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[Continued on next page]

(54) Title: ANTIVIRAL COMPOUNDS

Figure 1

Name or CAS No.	IUPAC Name	Structure
BMS-433771	1-cyclopropyl-3-[[1-(4-hydroxybutyl)benzimidazol-2-yl]methyl]imidazo[4,5-c]pyridin-2-one	
VP-14637 (MDT-637)	5,5'-bis[1-((5-amino-1H-tetrazolyl)imino)methyl]-2,2',4',4'-methylidynetrisphenol	
JNJ-2408068	2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-4-methyl-1H-benzimidazol-1-yl]-6-methyl-3-pyridinol	

(57) Abstract: Disclosed herein are new antiviral compounds, together with pharmaceutical compositions that include one or more antiviral compounds, and methods of synthesizing the same. Also disclosed herein are methods of ameliorating and/or treating a paramyxovirus viral infection with one or more small molecule compounds. Examples of paramyxovirus infection include an infection caused by human respiratory syncytial virus (RSV).



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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))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- *with international search report (Art. 21(3))*
- *with sequence listing part of description (Rule 5.2(a))*

ANTIVIRAL COMPOUNDS

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6.

REFERENCE TO SEQUENCE LISTING

[0002] The present application is filed with a Sequence Listing in Electronic format. The Sequence Listing is provided as a file entitled ALIOS093.txt, created February 24, 2016, which is approximately 4 kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

BACKGROUND

Field

[0003] The present application relates to the fields of chemistry, biochemistry and medicine. More particularly, disclosed herein are new antiviral compounds, together with pharmaceutical compositions, and methods of synthesizing the same. Also disclosed herein are methods of ameliorating and/or treating a paramyxovirus viral infection with one or more small molecule compounds.

Description

[0004] Respiratory viral infections, including upper and lower respiratory tract viral infections, are a leading cause of death of millions of people each year. Upper respiratory tract viral infections involve the nose, sinuses, pharynx and/or larynx. Lower respiratory tract viral infections involve the respiratory system below the vocal cords, including the trachea, primary bronchi and lungs. Human respiratory syncytial virus (RSV) is a common cause of respiratory tract infections. Up to 60% of human infants are infected with RSV within their first year of life. Children and adults are also infected with RSV,

where it is often manifesting as a lower respiratory tract infection with possible complications of bronchiolitis. RSV infections can be particularly severe in infants and elderly patients. RSV is a negative-sense, single-stranded RNA virus classified within the Paramyxoviridae family, which also includes viruses that cause Newcastle disease, parainfluenza, mumps, measles, and canine distemper.

SUMMARY

[0005] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0006] Some embodiments disclosed herein relate to a method of ameliorating and/or treating a paramyxovirus viral infection that can include administering to a subject suffering from the paramyxovirus viral infection an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to using one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ameliorating and/or treating a paramyxovirus viral infection. Still other embodiments described herein relate to compounds of Formula (I), or a pharmaceutically acceptable salt thereof, that can be used for ameliorating and/or treating a paramyxovirus viral infection. Yet still other embodiments disclosed herein relate to a method of ameliorating and/or treating a paramyxovirus viral infection that can include contacting a cell infected with the paramyxovirus with an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof. Some embodiments disclosed herein relate to a method of inhibiting the replication of a paramyxovirus that can include contacting a cell infected with the paramyxovirus with an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof. For example, the paramyxovirus viral infection can be caused by a henipavirus, a morbillivirus, a respirovirus, a rubulavirus, a pneumovirus (including a respiratory syncytial viral infection), a

metapneumovirus, hendravirus, nipahvirus, measles, sendai virus, mumps, a human parainfluenza virus (HPIV-1, HPIV-2, HPIV-3 and HPIV-4) and/or a metapneumovirus.

[0007] Some embodiments disclosed herein relate to a method of ameliorating and/or treating a paramyxovirus viral infection that can include administering to a subject suffering from the viral infection an effective amount of a compound described herein or a pharmaceutically acceptable salt thereof (for example, one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition that includes one or more compounds described herein, in combination with one or more agents described herein. Some embodiments disclosed herein relate to a method of ameliorating and/or treating a paramyxovirus viral infection that can include contacting a cell infected with the paramyxovirus with an effective amount of a compound described herein or a pharmaceutically acceptable salt thereof (for example, one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition that includes one or more compounds described herein, in combination with one or more agents described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Figure 1 illustrates examples of compounds of Formula (I), or pharmaceutically acceptable salt of any of the foregoing compounds.

DETAILED DESCRIPTION

[0009] *Paramyxoviridae* family is a family of single stranded RNA viruses. Several genera of the *paramyxoviridae* family include henipavirus, morbillivirus, respirovirus, rubulavirus, pneumovirus and metapneumovirus. These viruses can be transmitted person to person via direct or close contact with contaminated respiratory droplets or fomites. Species of henipavirus include hendravirus and nipahvirus. A species of morbillivirus is measles. Species of respirovirus include sendai virus and human parainfluenza viruses 1 and 3; and species of rubulavirus include mumps virus and human parainfluenza viruses 2 and 4. A species of metapneumovirus is human metapneumovirus.

[0010] Human Respiratory Syncytial Virus (RSV), a species of pneumovirus, can cause respiratory infections, and can be associated with bronchiolitis and pneumonia.

Symptoms of an RSV infection include coughing, sneezing, runny nose, fever, decrease in appetite, and wheezing. RSV is the most common cause of bronchiolitis and pneumonia in children under one year of age in the world, and can be the cause of tracheobronchitis in older children and adults. In the United States, between 75,000 and 125,000 infants are hospitalized each year with RSV. Among adults older than 65 years of age, an estimated 14,000 deaths and 177,000 hospitalizations have been attributed to RSV.

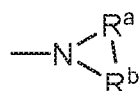
[0011] Treatment options for people infected with RSV are currently limited. Antibiotics, usually prescribed to treat bacterial infections, and over-the-counter medication are not effective in treating RSV. In severe cases, a nebulized bronchodilator, such as albuterol, may be prescribed to relieve some of the symptoms, such as wheezing. RespiGram® (RSV-IGIV, MedImmune, approved for high risk children younger than 24 months of age), Synagis® (palivizumab, MedImmune, approved for high risk children younger than 24 months of age), and Virzole® (ribavirin by aerosol, ICN pharmaceuticals) have been approved for treatment of RSV.

[0012] Symptoms of the measles include fever, cough, runny nose, red eyes and a generalized rash. Some individuals with measles can develop pneumonia, ear infections and bronchitis. Mumps leads to swelling of the salivary glands. Symptoms of mumps include fever, loss of appetite and fatigue. Individuals are often immunized against measles and mumps via a three-part MMR vaccine (measles, mumps, and rubella). Human parainfluenza virus includes four serotypes types, and can cause upper and lower respiratory tract infections. Human parainfluenza virus 1 (HPIV-1) can be associated with croup; human parainfluenza virus 3 (HPIV-3) can be associated with bronchiolitis and pneumonia. According to the Centers of Disease Control and Prevention (CDC), there are no vaccines against human parainfluenza virus.

Definitions

[0013] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0014] As used herein, any "R" group(s) such as, without limitation, $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}$, and R^A represent substituents that can be attached to the indicated atom. An R group may be substituted or unsubstituted. If two "R" groups are described as being "taken together" the R groups and the atoms they are attached to can form a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^a and R^b of an NR^aR^b group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



In addition, if two "R" groups are described as being "taken together" with the atom(s) to which they are attached to form a ring as an alternative, the R groups are not limited to the variables or substituents defined previously.

[0015] Whenever a group is described as being "optionally substituted" that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being "unsubstituted or substituted" if substituted, the substituent(s) may be selected from one or more of the indicated substituents. If no substituents are indicated, it is meant that the indicated "optionally substituted" or "substituted" group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, acylalkyl, hydroxy, alkoxy, alkoxyalkyl, aminoalkyl, amino acid, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), hydroxyalkyl, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, azido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amino group and a di-substituted amino group.

[0016] As used herein, " C_a to C_b " in which "a" and "b" are integers refer to the number of carbon atoms in an alkyl, alkenyl or alkynyl group, or the number of carbon atoms in the ring of a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heteroalicycyl group. That is,

the alkyl, alkenyl, alkynyl, ring(s) of the cycloalkyl, ring(s) of the cycloalkenyl, ring(s) of the aryl, ring(s) of the heteroaryl or ring(s) of the heteroalicycyl can contain from “a” to “b”, inclusive, carbon atoms. Thus, for example, a “C₁ to C₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)- and (CH₃)₃C-. If no “a” and “b” are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, aryl, heteroaryl or heteroalicycyl group, the broadest range described in these definitions is to be assumed.

[0017] As used herein, “alkyl” refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; *e.g.*, “1 to 20 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as “C₁-C₄ alkyl” or similar designations. By way of example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. The alkyl group may be substituted or unsubstituted.

[0018] As used herein, “alkenyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. Examples of alkenyl groups include allenyl, vinylmethyl and ethenyl. An alkenyl group may be unsubstituted or substituted.

[0019] As used herein, “alkynyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. Examples of alkynyls include ethynyl and propynyl. An alkynyl group may be unsubstituted or substituted.

[0020] As used herein, “cycloalkyl” refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused fashion. Cycloalkyl groups can

contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0021] As used herein, “cycloalkenyl” refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be “aryl,” as defined herein). Cycloalkenyl groups can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). When composed of two or more rings, the rings may be connected together in a fused fashion. A cycloalkenyl group may be unsubstituted or substituted.

[0022] As used herein, “aryl” refers to a carbocyclic (all carbon) monocyclic or polycyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C₆-C₁₄ aryl group, a C₆-C₁₀ aryl group, or a C₆ aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0023] As used herein, “heteroaryl” refers to a monocyclic or polycyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one, two, three or more heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s) of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). Furthermore, the term “heteroaryl” includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring, or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, those described herein and the following: furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine,

pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0024] As used herein, “heterocyclyl” or “heteroalicyclyl” refers to three-, four-, five-, six-, seven-, eight-, nine-, ten-, up to 18-membered monocyclic, bicyclic, and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur, and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused fashion. Additionally, any nitrogens in a heterocyclyl may be quaternized. Heterocyclyl or heteroalicyclic groups may be unsubstituted or substituted. Examples of such “heterocyclyl” or “heteroalicyclyl” groups include, but are not limited to, those described herein and the following: 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 1,3-thiazinane, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine *N*-Oxide, piperidine, piperazine, pyrrolidine, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone, and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline, and 3,4-methylenedioxyphenyl).

[0025] As used herein, “aralkyl” and “aryl(alkyl)” refer to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aralkyl may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenylalkyl, 3-phenylalkyl and naphthylalkyl.

[0026] As used herein, “heteroaralkyl” and “heteroaryl(alkyl)” refer to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene

and heteroaryl group of heteroaralkyl may be substituted or unsubstituted. Examples include but are not limited to 2-thienylalkyl, 3-thienylalkyl, furylalkyl, thienylalkyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl, imidazolylalkyl and their benzo-fused analogs.

[0027] A “heteroalicycyl(alkyl)” and “heterocycyl(alkyl)” refer to a heterocyclic or a heteroalicyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocycyl of a heteroalicycyl(alkyl) may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl(methyl), piperidin-4-yl(ethyl), piperidin-4-yl(propyl), tetrahydro-2H-thiopyran-4-yl(methyl), and 1,3-thiazinan-4-yl(methyl).

[0028] “Lower alkylene groups” are straight-chained $-\text{CH}_2-$ tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$), propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), and butylene ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$). A lower alkylene group can be substituted by replacing one or more hydrogen of the lower alkylene group with a substituent(s) listed under the definition of “substituted.”

[0029] As used herein, “alkoxy” refers to the formula $-\text{OR}$ wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocycyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocycyl(alkyl) is defined herein. A non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzoxy. An alkoxy may be substituted or unsubstituted.

[0030] As used herein, “acyl” refers to a hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocycyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocycyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl and acryl. An acyl may be substituted or unsubstituted.

[0031] As used herein, “acylalkyl” refers to an acyl connected, as a substituent, via a lower alkylene group. Examples include $\text{aryl-C(=O)-(CH}_2\text{)}_n-$ and $\text{heteroaryl-C(=O)-(CH}_2\text{)}_n-$, where n is an integer in the range of 1 to 6.

