mL) under nitrogen, was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (4.8 mg, 5% mol.). The mixture was stirred at room temperature under nitrogen for 15 minutes before heating at 80 $^\circ\text{C}$ for 48 h. The reaction mixture was cooled to room temperature, quenched by the addition of glacial acetic acid (5 drops) and filtered through a pad of celite, washed with DMF (1.5 mL). The resulting solution was purified by preparative HPLC to yield the *title compound* as an off-white solid (20.6 mg, 52%). $^1\text{H NMR } \delta$ (ppm)(DMSO- d_6): 3.15 (2 H, t, $J = 6.71$ Hz), 3.90 (3 H, s), 4.71 (2 H, t, $J = 6.71$ Hz), 6.93 (1 H, d, $J = 8.26$ Hz), 7.22 (1 H, d, $J = 9.29$ Hz), 7.40 (4 H, s), 7.51 (1 H, dd, $J = 8.28, 2.07$ Hz), 7.71 (1 H, d, $J = 2.06$ Hz), 8.12 (1 H, d, $J = 9.32$ Hz), 9.45 (1 H, s); LCMS(10cm_ESI_formic)Rt 3.67 min; m/z 357/359/360 $[\text{M}+\text{H}]^+$

Example 7**Synthesis of Benzyl-{6-[3-(1,1-dioxo-isothiazolidin-2-yl)-phenyl]-pyridazin-3-yl}-ethylamine (Compound 26)**

[0290] To a stirred mixture of *N*-benzyl-*N*-ethyl-6-iodopyridazin-3-amine (100 mg, 0.29 mmol), 3-(3-chloropropylsulfonamido)phenylboronic acid (88.5 mg, 0.32 mmol) and potassium carbonate (0.12 g, 0.83 mmol) in degassed toluene (2 mL), absolute ethanol (2 mL) and water (0.2 mL) under nitrogen, was added polymer-bound
 5 tetrakis(triphenylphosphine)palladium(0) (75 mg, 0.03 mmol, 0.5-0.9 mmol/g loading). The mixture was stirred at room temperature under nitrogen for 15 minutes before heating at 90 °C for 18 h. The mixture was cooled to room temperature, filtered through a pad of celite and concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to give the *title compound* as an off-white solid (14.1 mg, 11%). ¹H NMR δ (ppm)(DMSO-*d*₆):
 10 1.15 (3 H, t, J = 6.93 Hz), 2.39-2.47 (2 H, m), 3.53 (2 H, t, J = 7.38 Hz), 3.68 (2 H, q, J = 7.00 Hz), 3.81 (2 H, t, J = 6.45 Hz), 4.87 (2 H, s), 7.10 (1 H, d, J = 9.63 Hz), 7.19-7.34 (6 H, m), 7.45 (1 H, t, J = 7.96 Hz), 7.66 (1 H, d, J = 7.78 Hz), 7.84-7.90 (2 H, m); LCMS (10cm_ESCI_Bicarb_MeCN) Rt 3.75 min; m/z 409 [M+H]⁺

Formulation Examples

15

Formulation Preparation 1

[0291] Hard gelatin capsules containing the following ingredients are prepared:

Ingredients	Quantity (mg/capsule)
active ingredient	30.0
starch	305.0
magnesium stearate	5.0

[0292] The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Preparation 2

20

[0293] A tablet formula is prepared using the ingredients below:

Ingredients	Quantity (mg/tablet)
active ingredient	25.0

cellulose, microcrystalline	200.0
colloidal silicon dioxide	10.0
stearic acid	5.0

[0294] The components are blended and compressed to form tablets, each weighing 240 mg.