[0032] As used herein, “alkoxyalkyl” refers to an alkoxy group connected, as a substituent, via a lower alkylene group. Examples include C_{1-4} alkyl-O-(CH₂)_n, wherein n is an integer in the range of 1 to 6.

[0033] As used herein, “aminoalkyl” refers to an optionally substituted amino group connected, as a substituent, via a lower alkylene group. Examples include H₂N(CH₂)_n, wherein n is an integer in the range of 1 to 6.

[0034] As used herein, “hydroxyalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a hydroxy group. Exemplary hydroxyalkyl groups include but are not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, and 2,2-dihydroxyethyl. A hydroxyalkyl may be substituted or unsubstituted.

[0035] As used herein, “haloalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl and tri-haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloro-fluoroalkyl, chloro-difluoroalkyl and 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0036] As used herein, “haloalkoxy” refers to an alkoxy group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di-haloalkoxy and tri-haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloro-fluoroalkyl, chloro-difluoroalkoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0037] A “sulfenyl” group refers to an “-SR” group in which R can be hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A sulfenyl may be substituted or unsubstituted.

[0038] A “sulfinyl” group refers to an “-S(=O)-R” group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[0039] A “sulfonyl” group refers to an “SO₂R” group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0040] An “O-carboxy” group refers to a “RC(=O)O-” group in which R can be hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl,

heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. An O-carboxy may be substituted or unsubstituted.

[0041] The terms “ester” and “C-carboxy” refer to a “-C(=O)OR” group in which R can be the same as defined with respect to O-carboxy. An ester and C-carboxy may be substituted or unsubstituted.

[0042] A “thiocarbonyl” group refers to a “-C(=S)R” group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[0043] A “trihalomethanesulfonyl” group refers to an “X₃CSO₂-” group wherein each X is a halogen.

[0044] A “trihalomethanesulfonamido” group refers to an “X₃CS(O)₂N(R_A)-” group wherein each X is a halogen, and R_A hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl).

[0045] The term “amino” as used herein refers to a -NH₂ group.

[0046] As used herein, the term “hydroxy” refers to a -OH group.

[0047] A “cyano” group refers to a “-CN” group.

[0048] The term “azido” as used herein refers to a -N₃ group.

[0049] An “isocyanato” group refers to a “-NCO” group.

[0050] A “thiocyanato” group refers to a “-CNS” group.

[0051] An “isothiocyanato” group refers to an “-NCS” group.

[0052] A “carbonyl” group refers to a C=O group.

[0053] An “S-sulfonamido” group refers to a “-SO₂N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

[0054] An “N-sulfonamido” group refers to a “RSO₂N(R_A)-” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.

[0055] An “O-carbamyl” group refers to a “-OC(=O)N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-carbamyl may be substituted or unsubstituted.

[0056] An “N-carbamyl” group refers to an “ROC(=O)N(R_A)-” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-carbamyl may be substituted or unsubstituted.

[0057] An “O-thiocarbamyl” group refers to a “-OC(=S)-N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-thiocarbamyl may be substituted or unsubstituted.

[0058] An “N-thiocarbamyl” group refers to an “ROC(=S)N(R_A)-” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-thiocarbamyl may be substituted or unsubstituted.

[0059] A “C-amido” group refers to a “-C(=O)N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A C-amido may be substituted or unsubstituted.

[0060] An “N-amido” group refers to a “RC(=O)N(R_A)-” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0061] A “urea” group refers to “N(R)-C(=O)-NR_AR_B” group in which R can be hydrogen or an alkyl, and R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A urea may be substituted or unsubstituted.

[0062] The term “halogen atom” or “halogen” as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine.

[0063] As used herein, “-----” indicates a single or double bond, unless stated otherwise.

[0064] The term “interferon” is used herein as is commonly understood by one of ordinary skill in the art. Several types of interferons are known to those skilled in the art, such as Type I interferons, Type 2 interferons and Type 3 interferons. A non-limiting list of examples include: alpha-interferons, beta-interferons, delta-interferons, gamma interferons, lambda interferons, omega-interferons, tau-interferons, x-interferons, consensus interferons and asialo-interferons. Interferons can be pegylated. Examples of type 1 interferons include interferon alpha 1A, interferon alpha 1B, interferon alpha 2A, interferon alpha 2B, pegylated-interferon alpha 2a (PEGASYS, Roche), recombinant interferon alpha 2a (ROFERON, Roche), inhaled interferon alpha 2b (AERX, Aradigm), pegylated-interferon alpha 2b (ALBUFERON, Human Genome Sciences/Novartis, PEGINTRON, Schering), recombinant interferon alpha 2b (INTRON A, Schering), pegylated interferon alpha 2b (PEG-INTRON, Schering, VIRAFERONPEG, Schering), interferon beta-1a (REBIF, Serono, Inc. and Pfizer), consensus interferon alpha (INFERGEN, Valeant Pharmaceutical). Examples of type 2 interferons include interferon gamma 1, interferon gamma 2 and pegylated interferon gamma; and examples of type 3 interferons include interferon lambda 1, interferon lambda 2 and interferon lambda 3.

[0065] Where the numbers of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example “haloalkyl” may include one or more of the same or different halogens. As another example, “C₁-C₃ alkoxyphenyl” may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0066] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (See, Biochem. 11:942-944 (1972)).

[0067] As used herein, the term “amino acid” refers to any amino acid (both standard and non-standard amino acids), including, but not limited to, α -amino acids, β -

amino acids, γ -amino acids and δ -amino acids. Examples of suitable amino acids include, but are not limited to, alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Additional examples of suitable amino acids include, but are not limited to, ornithine, hypusine, 2-aminoisobutyric acid, dehydroalanine, gamma-aminobutyric acid, citrulline, beta-alanine, alpha-ethyl-glycine, alpha-propyl-glycine and norleucine. As used herein, "amino acid" also includes amino acids wherein the main-chain carboxylic acid group has been converted to an ester group.

[0068] The terms "protecting group" and "protecting groups" as used herein refer to any atom or group of atoms that is added to a molecule in order to prevent existing groups in the molecule from undergoing unwanted chemical reactions. Examples of protecting group moieties are described in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3. Ed. John Wiley & Sons, 1999, and in J.F.W. McOmie, *Protective Groups in Organic Chemistry* Plenum Press, 1973, both of which are hereby incorporated by reference for the limited purpose of disclosing suitable protecting groups. The protecting group moiety may be chosen in such a way, that they are stable to certain reaction conditions and readily removed at a convenient stage using methodology known from the art. A non-limiting list of protecting groups include benzyl; substituted benzyl; alkylcarbonyls and alkoxycarbonyls (e.g., t-butoxycarbonyl (BOC), acetyl, or isobutyryl); arylalkylcarbonyls and arylalkoxycarbonyls (e.g., benzyloxycarbonyl); substituted methyl ether (e.g. methoxymethyl ether); substituted ethyl ether; a substituted benzyl ether; tetrahydropyranyl ether; silyls (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, tri-*iso*-propylsilyloxymethyl, [2-(trimethylsilyl)ethoxy]methyl or t-butyldiphenylsilyl); esters (e.g. benzoate ester); carbonates (e.g. methoxymethylcarbonate); sulfonates (e.g. tosylate or mesylate); acyclic ketal (e.g. dimethyl acetal); cyclic ketals (e.g., 1,3-dioxane, 1,3-dioxolanes, and those described herein); acyclic acetal; cyclic acetal (e.g., those described herein); acyclic hemiacetal; cyclic hemiacetal; cyclic dithioketals (e.g., 1,3-dithiane or 1,3-dithiolane); orthoesters (e.g., those described herein) and triarylmethyl groups (e.g., trityl; monomethoxytrityl (MMTr); 4,4'-dimethoxytrityl (DMTr); 4,4',4''-trimethoxytrityl (TMTr); and those described herein).

[0069] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C₁-C₇ alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0070] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term ‘including’ should be read to mean ‘including, without limitation,’ ‘including but not limited to,’ or the like; the term ‘comprising’ as used herein is synonymous with ‘including,’ ‘containing,’ or ‘characterized by,’ and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term ‘having’ should be interpreted as ‘having at least,’ the term ‘includes’ should be interpreted as ‘includes but is not limited to;’ the term ‘example’ is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; and use of terms like ‘preferably,’ ‘preferred,’ ‘desired,’ or ‘desirable,’ and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment. In addition, the term “comprising” is to be interpreted synonymously with the phrases “having at least” or “including at least”. When used in the context of a process, the term “comprising” means that the process includes at least the recited steps, but

may include additional steps. When used in the context of a compound, composition or device, the term "comprising" means that the compound, composition or device includes at least the recited features or components, but may also include additional features or components. Likewise, a group of items linked with the conjunction 'and' should not be read as requiring that each and every one of those items be present in the grouping, but rather should be read as 'and/or' unless expressly stated otherwise. Similarly, a group of items linked with the conjunction 'or' should not be read as requiring mutual exclusivity among that group, but rather should be read as 'and/or' unless expressly stated otherwise.

[0071] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality. A single processor or other unit may fulfill the functions of several items recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

[0072] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z, or a mixture thereof.

[0073] Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

[0074] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

[0075] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

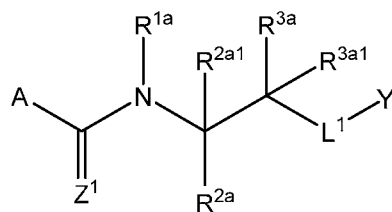
[0076] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates, and hydrates. In some embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, or the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[0077] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

Compounds

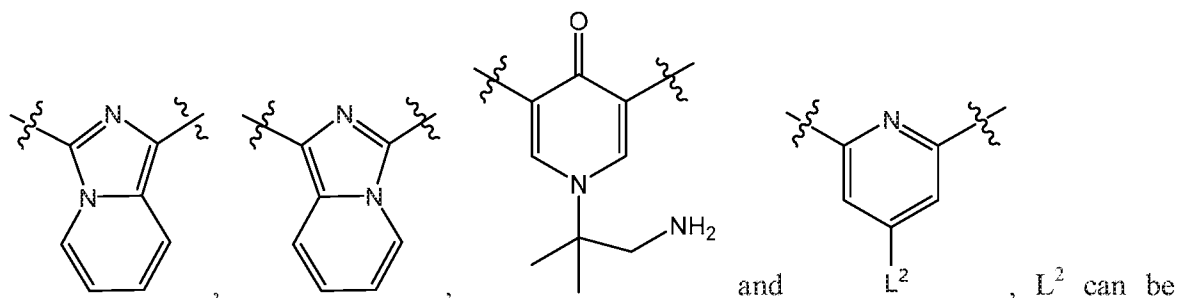
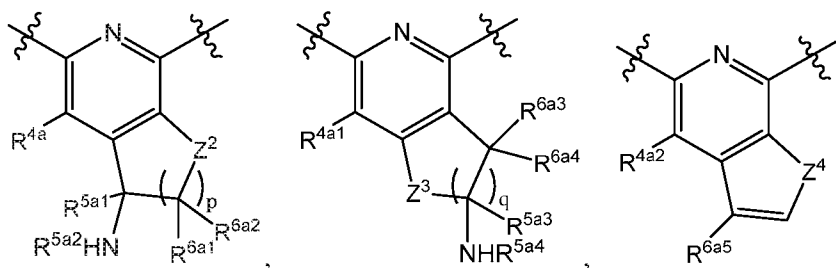
Formula (I)

[0078] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:

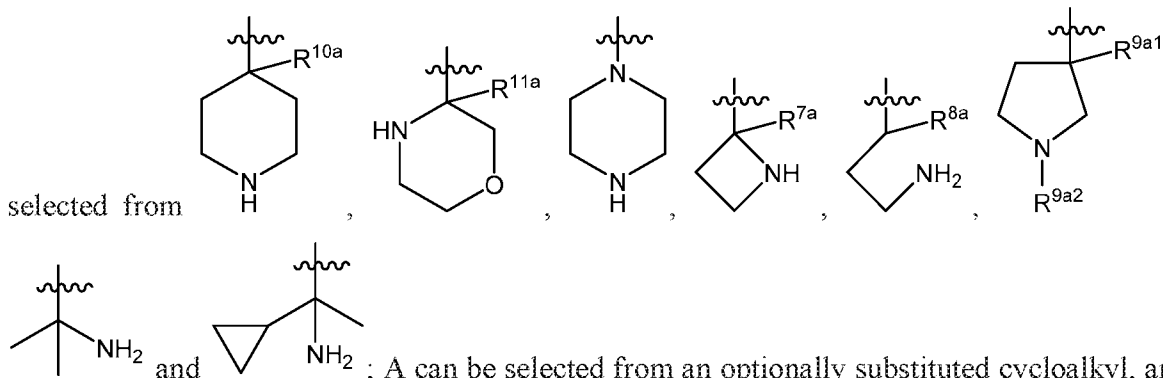


(I)

wherein: L^1 can be



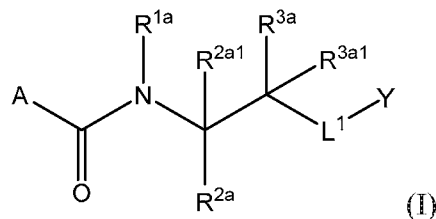
selected from



; A can be selected from an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl; Y can be selected from an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl; R^{1a} can be hydrogen or an unsubstituted C_{1-4} alkyl; R^{2a} and R^{2a1} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; R^{3a} and R^{3a1} can be each independently hydroxy, CHF_2 , CF_3 or NH_2 ; R^{4a} , R^{4a1} and R^{4a2} can be independently selected from hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{1-8} alkoxy and haloalkyl; R^{5a1} and R^{5a3} can be independently an unsubstituted

C₁₋₆ alkyl, an unsubstituted C₃₋₆ cycloalkyl or $-(CH_2)_{1-4}OH$; R^{5a2} and R^{5a4} can be independently hydrogen, hydroxy, an unsubstituted C₁₋₆ alkyl, an optionally substituted monocyclic heterocyclyl, $-C(=O)R^{5a5}$, an unsubstituted $-C$ -amido, $-C(=NH)-$ an unsubstituted C₁₋₆ alkyl; or R^{5a1} and R^{5a2} can be taken together with the atoms they are attached to form an optionally substituted 4 to 6 membered ring; R^{5a3} and R^{5a4} can be taken together with the atoms they are attached to form an optionally substituted 4 to 6 membered ring; R^{5a5} can be an unsubstituted C₁₋₄ alkyl; each R^{6a1}, each R^{6a2}, each R^{6a3} and each R^{6a4} can be independently selected from hydrogen, halogen, an unsubstituted C₁₋₆ alkyl and hydroxy; R^{6a5} can be selected from halogen, an unsubstituted C₁₋₆ alkyl and hydroxy; R^{7a} and R^{8a} can be each independently an unsubstituted C₁₋₆ alkyl; R^{9a1}, R^{9a2}, R^{10a} and R^{11a} can be independently hydrogen or an unsubstituted C₁₋₆ alkyl; Z¹ can be O (oxygen) or S (sulfur); Z² can be O (oxygen), NR^Z or CR^{Z1}R^{Z2}; Z³ can be O (oxygen), NR^{Z3} or CR^{Z4}R^{Z5}; Z⁴ can be O (oxygen), NR^{Z6} or CR^{Z7}R^{Z8}; R^Z, R^{Z1}, R^{Z2}, R^{Z3}, R^{Z4}, R^{Z5}, R^{Z6}, R^{Z7} and R^{Z8} can be independently hydrogen or an unsubstituted C₁₋₄ alkyl; and p and q can be independently 1 or 2.

[0079] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



wherein: L¹ can be

or

, L² can be selected

and

and

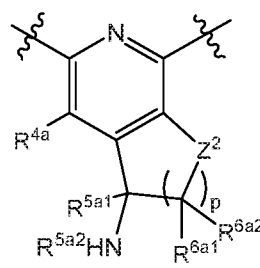
; A can be selected from an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl; Y can be selected from an optionally

substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl; R^{1a} can be hydrogen or an unsubstituted C_{1-4} alkyl; R^{2a} and R^{2a1} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; R^{3a} and R^{3a1} can be each independently hydroxy, CHF_2 or CF_3 ; R^{4a} can be selected from hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{1-8} alkoxy and haloalkyl; R^{5a1} can be an unsubstituted C_{1-6} alkyl or $-(CH_2)_{1-4}OH$; R^{6a1} and R^{6a2} can be each independently selected from hydrogen, halogen, an unsubstituted C_{1-6} alkyl and hydroxy; and R^{7a} and R^{8a} can be each independently an unsubstituted C_{1-6} alkyl.

[0080] In some embodiments, R^{1a} can be hydrogen. In other embodiments, R^{1a} can be an unsubstituted C₁₋₄ alkyl. For example, R^{1a} can be methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl or tert-butyl.

[0081] In some embodiments, both R^{2a} and R^{2a1} can be hydrogen. In other embodiments, R^{2a} can be hydrogen and R^{2a1} can be an unsubstituted C₁₋₄ alkyl. In still other embodiments, R^{2a} and R^{2a1} each can be an unsubstituted C₁₋₄ alkyl.

[0082] In some embodiments, R^{3a} can be hydroxy, and R^{3a1} can be CF_3 . In other embodiments, R^{3a} can be hydroxy, and R^{3a1} can be CHF_2 . In still other embodiments, R^{3a} can be hydroxy, and R^{3a1} can be NH_2 . In some embodiments, the carbon to which R^{3a} and R^{3a1} are attached can be a chiral center. When the carbon to which R^{3a} and R^{3a1} are attached a chiral center, in some embodiments, the carbon can have a (R)-configuration. In other embodiments, the carbon to which R^{3a} and R^{3a1} are attached can have a (S)-configuration.



[0083] In some embodiments, L^1 can be $R^{5a2}HN(R^{6a1})R^{6a2}$. Various substituents can be present at the position indicated with R^{4a} . In some embodiments, R^{4a} can be hydrogen. In other embodiments, R^{4a} can be halogen (such as fluoro, chloro, bromo or iodo). In still other embodiments, R^{4a} can be hydroxy. In yet still other embodiments, R^{4a} can be an optionally substituted C_{1-8} alkyl. In some embodiments, R^{4a} can be an unsubstituted C_{1-8} alkyl or an unsubstituted C_{1-4} alkyl. In other embodiments, R^{4a} can be a

substituted C₁₋₈ alkyl or a substituted C₁₋₄ alkyl. In some embodiments, R^{4a} can be an optionally substituted C₁₋₈ alkoxy. In some embodiments, R^{4a} can be an unsubstituted C₁₋₈ alkoxy. In other embodiments, R^{4a} can be a substituted C₁₋₈ alkoxy. Examples of suitable alkoxy groups include, but are not limited to, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, tert-butoxy, pentoxy (branched or straight-chained) and hexoxy (branched or straight-chained). In other embodiments, R^{4a} can be a haloalkyl, for example, CF₃, CHF₂, -(CH₂)₁₋₄CF₃ and -(CH₂)₁₋₄CHF₂.

[0084] A variety of substituents can also be present on lower ring of the bicyclic ring of Formula (I). In some embodiments, R^{5a1} can be an unsubstituted C₁₋₆ alkyl. Examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl (branched or straight-chained) and hexyl (branched or straight-chained). In some embodiments, R^{5a1} can be methyl. In other embodiments, R^{5a1} can be an unsubstituted C₃₋₆ cycloalkyl. For example, R^{5a1} can be one of the following unsubstituted cycloalkyls: cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In still other embodiments, R^{5a1} can be -(CH₂)₁₋₄OH. For example, R^{5a1} can be -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH or -CH₂CH₂CH₂CH₂OH.

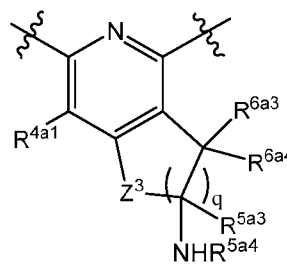
[0085] In some embodiments, R^{5a2} can be hydrogen. In other embodiments, R^{5a2} can be hydroxy. In still other embodiments, R^{5a2} can be an unsubstituted C₁₋₆ alkyl. In yet still other embodiments, R^{5a2} can be an optionally substituted monocyclic heterocyclyl. For example, R^{5a2} can be an optionally substituted 3-6 membered monocyclic heterocyclyl. In some embodiments, R^{5a2} can be an unsubstituted 3-6 membered monocyclic heterocyclyl. In some embodiments, R^{5a2} can be -C(=O)R^{5a5}, wherein R^{5a5} can be an unsubstituted C₁₋₄ alkyl (such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl and tert-butyl). In other embodiments, R^{5a2} can be an unsubstituted -C-amido. An example of a suitable an unsubstituted -C-amido is -C(=O)NH₂. In other embodiments, R^{5a2} can be -C(=NH)-an unsubstituted C₁₋₆ alkyl. Suitable C₁₋₆ alkyls are described herein. In some embodiments, R^{5a2} can be -C(=NH)CH₃.

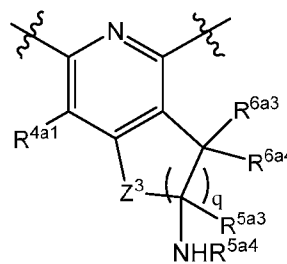
[0086] In some embodiments, R^{5a1} and R^{5a2} can each be hydrogen. In other embodiments, R^{5a1} can be an unsubstituted C₁₋₆ alkyl, and R^{5a2} can be hydrogen. In still other embodiments, R^{5a1} can be an unsubstituted C₃₋₆ cycloalkyl, and R^{5a2} can be hydrogen. In yet still other embodiments, R^{5a1} can be an unsubstituted C₁₋₆ alkyl, and R^{5a2} can be hydroxy. In

some embodiments, R^{5a1} can be an unsubstituted C_{1-6} alkyl, and R^{5a2} can be $-C(=O)R^{5a5}$. In other embodiments, R^{5a1} and R^{5a2} can each be an unsubstituted C_{1-6} alkyl. In still other embodiments, R^{5a1} can be an unsubstituted C_{1-6} alkyl, and R^{5a2} can be an optionally substituted 3-6 membered monocyclic heterocyclyl. In yet still other embodiments, R^{5a1} can be an unsubstituted C_{1-6} alkyl, and R^{5a2} can be an unsubstituted $-C$ -amido. In some embodiments, R^{5a1} can be an unsubstituted C_{1-6} alkyl, and R^{5a2} can be $-C(=NH)$ -an unsubstituted C_{1-6} alkyl.

[0087] In some embodiments, p can be 1, and the lower ring can be a five-membered ring. In other embodiments, p can be 2, and the lower ring can be a six-membered ring. In some embodiments, R^{6a1} and R^{6a2} can be the same. In other embodiments, R^{6a1} and R^{6a2} can be different. In some embodiments, one of R^{6a1} and R^{6a2} can be hydrogen and the other of R^{6a1} and R^{6a2} can be halogen, an unsubstituted C_{1-6} alkyl or hydroxy. In some embodiments, one of R^{6a1} and R^{6a2} can be hydrogen and the other of one of R^{6a1} and R^{6a2} can be halogen. In other embodiments, one of R^{6a1} and R^{6a2} can be hydrogen and the other of one of R^{6a1} and R^{6a2} can be an unsubstituted C_{1-6} alkyl, such as those described herein. In still other embodiments, one of R^{6a1} and R^{6a2} can be hydrogen and the other of one of R^{6a1} and R^{6a2} can be hydroxy. In some embodiments, R^{6a1} and R^{6a2} can be each hydrogen.

[0088] In some embodiments, Z^2 can be O (oxygen). In other embodiments, Z^2 can be NR^Z . When Z^2 is NR^Z , Z^2 can be NH. Alternatively, NR^Z can be N(an unsubstituted C_{1-4} alkyl). Examples of unsubstituted C_{1-4} alkyl groups are described herein. In some embodiments, NR^Z can be $N(CH_3)$. In other embodiments, Z^2 can be $CR^{Z1}R^{Z2}$, wherein R^{Z1} and R^{Z2} can be independently hydrogen or an unsubstituted C_{1-4} alkyl. In some embodiments, R^{Z1} and R^{Z2} can each be hydrogen. In other embodiments, R^{Z1} and R^{Z2} can each be an unsubstituted C_{1-4} alkyl. In still other embodiments, R^{Z1} can be hydrogen, and R^{Z2} can be an unsubstituted C_{1-4} alkyl.



[0089] In other embodiments, L^1 can be . In some embodiments, R^{5a3} can be an unsubstituted C_{1-6} alkyl. Examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl (branched or straight-chained) and hexyl (branched or straight-chained). In some embodiments, R^{5a3} can be methyl. In other embodiments, R^{5a3} can be an unsubstituted C_{3-6} cycloalkyl. For example, R^{5a3} can be one of the following unsubstituted cycloalkyls: cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In still other embodiments, R^{5a3} can be $-(CH_2)_{1-4}OH$. For example, R^{5a3} can be $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH_2CH_2CH_2CH_2OH$.