Biological Assays

Example 1

5

T84 Assay

[0295] Human colonic T84 cells are acquired from the European Collection of Cell Cultures (ECACC) and are grown in standard culture conditions as described by the supplier. On the day before assay 25,000 T84 cells per well are plated into standard black walled, clear bottom 384-well assay plates in standard growth medium consisting of
10 DMEM:F12 with 10% FBS and incubated overnight. On the day of the assay the plates are washed using a standard assay buffer (HBSS with 10 mM Hepes) and incubated for 15 minutes in serum free cell culture medium before the addition of a commercially available membrane potential sensitive fluorescent dye (FLIPR Red membrane potential dye, Molecular Devices Corporation). T84 cells are incubated with the FLIPR Red membrane
15 potential dye for 45 minutes in the presence and absence of test compound before being transferred to a commercially available fluorescence imaging plate reader (FLIPR384, Molecular Devices Corporation). Fluorescence levels are monitored continuously every second for 150 seconds; after an initial 10 second baseline, CFTR channel activity is stimulated through the addition of 10 μ M forskolin in the presence of 100 μ M of the
20 phosphodiesterase inhibitor iso-butyl-methylxanthine (IBMX). Addition of the forskolin leads to the activation of intracellular adenylyl cyclase I, elevating cAMP levels and results in the phosphorylation and opening of CFTR anion channels. CFTR channel opening causes chloride ion efflux and subsequent depolarization of the cells, which is measured by an increase in fluorescence. CFTR inhibitor compounds prevent cell depolarization and the
25 associated increase in fluorescence.

Example 2

FRT Assay

[0296] Fisher Rat Thyroid (FRT) cells stably co-expressing wildtype human CFTR and a reporter protein such as green fluorescent protein (GFP) or a mutant such as the yellow fluorescent protein-based $\text{Cl}^{31}/\text{I}^{-}$ halide sensor *e.g.* YFP-H148Q can be cultured on 96-well plates as described in Gruenert (2004), *supra* or Ma *et al.* (2002) J. Clin. Invest. **110**:1651-1658. Following a 48 hour incubation confluent FRT-CFTR-YFP-H148Q cells in 96-well plates are washed three times with phosphate buffered saline (PBS) and then CFTR halide conductance is activated by incubation for 5 minutes with a cocktail containing 5 μM , forskolin, 25 μM apigenin and 100 μM isobutylmethyl-xanthine (IBMX). Test compounds at a final concentration of 10 μM and 20 μM are added five minutes prior to assay of iodide influx in which cells are exposed to a 100 mM inwardly-directed iodide gradient. Baseline YFP fluorescence is recorded for two seconds followed by 12 seconds of continuous recording of fluorescence after rapid addition of the I^{-} containing solution to create a I^{-} gradient. Initial rates of I^{-} influx can be computed from the time course of decreasing fluorescence after the I^{-} gradient as known to those skilled in the art and described in Yang *et al.* (2002) J. Biol. Chem.: 35079-35085.

[0297] Activity of the CFTR channel can also be measured directly using electrophysiological methods. An example protocol for measuring CFTR current is described as whole cell patch clamp method. As an illustration, recordings are conducted at room temperature ($\sim 21^{\circ}\text{C}$) using a HEKA EPC-10 amplifier. Electrodes are fabricated from 1.7 mm capillary glass with resistances between 2 and 3 $\text{M}\Omega$ using a Sutter P-97 puller. For recording the CFTR channels, the extracellular solution can contain (in mM) 150 NaCl, 1 CaCl_2 , 1 MgCl_2 , 10 glucose, 10 mannitol, and 10 TES (pH 7.4), and the intracellular (pipette) solution can contain 120 CsCl, MgCl_2 , 10 TEA-Cl, 0.5 EGTA, 1 Mg-ATP and 10 HEPES (pH 7.3).

[0298] The CFTR channels are activated by forskoin (5 μM) in the extracellular solution. The cells are held at a potential of 0 mV and currents are recorded by a voltage ramp protocol from -120 mV to +80 mV over 500 ms every 10 seconds. No leak subtraction was employed. Compounds are superfused to individual cells using a Biologic MEV-9/EVH-9 rapid perfusion system.