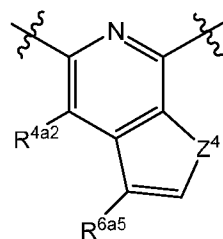
[0090] In some embodiments, R^{5a4} can be hydrogen. In other embodiments, R^{5a4} can be hydroxy. In still other embodiments, R^{5a4} can be an unsubstituted C_{1-6} alkyl. In yet still other embodiments, R^{5a4} can be an optionally substituted monocyclic heterocyclyl. For example, R^{5a4} can be an optionally substituted 3-6 membered monocyclic heterocyclyl. In some embodiments, R^{5a4} can be an unsubstituted 3-6 membered monocyclic heterocyclyl. In some embodiments, R^{5a4} can be $-C(=O)R^{5a5}$, wherein R^{5a5} can be an unsubstituted C_{1-4} alkyl (such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl and tert-butyl). In other embodiments, R^{5a4} can be an unsubstituted $-C$ -amido. An example of a suitable an unsubstituted $-C$ -amido is $-C(=O)NH_2$. In other embodiments, R^{5a4} can be $-C(=NH)$ -an unsubstituted C_{1-6} alkyl. Suitable C_{1-6} alkyls are described herein. In some embodiments, R^{5a4} can be $-C(=NH)CH_3$.

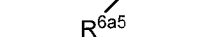
[0091] In some embodiments, R^{5a3} and R^{5a4} can each be hydrogen. In other embodiments, R^{5a3} can be an unsubstituted C_{1-6} alkyl, and R^{5a4} can be hydrogen. In still other embodiments, R^{5a3} can be an unsubstituted C_{3-6} cycloalkyl, and R^{5a4} can be hydrogen. In yet still other embodiments, R^{5a3} can be an unsubstituted C_{1-6} alkyl, and R^{5a4} can be hydroxy. In some embodiments, R^{5a3} can be an unsubstituted C_{1-6} alkyl, and R^{5a4} can be $-C(=O)R^{5a5}$. In other embodiments, R^{5a3} and R^{5a4} can each be an unsubstituted C_{1-6} alkyl. In still other embodiments, R^{5a3} can be an unsubstituted C_{1-6} alkyl, and R^{5a4} can be an optionally

substituted 3-6 membered monocyclic heterocyclyl. In yet still other embodiments, R^{5a3} can be an unsubstituted C_{1-6} alkyl, and R^{5a4} can be an unsubstituted $-C$ -amido. In some embodiments, R^{5a3} can be an unsubstituted C_{1-6} alkyl, and R^{5a4} can be $-C(=NH)$ -an unsubstituted C_{1-6} alkyl.

[0092] In some embodiments, q can be 1, and the lower ring can be a five-membered ring. In other embodiments, q can be 2, and the lower ring can be a six-membered ring. In some embodiments, R^{6a3} and R^{6a4} can be the same. In other embodiments, R^{6a3} and R^{6a4} can be different. In some embodiments, one of R^{6a3} and R^{6a4} can be hydrogen and the other of R^{6a3} and R^{6a4} can be halogen, an unsubstituted C_{1-6} alkyl or hydroxy. In some embodiments, one of R^{6a3} and R^{6a4} can be hydrogen and the other of one of R^{6a3} and R^{6a4} can be halogen. In other embodiments, one of R^{6a3} and R^{6a4} can be hydrogen and the other of one of R^{6a3} and R^{6a4} can be an unsubstituted C_{1-6} alkyl, such as those described herein. In still other embodiments, one of R^{6a3} and R^{6a4} can be hydrogen and the other of one of R^{6a3} and R^{6a4} can be hydroxy. In some embodiments, R^{6a3} and R^{6a4} can be each hydrogen.

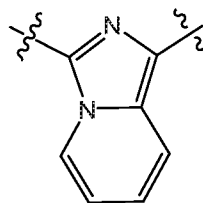
[0093] In some embodiments, Z^3 can be O (oxygen). In other embodiments, Z^3 can be NR^{Z3} . When Z^3 is NR^{Z3} , Z^3 can be NH. Alternatively, NR^{Z3} can be N(an unsubstituted C_{1-4} alkyl). Examples of unsubstituted C_{1-4} alkyl groups are described herein. In some embodiments, NR^{Z3} can be $N(CH_3)$. In other embodiments, Z^3 can be $CR^{Z4}R^{Z5}$, wherein R^{Z4} and R^{Z5} can be independently hydrogen or an unsubstituted C_{1-4} alkyl. In some embodiments, R^{Z4} and R^{Z5} can each be hydrogen. In other embodiments, R^{Z4} and R^{Z5} can each be an unsubstituted C_{1-4} alkyl. In still other embodiments, R^{Z4} can be hydrogen, and R^{Z5} can be an unsubstituted C_{1-4} alkyl.



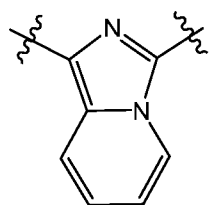
[0094] In still other embodiments, L^1 can be . In some embodiments, R^{4a2} can be hydrogen. In other embodiments, R^{4a2} can be halogen. In still other embodiments, R^{4a2} can be hydroxy. In yet still other embodiments, R^{4a2} can be an optionally substituted C_{1-8} alkyl, such as those described herein. In some embodiments, R^{4a2} can be an optionally substituted C_{1-8} alkoxy. In other embodiments, R^{4a2} can be haloalkyl,

for example, CF_3 . In some embodiments, R^{6a5} can be halogen. In other embodiments, R^{6a5} can be an unsubstituted C_{1-6} alkyl. Suitable unsubstituted C_{1-6} alkyls are described herein. In still other embodiments, R^{6a5} can be hydroxy. In some embodiments, Z^4 can be O. In some embodiments, Z^4 can be NR^{Z6} , for example, NH or N(an unsubstituted C_{1-4} alkyl). In still other embodiments, Z^4 can be $\text{CR}^{Z7}\text{R}^{Z8}$. When Z^4 is $\text{CR}^{Z7}\text{R}^{Z8}$, each of R^{Z7} and R^{Z8} can be hydrogen. Alternatively, when Z^4 is $\text{CR}^{Z7}\text{R}^{Z8}$, at least one of R^{Z7} and R^{Z8} can be unsubstituted C_{1-6} alkyl. In some embodiments, one of R^{Z7} and R^{Z8} can be unsubstituted C_{1-6} alkyl, and the other of R^{Z7} and R^{Z8} can be hydrogen. In other embodiments, R^{Z7} and R^{Z8} can each be hydrogen.

[0095] In some embodiments, L^1 can be

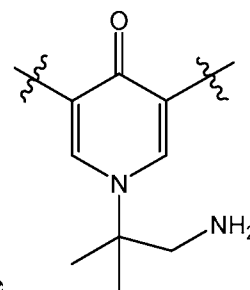


. In other embodiments,

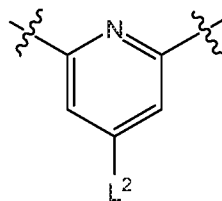


L^1 can be

. In still other embodiments, L^1 can be

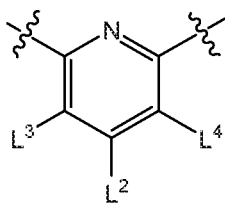


[0096] In some embodiments, L^1 can be



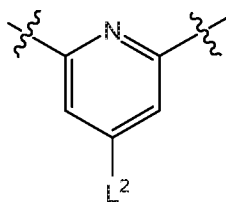
. In addition to L^2 , the

pyridinyl ring can be not be further substituted (as shown) or substituted with one or two substituents, such as those substituents listed in the term “substituted.” When two or more substituents are present, the substituents can be the same or different. As an example, L^1 can

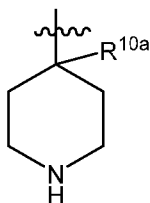


be L^2 , wherein L^3 and L^4 can be independently selected from hydrogen,

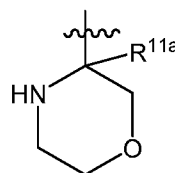
halogen, hydroxy, an optionally substituted C₁₋₈ alkyl, an optionally substituted C₂₋₈ alkenyl, an optionally substituted C₂₋₈ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C₁₋₈ alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C₁₋₈ alkyl), haloalkyl, an optionally substituted O-amido and an optionally substituted C-carboxy. In some embodiments, L³ and L⁴ can be each hydrogen.



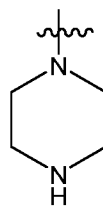
[0097] When L¹ is , in some embodiments, L² can be



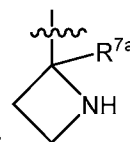
. In some embodiments, the piperidynyl can be unsubstituted (wherein R^{10a} is hydrogen). In other embodiments, the piperidynyl ring can be substituted with one or more substituents from those substituents listed in the term “substituted.” As an example, in some embodiments, R^{10a} can be an unsubstituted C₁₋₆ alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, pentyl (straight-chained or branched) or hexyl (straight-chained or branched)).



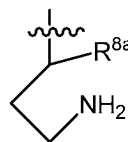
[0098] In other embodiments, L² can be . In some embodiments, the morpholinyl ring can be unsubstituted when R^{11a} is hydrogen. In other embodiments, the morpholinyl ring can be substituted, for example, with one or more substituents including those listed in the term “substituted.” In some embodiments, R^{11a} can be an unsubstituted C₁₋₆ alkyl. Examples of suitable C₁₋₆ alkyls are described herein.



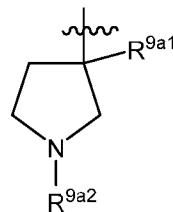
[0099] In still other embodiments, L^2 can be . The piperazinyl ring can be unsubstituted or substituted with one or more substituents including those listed in the term “substituted.”



[0100] In yet still other embodiments, L^2 can be , wherein R^{7a} can be an unsubstituted C_{1-6} alkyl. Suitable unsubstituted C_{1-6} alkyls are described herein. In some embodiments, R^{7a} can be an unsubstituted C_{1-4} alkyl. In some embodiments, R^{7a} can be methyl. The four-membered ring of L^2 can be unsubstituted (as shown) or substituted. When substituted, one or more substituents can be present, and the possible substituents include those listed in the term “substituted.”

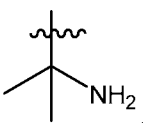
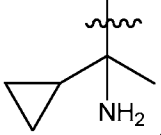


[0101] In some embodiments, L^2 can be , wherein R^{8a} can be an unsubstituted C_{1-6} alkyl. Examples of unsubstituted C_{1-6} alkyls are described herein. In some embodiments, R^{8a} can be an unsubstituted C_{1-4} alkyl. In some embodiments, R^{8a} can be methyl. The alkylene chain between the pyridinyl ring and the NH_2 group of L^2 can be further substituted or be unsubstituted, as shown. One or more substituents can be present on the alkylene chain when substituted. Examples of suitable substituents that can be present include those listed in the term “substituted.”