[0299] Each of the above compounds were active in at least one of these assays. Activity was assessed by the compounds exhibiting an IC_{50} of less than 30 μM in the T84 assay, a greater than 30% inhibition at 20 μM in the FRT assay, and/or a greater than 35% inhibition at 50 μM in a T84 assay, provided that the compound does not have an IC_{50} greater than 30 μM .

[0300] The IC_{50} values of the compounds described herein in the T84 assay are as provided in Table 8 below. Unless otherwise indicated, the IC_{50} values are reported as an average of at least 2 runs. Where only 1 run is used, it is indicated by the annotation "n = 1."

Table 8

Cmpd No.	IC_{50} (μM)
1	9.79
2	5.79
3	17.17
4	5.55
5	27.68
6	1.40
7	2.23
8	0.05
9	0.05
10	7.92 (n=1)
11	11.42
12	11.66
13	18.72 (n=1)
14	20.12 (n=1)
15	27.74 (n=1)
16	2.24
17	6.05
18	8.09
19	13.91
20	14.76
21	18.65
22	2.84
23	3.03
24	15.44
26	3.77

In vivo study

Example 1

[0301] For *in vivo* studies for the treatment of diarrhea, mice (CD1 strain, approximately 25 g) were deprived of food for at least 20 hours and anaesthetized with an intraperitoneal injection of ketamine (80 mg/kg) and xylazine (16 mg/kg) prior to surgery. Anesthesia was maintained as needed. Body temperature was maintained using a heated operating table. The abdominal area was shaved and disinfected with 70 % alcohol swabs. An incision was made on the abdomen for exposure of the small intestine. Following the abdominal incision two different closely-spaced locations of the small intestine were isolated and looping was performed. Loop 1 started around 6 cm from the junction of stomach and duodenum. Loop 1 and Loop 2 were intestinal loops of around 25 mm in length with inter-loop space of around 5-10 mm. One hundred microliters of the PBS pH 8.5 or the PBS pH 8.5 containing 2.0 µg cholera toxin (CTX) (with or without test article) was injected into each loop. The abdominal incision was then closed with sutures and mice were allowed to recover from anesthesia. During this recovery period, close monitoring was performed. At 4 hours after the injection of the test article or control article dose formulation, the mice were euthanized via CO₂ inhalation plus diaphragm severance, the intestinal loops were exteriorized, and loop length and loop weight were measured after removal of mesentery and connective tissue to quantify the net fluid secretion (measured as g/cm of loop).

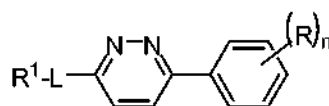
[0302] For **compound 2**, the closed loop % inhibition @ 100 µg was 98.2 (p<0.001).

[0303] For closed-loop data: the p-value is a measure of probability derived from a Dunnett's test statistical analysis when comparing the values obtained with test compound and CTX and values obtained with vehicle and CTX. A value of $p < 0.05$ is considered statistically significant.

[0304] It is to be understood that while the invention has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

WHAT IS CLAIMED IS:

1. A compound of formula I:

**I**

5 wherein

n is 1, 2, 3, 4, or 5;

L is a bond or a linker of 1 to 6 linear or branched covalently linked atoms;

R¹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, aryloxy and substituted aryloxy;

15 or R¹ and L are taken together with the atom to which they are bonded to form a heterocycle or substituted heterocycle; and

each R are independently selected from the group consisting of hydrogen, hydroxyl, alkyl, substituted alkyl, halo, amino, sulfonylamino, aminocarbonyl, alkoxy and substituted alkoxy, provided that at least one R is sulfonylamino or aminocarbonyl;

20 or a pharmaceutically acceptable salt, isomer, or tautomer thereof;

wherein said compound exhibits at least one of the following:

a) an IC₅₀ of less than 30 μM in the T84 assay;

b) a greater than 30% inhibition at 20 μM in the FRT assay; or

25 c) a greater than 35% inhibition at 50 μM in a T84 assay, provided that the compound does not have an IC₅₀ greater than 30 μM.