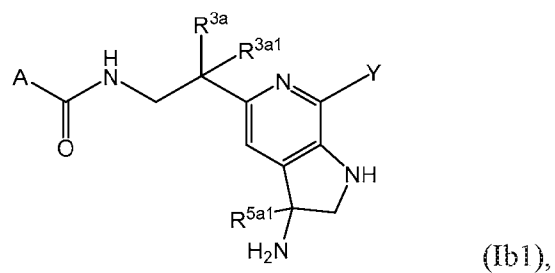
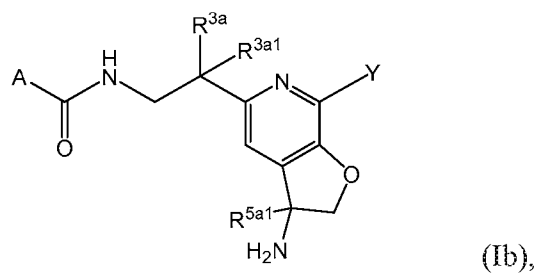
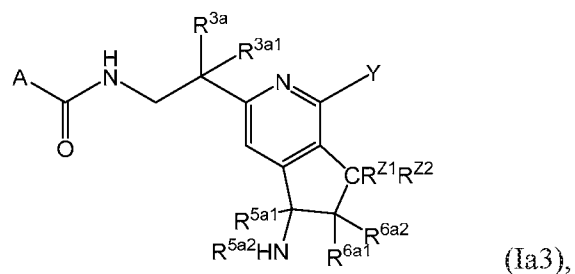
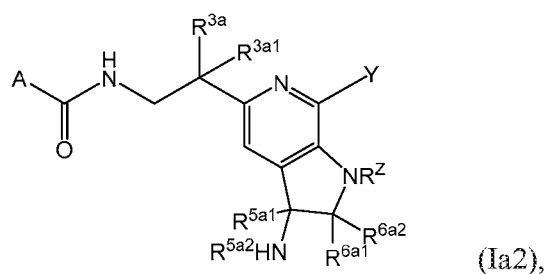
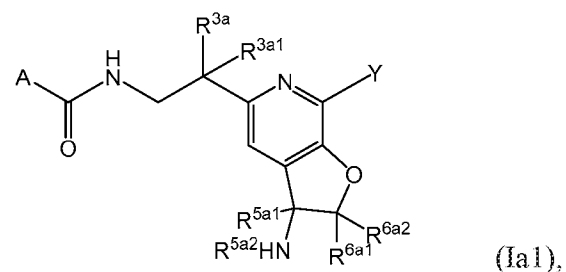
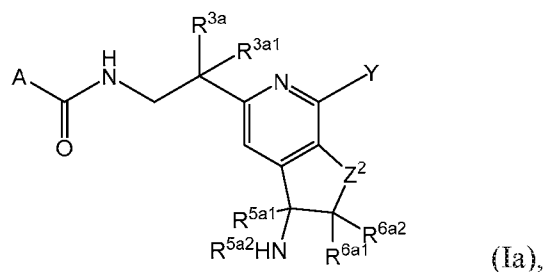


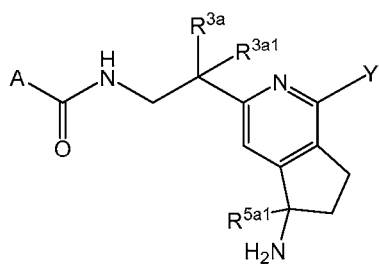
[0102] In other embodiments, L^2 can be . In some embodiments, R^{9a1} and R^{9a2} can each be hydrogen. In other embodiments, R^{9a1} can be hydrogen, and R^{9a2} can be an unsubstituted C_{1-6} alkyl. In still other embodiments, R^{9a1} can be an unsubstituted C_{1-6} alkyl, and R^{9a2} can be hydrogen. In yet still other embodiments, R^{9a1} and R^{9a2} can each

be an unsubstituted C₁₋₆ alkyl. Examples of suitable an unsubstituted C₁₋₆ alkyl groups are described herein.

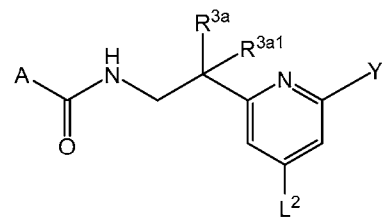
[0103] In still other embodiments, L² can be . In yet still other embodiments, L² can be .

[0104] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, has a structure selected from Formula (Ia), Formula (Ia1), Formula (Ia2), Formula (Ia3), Formula (Ib), Formula (Ib1), Formula (Ib2), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ig), Formula (Ig1), Formula (Ig2), Formula (Ig3), Formula (Ig4), Formula (Ig5), Formula (Ig6), Formula (Ih), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (In), Formula (In1), Formula (In2), Formula (In3), Formula (Io), Formula (Io1), Formula (Io2), Formula (Ip), Formula (Iq) and Formula (Ir):

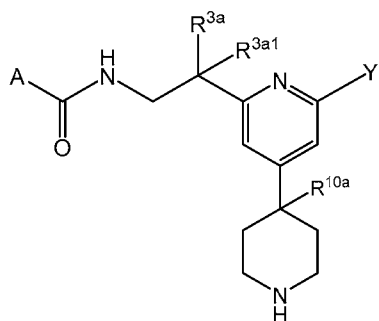




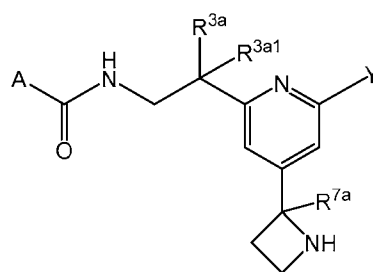
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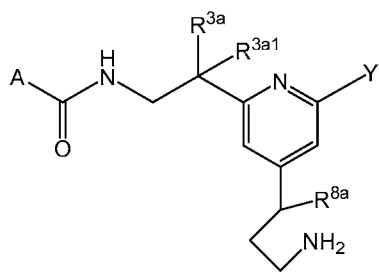
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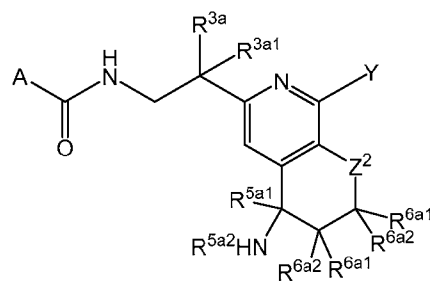
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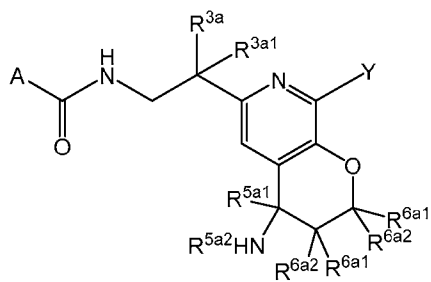
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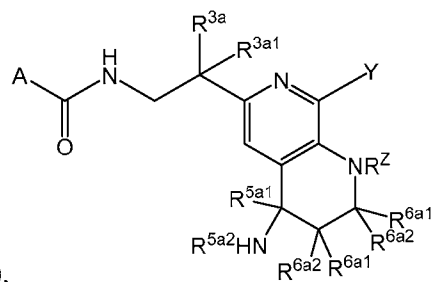
(If),



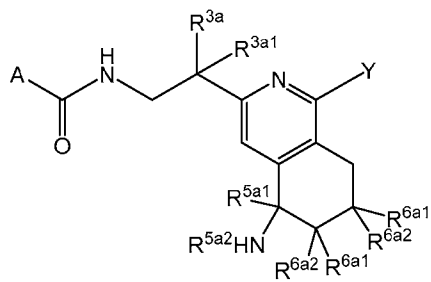
(Ig),



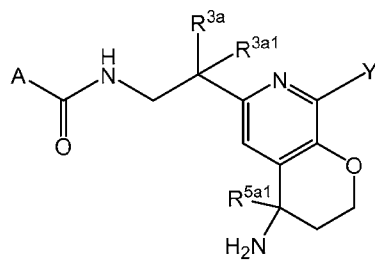
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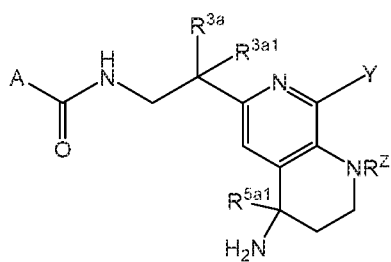
(Ig2),



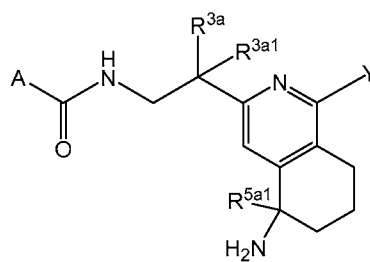
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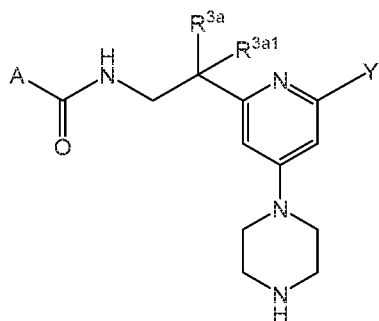
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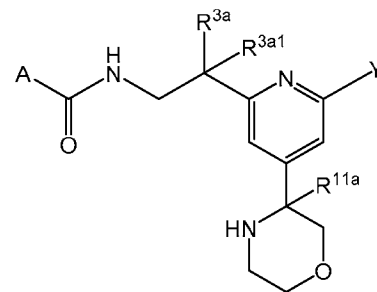
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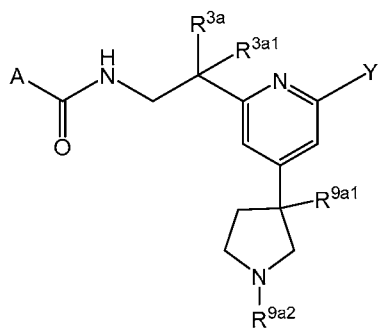
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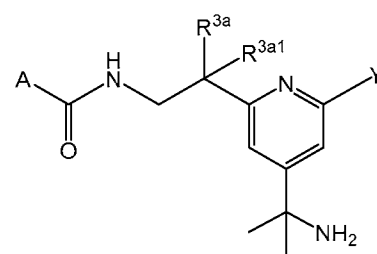
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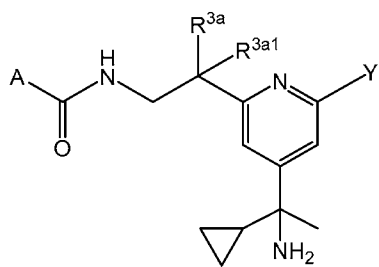
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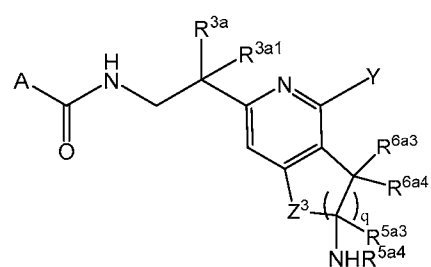
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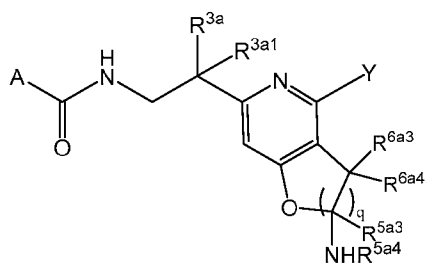
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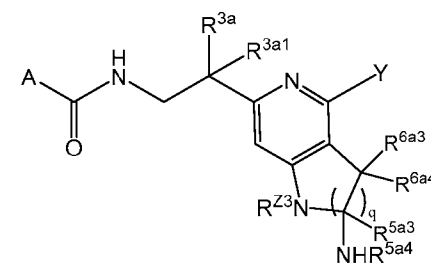
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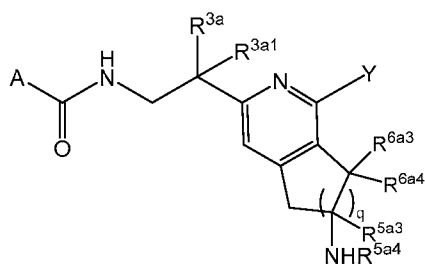
(In),



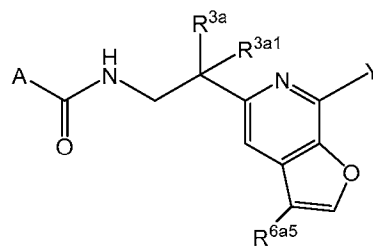
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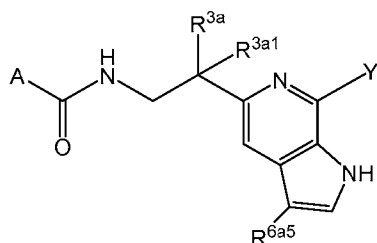
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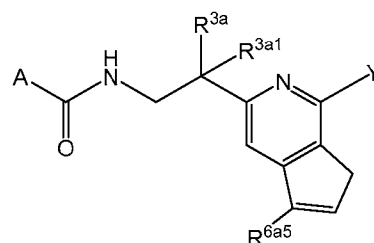
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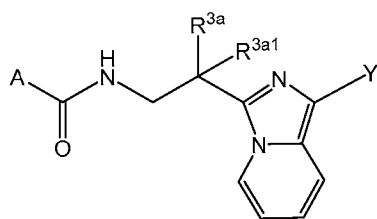
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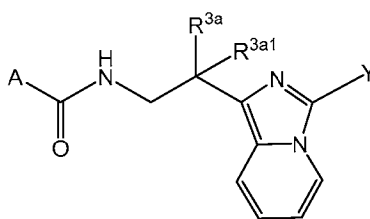
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(Io2),

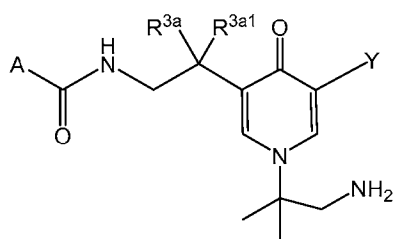


(Ip),



(Iq)

and

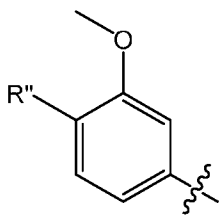
(Ir). In some embodiments of this paragraph, R^{3a} can be

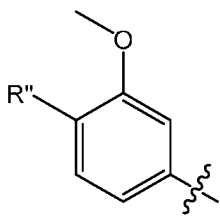
hydroxy, and R^{3a1} can be CF₃. In some embodiments of this paragraph, Y can be a substituted phenyl (for example, a para-substituted phenyl). In some embodiments of this paragraph, A can be a substituted phenyl. In some embodiments of this paragraph, A can be a substituted heteroaryl. In some embodiments of this paragraph, A can be a substituted heterocyclyl.