2. The compound of claim 1, wherein said compound exhibits an IC₅₀ of less than 30 μM in the T84 assay.

3. The compound of any of the preceding claims, wherein said compound exhibits a greater than 30% inhibition at 20 μ M in the FRT assay.
4. The compound of any of the preceding claims, wherein said compound exhibits a greater than 35% inhibition at 50 μ M in a T84 assay, provided that the compound
5 does not have an IC_{50} greater than 30 μ M.
5. The compound of any of the preceding claims, wherein R is hydrogen, hydroxyl, bromo, chloro, methoxy, amino, $-NH-S(O)_2-R^2$, or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino.
- 10 6. The compound of any of the preceding claims, wherein R is $-NH-S(O)_2-R^2$, where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino.
7. The compound of claim 6, wherein substituted aryl is substituted with a substituent selected from the group consisting of halo, alkyl, alkoxy, halo, cyano, amino,
15 substituted amino, heterocycle, and substituted heterocycle.
8. The compound of claim 6, wherein substituted alkyl is substituted with a halo or aryl.
9. The compound of any of claims 1-5, wherein R is $-C(O)NH-S(O)_2-R^2$, where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino.
- 20 10. The compound of claim 9, wherein substituted aryl is substituted with a group selected from the group consisting of alkyl, alkoxy, halo, cyano, amino, substituted amino, heterocycle, and substituted heterocycle.
11. The compound of claim 9, wherein substituted alkyl is substituted with a halo or aryl.
12. The compound of any of the preceding claims, wherein R^1 is selected from the
25 group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl.
13. The compound of claim 1, wherein R^1 and L are taken together with the atom to which they are bonded to form a heterocycle or substituted heterocycle.

14. The compound of claim 1, wherein R^1 is substituted alkyl substituted with aryl or substituted aryl.

15. The compound of claim 14, wherein R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl.

5 16. The compound of any of claims 1-12, wherein R^1 is substituted alkyl substituted with a substituent selected from the group consisting of phenyl, 4-chlorophenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, and 3-trifluoromethylphenyl.

10 17. The compound of any of the preceding claims, wherein L is selected from the group consisting of alkylene, substituted alkylene, $-O-$, $-NR^3-$, $-S-$, $-NR^3C(O)-$, and $-C(OH)R^3-$; where

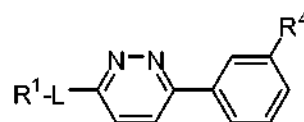
R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, aryloxy and substituted aryloxy;
or R^1 and R^3 are taken together with the atom to which they are bonded to
20 form a heterocycle or substituted heterocycle.

18. The compound of any of the preceding claims, wherein L is selected from the group consisting of $-O-$, $-NR^3-$, and $-NR^3C(O)-$, where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl.

19. The compound of any of the preceding claims, wherein L is $-O-$ or $-N(CH_2CH_3)-$.

25 20. The compound of any of the preceding claims, wherein n is 1 or 2.

21. The compound of claim 1, wherein the compound is of formula II:



II

wherein

L is $-O-$, $-NR^3-$, and $-NR^3C(O)-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl;

R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, aryloxy and substituted aryloxy;

or R^1 and L are taken together with the atom to which they are bonded to form a heterocycle or substituted heterocycle; and

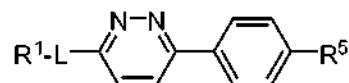
R^4 is sulfonylamino or aminocarbonyl;

or a pharmaceutically acceptable salt, isomer, or tautomer thereof.