[0105] In some embodiments, A can be substituted. In other embodiments, A can be unsubstituted. When A is substituted, possible substituent(s) includes those provided in the list of “substituted” along with those described herein.

[0106] In some embodiments, A can be an optionally substituted aryl. For example, A can be an optionally substituted phenyl. In some embodiments, A can be a para-substituted phenyl, a meta-substituted phenyl or an ortho-substituted phenyl. In some

embodiments, A can be a di-substituted phenyl. For example, A can be a 3,4-substituted

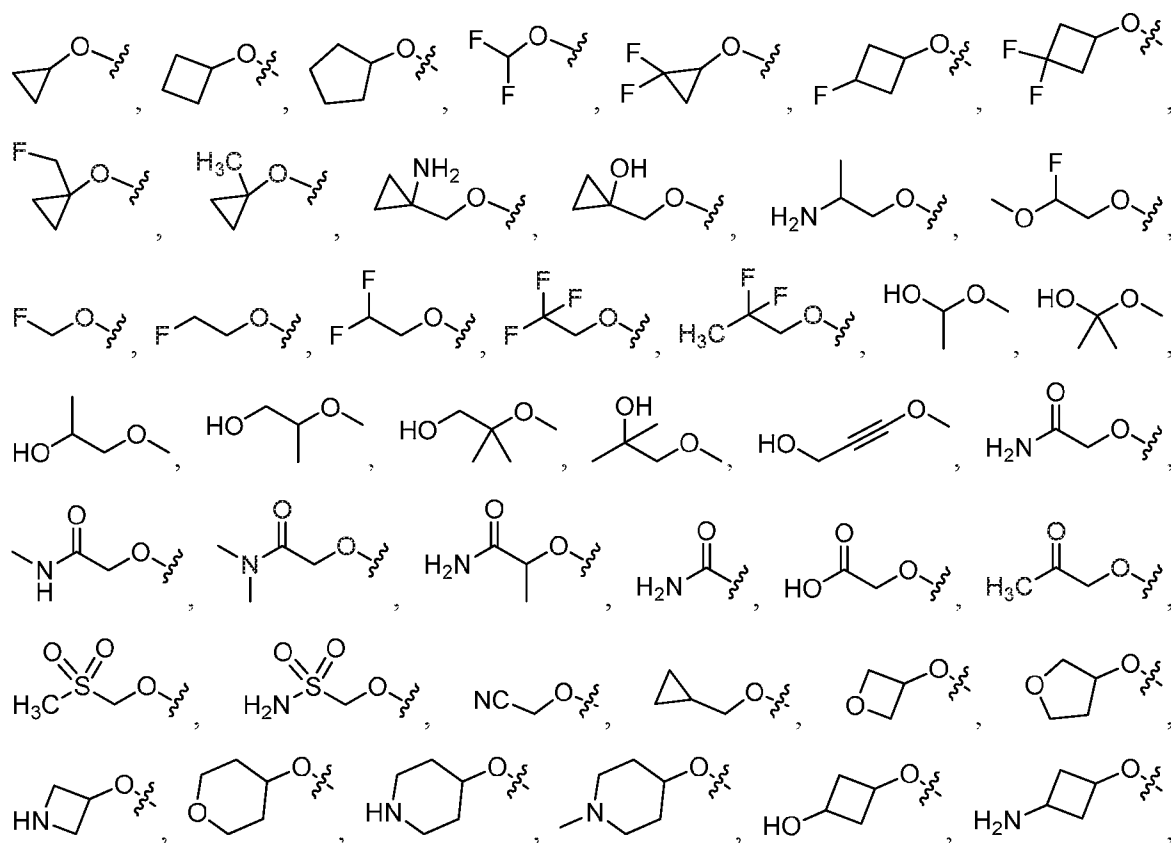


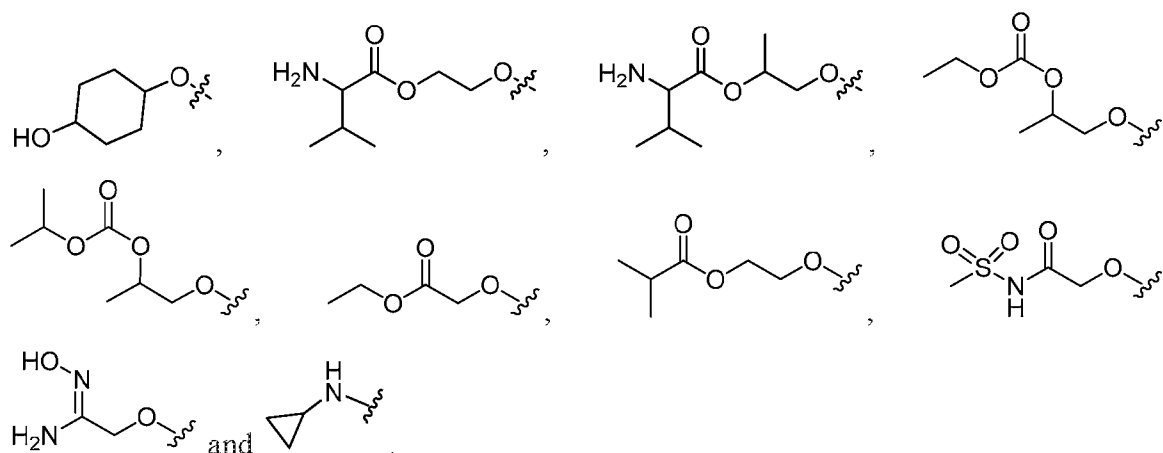
phenyl, such as , wherein R'' can be a substituent from the list of "substituted" along with those substituents described herein. In some embodiments, A can be a substituted phenyl that is substituted with 3 more substituents. In other embodiments, A can be unsubstituted phenyl. In some embodiments, A can be an optionally substituted naphthyl.

[0107] In some embodiments and without limitation, A can be a phenyl substituted with one or more substituents selected from an unsubstituted C₁₋₄ alkyl, an optionally substituted C₁₋₄ alkyl, cycloalkyl, hydroxy, an optionally substituted C₁₋₄ alkoxy, C₁₋₄ alkoxy, halogen, haloalkyl, an optionally substituted haloalkoxy, nitro, amino, mono-substituted amino, di-substituted amino, -O-amido, sulfenyl, alkoxyalkyl, an optionally substituted aryl (for example, an optionally substituted phenyl), an optionally substituted monocyclic heteroaryl, an optionally substituted monocyclic heterocyclyl, an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted monocyclic heteroaryl(C₁₋₄ alkyl), an optionally substituted monocyclic heterocyclyl(C₁₋₄ alkyl), hydroxyalkyl and aminoalkyl. In some embodiments, the optionally substituted C₁₋₄ alkoxy can be further substituted, for example, further substituted with a substituent selected from C₁₋₄ alkyl, halo, hydroxy, C-carboxy, C-amido, amino, mono-alkyl amine, di-alkyl amine and an amino acid. In some embodiments, the optionally substituted haloalkoxy can be further substituted, for example, further substituted with an C₁₋₄ alkoxy. In some embodiments, the optionally substituted heteroaryl can be further substituted, for example, further substituted with an C₁₋₄ alkyl.

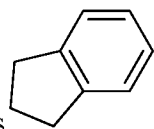
[0108] Examples of suitable substituents include, but are not limited to, methyl, ethyl, propyl, butyl, hydroxy, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, t-butoxy, phenoxy, bromo, chloro, fluoro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, cyano, N,N-di-methyl-amine, N,N-di-ethyl-amine, N-methyl-N-ethyl-amine, N-methyl-amino, N-ethyl-amino, amino, N-amido, N-sulfonamido, alkylthio, an optionally substituted phenyl, an optionally substituted imidazole, an optionally substituted

morpholinyl, an optionally substituted pyrazole, an optionally substituted pyrrolidinyl, an optionally substituted pyridinyl, an optionally substituted piperidinyl, an optionally substituted piperidinone, an optionally substituted pyrrolidinone, an optionally substituted pyrimidine, an optionally substituted pyrazine, an optionally substituted 1,2,4-oxadiazole, $-(CH_2)_{1-4}-OH$, $-(CH_2)_{1-2}-NH(CH_3)$, an optionally substituted $-(CH_2)_{1-2}$ -imidazole, an optionally substituted $-(CH_2)_{1-2}$ -pyrrolidinone, an optionally substituted $-(CH_2)_{1-2}$ -imidazolidinone, $-O(CH_2)_2-NH_2$, $-O(CH_2)_2-NH(CH_3)$, $-O(CH_2)_2-N(CH_3)_2$, $-O-(CH_2)_{2-4}OH$, $-O(CH_2)_2OCH_3$, an optionally substituted $-O(CH_2)_{0-2}$ -cyclopentanone, an optionally substituted $-O(CH_2)_{0-2}$ -pyrrolidinone, an optionally substituted $-O(CH_2)_{0-2}$ -morpholinyl, an optionally substituted $-O(CH_2)_{0-2}$ -triazole, an optionally substituted $-O(CH_2)_{0-2}$ -imidazole, an optionally substituted $-O(CH_2)_{0-2}$ -pyrazole, an optionally substituted $-O(CH_2)_{0-2}$ -tetrahydrofuran, an optionally substituted $-O(CH_2)_{0-2}$ -pyrrolidinone, an optionally substituted $-O(CH_2)_{0-2}$ -tetrazole, an optionally substituted $-O(CH_2)_{0-2}$ -tetrazolone, $-NH(CH_2)_{1-2}OH$,





[0109] In some embodiments, A can be an optionally substituted cycloalkyl. Suitable examples of optionally substituted cycloalkyls include, but are not limited to, an optionally substituted cyclohexyl and an optionally substituted cycloheptyl. In other embodiments, A can be an optionally substituted cycloalkenyl, for example, an optionally substituted cyclohexenyl. In some embodiments, A can be an optionally substituted bi-cyclic



cycloalkenyl, such as

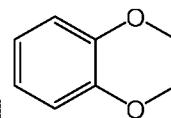
[0110] In some embodiments, A can be an optionally substituted mono-cyclic heteroaryl. In some embodiments, A can be an optionally substituted mono-cyclic 5-membered heteroaryl. In other embodiments, A can be an optionally substituted mono-cyclic 6-membered heteroaryl. In some embodiments, A can be an optionally substituted bi-cyclic heteroaryl.

[0111] In some embodiments, the optionally substituted heteroaryl can be selected from an optionally substituted imidazole, an optionally substituted indole, an optionally substituted thiazole, an optionally substituted furan, an optionally substituted thiophene, an optionally substituted pyrrole, an optionally substituted pyridine, an optionally substituted pyrimidine, an optionally substituted pyrazine, an optionally substituted pyrazole, an optionally substituted quinolone, an optionally substituted imidazole, an optionally substituted oxazole, an optionally substituted isoxazole, an optionally substituted benzoimidazole, an optionally substituted benzoxazole, an optionally substituted benzothiazole and an optionally substituted imidazo[1,2-a]pyrimidine. In some

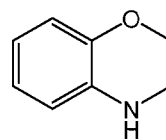
embodiments, A can be an optionally substituted thiophene. In other embodiments, A can be an optionally substituted thiazole. In still other embodiments, A can be an optionally substituted pyridine. In yet still other embodiments, A can be an optionally substituted pyrimidine. In some embodiments, A can be an optionally substituted pyrazine. In other embodiments, A can be an optionally substituted imidazole. In still other embodiments, A can be an optionally substituted benzoimidazole, an optionally substituted benzoxazole or an optionally substituted benzothiazole. In yet still other embodiments, A can be an optionally substituted indole. In some embodiments, A can be an optionally substituted pyrazole.