22. The compound of claim 21, wherein L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl.
23. The compound of claim 21 or 22, wherein R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl.
24. The compound of any of claims 21-23, wherein R^4 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino.
25. The compound of claim 21, wherein L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl; R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl; and R^4 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino.
26. The compound of claim 21, wherein L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl; R^1 is substituted alkyl substituted

with phenyl or halo substituted phenyl; and R^4 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl; substituted alkyl substituted with halo or aryl; aryl; substituted aryl substituted with halo, alkyl, alkoxy, cyano, or acylamino; heteroaryl; substituted heteroaryl substituted with heterocycle; amino; and substituted amino substituted with alkyl.

27. The compound of claim 1, wherein the compound is of formula III:



III

wherein

L is $-O-$, $-NR^3-$, and $-NR^3C(O)-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl;

R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, aryloxy and substituted aryloxy;

or R^1 and L are taken together with the atom to which they are bonded to form a heterocycle or substituted heterocycle; and

R^5 is sulfonylamino or aminocarbonyl;

or a pharmaceutically acceptable salt, isomer, or tautomer thereof.

28. The compound of claim 27, wherein L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl.

29. The compound of claim 27 or 28, wherein R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl.

30. The compound of any of claims 27-29, wherein R^5 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl, substituted alkyl,

aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, and substituted amino.

31. The compound of claim 27, wherein L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl; R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl; and R^5 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, and substituted aryl.
32. The compound of claim 27, wherein L is $-O-$ or $-NR^3-$ where R^3 is selected from the group consisting of hydrogen, methyl, and ethyl; R^1 is substituted alkyl substituted with phenyl or halo substituted phenyl; and R^5 is $-NH-S(O)_2-R^2$ or $-C(O)NH-S(O)_2-R^2$ where R^2 is selected from the group consisting of alkyl; substituted alkyl substituted with halo; aryl; substituted aryl substituted with halo or alkyl.
33. A compound selected from the group consisting of:
N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)methanesulfonamide;
N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-4-cyanobenzenesulfonamide;
N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-6-morpholinopyridine-3-sulfonamide;
N-(4-(N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)sulfamoyl)phenyl)acetamide;
4-(6-(4-chlorophenethoxy)pyridazin-3-yl)-2-methoxyphenol;
N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)dimethylaminosulfonamide;
N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)methanesulfonamide;
N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-4-methylbenzenesulfonamide;
N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-3-bromobenzenesulfonamide;
N-(3-(6-(benzyl(ethyl)amino)pyridazin-3-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

- 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(4-methoxyphenylsulfonyl)benzamide;
 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(4-fluorophenylsulfonyl)benzamide;
 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(ethylsulfonyl)benzamide;
 N-(4-tert-butylphenylsulfonyl)-3-(6-(4-chlorophenethoxy)pyridazin-3-yl)benzamide;
 5 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(3,4-
 difluorophenylsulfonyl)benzamide;
 N-(3-(6-(benzylamino)pyridazin-3-yl)phenyl)-4-methylbenzenesulfonamide;
 N-(benzylsulfonyl)-3-(6-(4-chlorophenethoxy)pyridazin-3-yl)benzamide;
 4-tert-butyl-N-(3-(6-(4-chlorophenethoxy)pyridazin-3-
 10 yl)phenyl)benzenesulfonamide;
 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(3,4-
 difluorophenylsulfonyl)benzamide;
 N-(3-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-2,2,2-
 trifluoroethanesulfonamide;
 15 3-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-(2,4-
 difluorophenylsulfonyl)benzamide;
 N-(4-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 4-(6-(4-chlorophenethoxy)pyridazin-3-yl)-N-tosylbenzamide;
 20 Benzyl-{6-[3-(1,1-dioxo-isothiazolidin-2-yl)-phenyl]-pyridazin-3-yl}-ethylamine;
 and
 N-(4-(6-(4-chlorophenethoxy)pyridazin-3-yl)phenyl)-2-methylpropane-1-
 sulfonamide;
 or a pharmaceutically acceptable salt, isomer, or tautomer thereof.
- 25 34. A composition comprising a compound of any one of claims 1-33 and a carrier.
35. A pharmaceutical composition comprising a compound of any one of claims 1-33
 and a pharmaceutically acceptable carrier.