[0112] In some embodiments, A can be an optionally substituted heterocyclyl, for example, an optionally substituted mono-cyclic heterocyclyl or an optionally substituted bi-

cyclic heterocyclyl. In some embodiments, A can be an optionally substituted

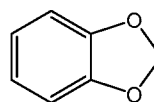


In other embodiments, A can be an optionally substituted



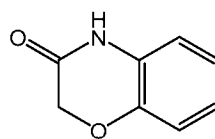
. In still other

embodiments, A can be an optionally substituted



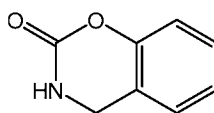
. In yet still other

embodiments, A can be an optionally substituted



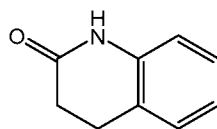
. In some embodiments,

A can be an optionally substituted



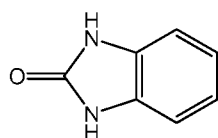
. In other embodiments, A can be an

optionally substituted

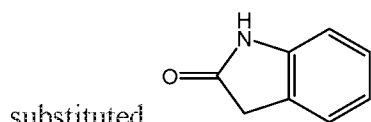


. In still other embodiments, A can be an optionally

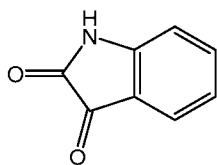
substituted



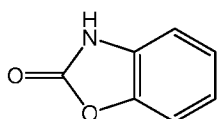
. In yet still other embodiments, A can be an optionally



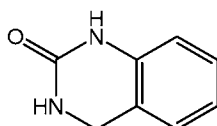
In some embodiments, A can be an optionally substituted



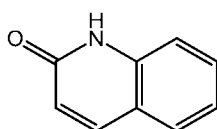
In other embodiments, A can be an optionally substituted



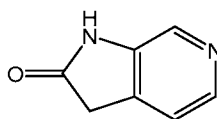
In still other embodiments, A can be an optionally substituted



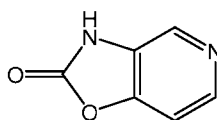
In yet still other embodiments, A can be an optionally substituted



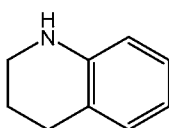
In some embodiments, A can be an optionally substituted



In other embodiments, A can be an optionally substituted



In still other embodiments, A can be an optionally substituted

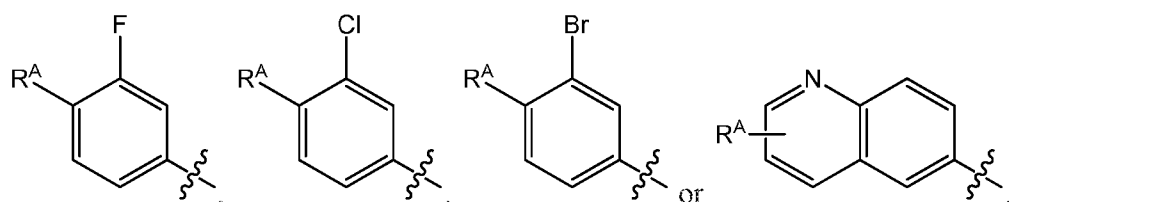


In the moieties shown above for A, the moieties can be attached to the carbon of the C(=Z¹) group of Formula (I) at any carbon atom of A. Furthermore, any hydrogens in the moiety A can be substituted with one or more substituents listed in the term “substituted.”

[0113] In some embodiments, A can be substituted with one or more R^A's. In some embodiments, one R^A can be present. In some embodiments, two R^A's can be present. In some embodiments, three R^A's can be present. In some embodiments, four or more R^A's can be present. When two or more R^A's are present, two or more R^A's can be the same or two or more R^A's can be different. In some embodiments, at least two R^A's can be the same. In some embodiments, at least two R^A's can be different. In some embodiments, all the R^A's

can be the same. In other embodiments, all the R^A 's can be different. In some embodiments,

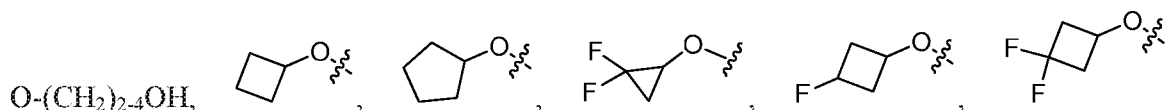
A can have one of the following structures:

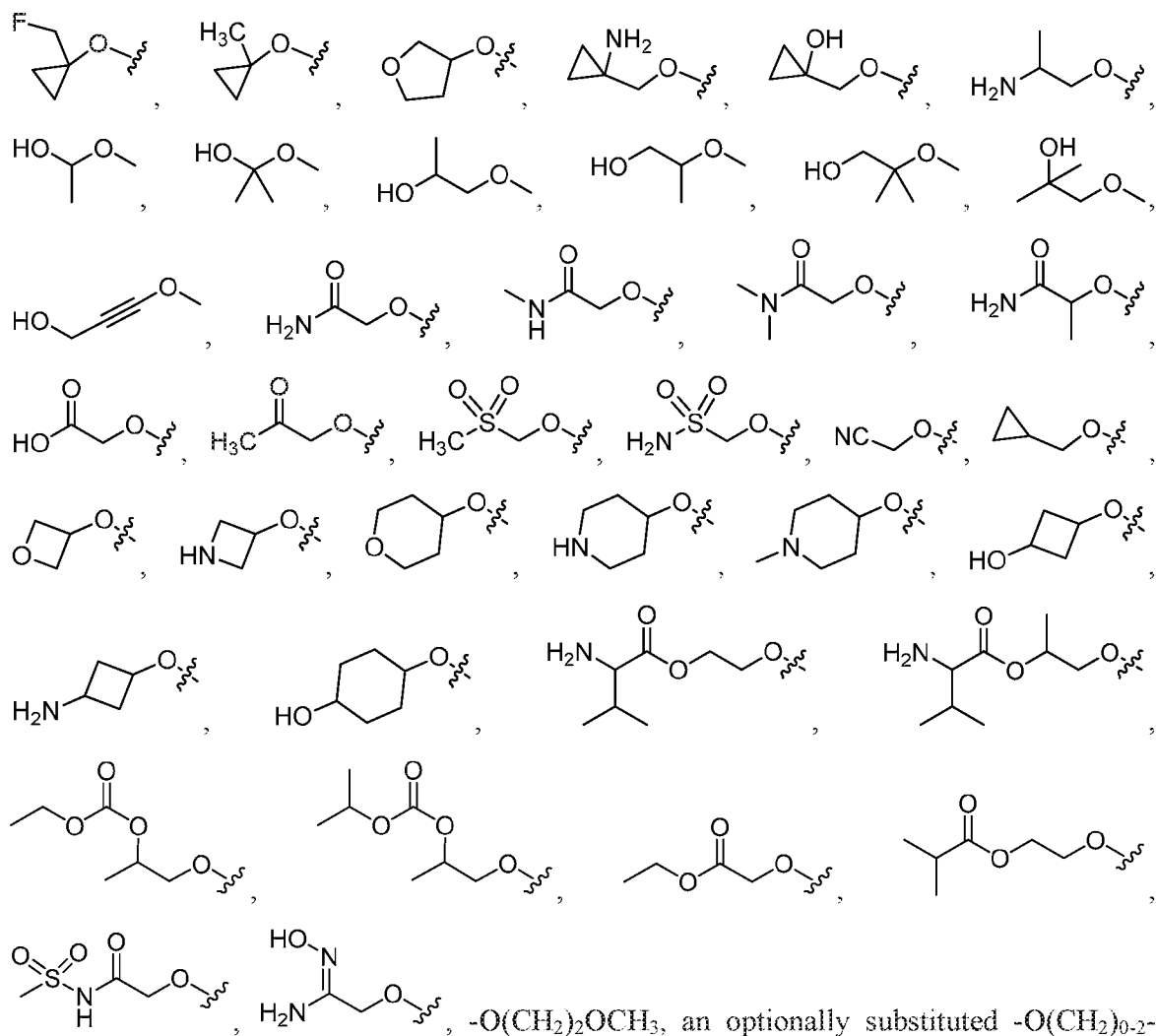


[0114] In some embodiments, R^A can be each independently selected from an unsubstituted C_{1-4} alkyl, an optionally substituted C_{1-4} alkyl, cycloalkyl, hydroxy, an optionally substituted C_{1-4} alkoxy, C_{1-4} alkoxy, halogen, haloalkyl, an optionally substituted haloalkoxy, nitro, amino, mono-substituted amino, di-substituted amine, sulfenyl, alkoxyalkyl, aryl, monocyclic heteroaryl, monocyclic heterocyclyl and aminoalkyl. In some embodiments, the optionally substituted C_{1-4} alkoxy can be further substituted, for example, further substituted with a substituent selected from C_{1-4} alkyl, halo, hydroxy, C-carboxy, C-amido, N-amido, amino, mono-alkyl amine, di-alkyl amine and an amino acid. In some embodiments, the optionally substituted haloalkoxy can be further substituted, for example, further substituted with an C_{1-4} alkoxy. In some embodiments, the optionally substituted heteroaryl can be further substituted, for example, further substituted with an C_{1-4} alkyl.

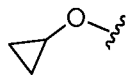
[0115] In some embodiments, each R^A can be an alkyl, such as methyl, ethyl, propyl (n-propyl and iso-propyl) and/or butyl (n-butyl, iso-butyl and t-butyl).

[0116] In some embodiments, each R^A can be an optionally substituted alkoxy, for example, methoxy, ethoxy, propoxy (n-propoxy and iso-propoxy), butoxy (n-butoxy, iso-butoxy and t-butoxy), phenoxy, $-O(CH_2)_2-NH_2$, $-O(CH_2)_2-NH(CH_3)$, $-O(CH_2)_2-N(CH_3)_2$, -





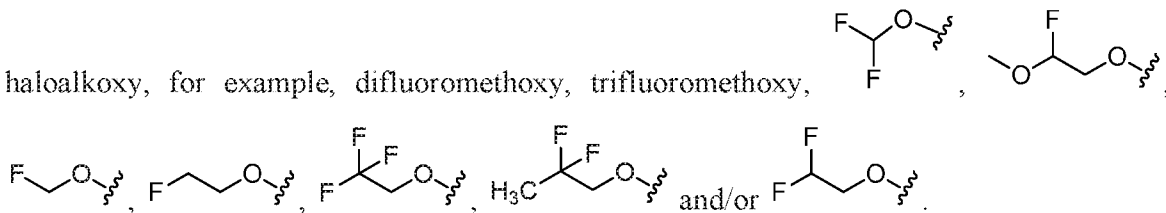
morpholinyl, an optionally substituted $-O(CH_2)_{0-2}$ -triazole, an optionally substituted $-O(CH_2)_{0-2}$ -imidazole, an optionally substituted $-O(CH_2)_{0-2}$ -cyclopentanone, an optionally substituted $-O(CH_2)_{0-2}$ -pyrrolidinone, an optionally substituted $-O(CH_2)_{0-2}$ -pyrazole, an optionally substituted $-O(CH_2)_{0-2}$ -tetrahydrofuran, an optionally substituted $-O(CH_2)_{0-2}$ -pyrrolidinone, an optionally substituted $-O(CH_2)_{0-2}$ -tetrazole, an optionally substituted -



O(CH₂)₀₋₂-tetrazolone and/or . In some embodiments, R^A can be substituted C₁₋₆ alkoxy substituted by one or more of the following: halo, hydroxy, C₁₋₄ alkyl, cyano, amino, mono-substituted amino, di-substituted amino, sulfonamidocarbonyl, hydroxamidine, C-amido, acyl, C-carboxy, O-carboxy, sulfonyl, S-sulfonamido, O-linked amino acid and carbonate ester.

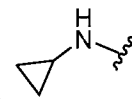
[0117] In some embodiments, each R^A can be haloalkyl, for example, trifluoromethyl.