36. A method for treating diarrhea in an animal in need thereof comprising administering to the animal an effective amount of the compound of any of claims 1-33 or the composition of claim 35, thereby treating diarrhea.

37. The method of claim 36, wherein the composition is administered in a pharmaceutical formulation suitable for administration orally, intraluminely or by suppository.

38. The method of claim 36 or 37, wherein the pharmaceutical formulation is a sustained release formulation.

39. The method of any of claims 36-38, wherein the animal is a human patient or a farm animal.

40. The method of any of claims 36-39, wherein the diarrhea is secretory diarrhea.

41. The method of any of claims 36-40, wherein the diarrhea is selected from the group consisting of infectious diarrhea, inflammatory diarrhea and diarrhea associated with chemotherapy.

42. The method of any of claims 36-41, further comprising administering an effective amount of an oral glucose-electrolyte solution or an effective amount of a micronutrient to the animal.

43. A method for treating polycystic kidney disease (PKD) in an animal in need thereof, comprising administering to the animal an effective amount of the compound of any of claims 1-33 or the composition of claim 35, thereby treating PKD.

44. A method of treating a disease in an animal, which disease is responsive to inhibiting of functional cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide, comprising administering to an animal in need thereof an effective amount of the compound of any of claims 1-33 or the composition of claim 35, thereby treating the disease.

45. The method of claim 44, wherein the compound inhibits halide ion transport by CFTR.

46. The method of claim 44 or 45, wherein the disease is selected from the group consisting of secretory diarrhea, inflammatory diarrhea, inflammatory bowel disease,

infectious diarrhea, polycystic kidney disease (PKD), cardiac arrhythmia, male infertility and disorders associated with neovascularization.

47. A method for inhibiting the transport of a halide ion across a mammalian cell membrane expressing functional cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide, comprising contacting the CFTR polypeptide with an effective amount
5 of the compound of any of claims 1-33 or the composition of claim 35, thereby inhibiting the transport of the halide ion.

48. The method of claim 47, wherein the halide ion is at least one of F^- , Cl^- or Br^- .

49. The method of claim 47 or 48, wherein the halide ion is Cl^- .

10 50. The method of any of claims 47-49, wherein the functional CFTR is wild-type full length CFTR.

51. The method of any of claims 47-50, wherein the mammalian cell is an epithelial cell, luminal epithelial cell or a kidney cell.

15 52. The method of any of claims 47-51, wherein the mammalian cell is an intestinal epithelial cell or a colon epithelial cell.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/31608

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 43/58; A61K 31/50 (2010.01) USPC - 514/247-248 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) USPC: 514/247-248		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 514/117, 236.5, 601-602 (see search terms below)		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWEST (PGPB,USPT,EPAB,JPAB), Google Scholar, Patentscope (worldwide) pyridazine, phenylpyridazine, pyridazin\$, \$pyridazine, \$sulfonamide, \$carboxamide, diarrhea, polycystic kidney disease, CFTR,inhibit\$, modulat\$, T84, FRT, IC50		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0269206 A1 (RUSSELL et al.) 30 October 2008 (30.10.2008) para [0011]-[0014], [0017], [01029]-[0030], [0032], [0150], [0155], [0166]-[0169], [0593]-[0594]	1-3, 13-15, 21-23, 25-29, 31-33
Y	US 2008/0293717 A1 (UGASHE et al.) 27 November 2008 (27.11.2008) para [0049]-[0057], [0420]	1-3, 13-15, 21-23, 25-29, 31-33
Y	US 2008/0051410 A1 (WATTERSON et al.) 28 February 2008 (28.02.2008) para [0008], [0046]	13-15, 21-23, 25-26, 29, 31-33
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 02 June 2010 (02.06.2010)		Date of mailing of the international search report 16 JUN 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/31608

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-12, 16-20, 24, 30 and 34-52
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.