[0118] In some embodiments, each R^A can be an optionally substituted haloalkoxy, for example, difluoromethoxy, trifluoromethoxy,



[0119] In some embodiments, each R^A can be halogen, for example, chloro, bromo and/or fluoro.

[0120] In some embodiments, each R^A can be amino, a mono-substituted amine or a di-substituted amine. For examples, R^A can be N,N-di-methyl-amine, N,N-di-ethyl-amine, N-methyl-N-ethyl-amine, N-methyl-amino, N-ethyl-amino, amino,



and/or -NH(CH₂)₁₋₂OH.

[0121] In some embodiments, each R^A can be hydroxy.

[0122] In some embodiments, each R^A can be alkylthio, for example ethylthio.

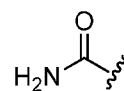
[0123] In some embodiments, each R^A can be aminoalkyl, such as -(CH₂)₁₋₂-NH(CH₃).

[0124] In some embodiments, each R^A can be alkoxyalkyl, for example, -CH₂-O-CH₃.

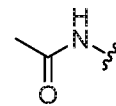
[0125] In some embodiments, each R^A can be an optionally substituted aryl(C₁₋₄ alkyl). In some embodiments, each R^A can be an optionally substituted monocyclic heteroaryl(C₁₋₄ alkyl). In some embodiments, each R^A can be an optionally substituted monocyclic heterocyclyl(C₁₋₄ alkyl). Non-limiting examples include an optionally substituted -(CH₂)₁₋₂-imidazole, an optionally substituted -(CH₂)₁₋₂-pyrrolidinone, an optionally substituted -(CH₂)₁₋₂-imidazolidinone.

[0126] In some embodiments, each R^A can be hydroxyalkyl, for example, -(CH₂)₁₋₄-OH.

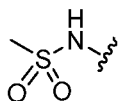
[0127] In some embodiments, each R^A can be -O-amido, for example,



[0128] In some embodiments, each R^A can be -N-amido, for example,



[0129] In some embodiments, each R^A can be -N-sulfonamido, for example,



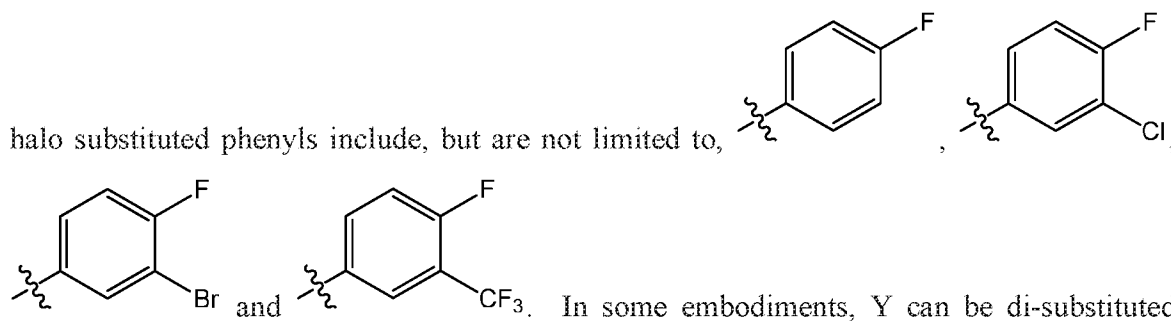
[0130] In some embodiments, each R^A can be aminoalkyl, for example, -CH₂-NH₂ and/or -CH₂-N(CH₃)H.

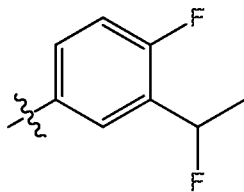
[0131] In some embodiments, each R^A can be an optionally substituted aryl, for example, an optionally substituted phenyl.

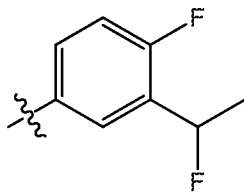
[0132] In some embodiments, each R^A can be an optionally substituted monocyclic heteroaryl, such as an optionally substituted imidazole, an optionally substituted pyrazole, an optionally substituted pyridinyl, an optionally substituted pyrimidine, an optionally substituted pyrazine and/or an optionally substituted 1,2,4-oxadiazole.

[0133] In some embodiments, each R^A can be an optionally substituted monocyclic heterocyclyl, for example, an optionally substituted pyrrolidinyl, an optionally substituted piperidinyl, an optionally substituted morpholinyl and/or an optionally substituted pyrrolidinone.

[0134] In some embodiments, Y can be an optionally substituted aryl. In some embodiments, Y can be a para-substituted phenyl, a meta-substituted phenyl or an ortho-substituted phenyl. In some embodiments, Y can be a mono-substituted phenyl, such as a mono-halo substituted phenyl. In some embodiments, Y can be a di-substituted phenyl, for example a di-halo substituted phenyl. For example, mono-halo substituted phenyls and di-

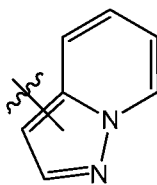




phenyl of the structure . In some embodiments, Y can be a substituted phenyl that is substituted with 3 more substituents. In other embodiments, Y can be unsubstituted phenyl. In some embodiments, Y can be a substituted naphthyl. In other embodiments, Y can be an unsubstituted naphthyl.

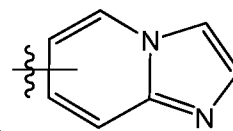
[0135] In some embodiments, Y can be an optionally substituted mono-cyclic heteroaryl. In some embodiments, Y can be selected from an optionally substituted imidazole, an optionally substituted furan, an optionally substituted thiophene, an optionally substituted pyrrole, an optionally substituted pyrimidine, an optionally substituted pyrazine, an optionally substituted pyridine, an optionally substituted pyrazole, an optionally substituted oxazole and an optionally substituted isoxazole. In some embodiments, Y can be a substituted mono-cyclic heteroaryl, including those described herein. In some embodiments, Y can be an unsubstituted mono-cyclic heteroaryl, including those described herein.

[0136] In some embodiments, Y can be an optionally substituted bi-cyclic heteroaryl. In some embodiments, Y can be selected from an optionally substituted benzothiophene, an optionally substituted benzofuran, an optionally substituted indole, an optionally substituted quinoline, an optionally substituted isoquinoline, an optionally substituted benzoxazole, an optionally substituted benzoisoxazole, an optionally substituted benzoisothiazole, an optionally substituted benzothiazole, an optionally substituted benzoimidazole, an optionally substituted benzotriazole, an optionally substituted 1H-indazole and an optionally substituted 2H-indazole. In some embodiments, Y can be selected

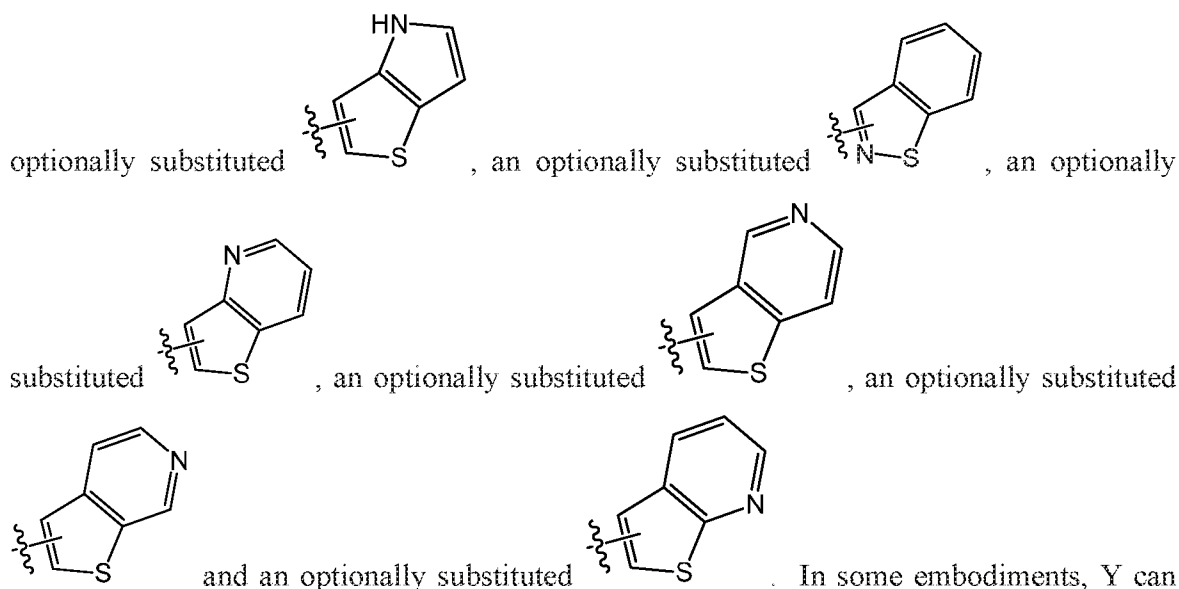


from an optionally substituted

, an optionally substituted

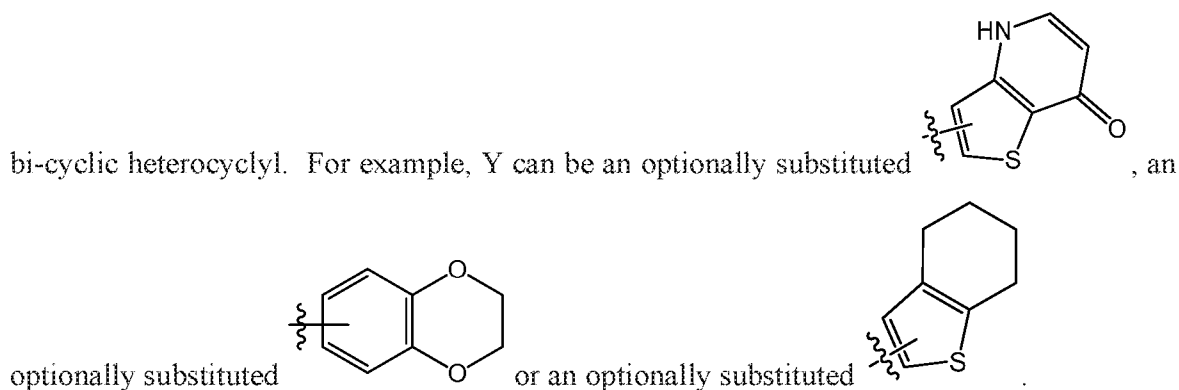


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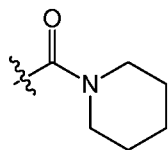
be a substituted bi-cyclic heteroaryl, including those described herein. In some embodiments, Y can be an unsubstituted bi-cyclic heteroaryl, including those described herein.

[0137] In some embodiments, Y can be an optionally substituted heterocyclyl. In some embodiments, Y can be an optionally substituted mono-cyclic heterocyclyl, such as an optionally substituted pyridinone. In other embodiment, Y can be an optionally substituted



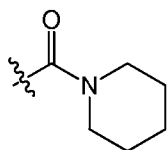
[0138] When Y is substituted, Y can be substituted with one or more R^B's. In some embodiments, each R^B can be independently selected from cyano, halogen, an optionally substituted C₁₋₄ alkyl, an unsubstituted C₂₋₄ alkenyl, an unsubstituted C₂₋₄ alkynyl, an optionally substituted aryl, an optionally substituted 5 or 6 membered heteroaryl, an optionally substituted 5 or 6 membered heterocyclyl, hydroxy, C₁₋₄ alkoxy, alkoxyalkyl, C₁₋₄ haloalkyl, haloalkoxy, an unsubstituted acyl, an optionally substituted -C-carboxy, an

optionally substituted $-C$ -amido, sulfonyl, carbonyl, amino, mono-substituted amine, di-



substituted amine and

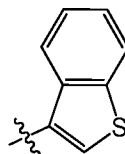
[0139] In some embodiments, when Y is an optionally substituted phenyl, the phenyl can be substituted 1, 2, 3 or more times with cyano, halogen, an optionally substituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an optionally substituted aryl, an optionally substituted 5 or 6 membered heteroaryl, an optionally substituted 5 or 6 membered heterocyclyl, hydroxy, C_{1-4} alkoxy, C_{1-4} haloalkyl (such as CF_3 , CHF_2), haloalkoxy (such as OCF_3), an unsubstituted acyl, an optionally substituted $-C$ -carboxy, an optionally substituted $-C$ -amido, sulfonyl, amino, mono- C_{1-4} alkyl amine, di- C_{1-4}



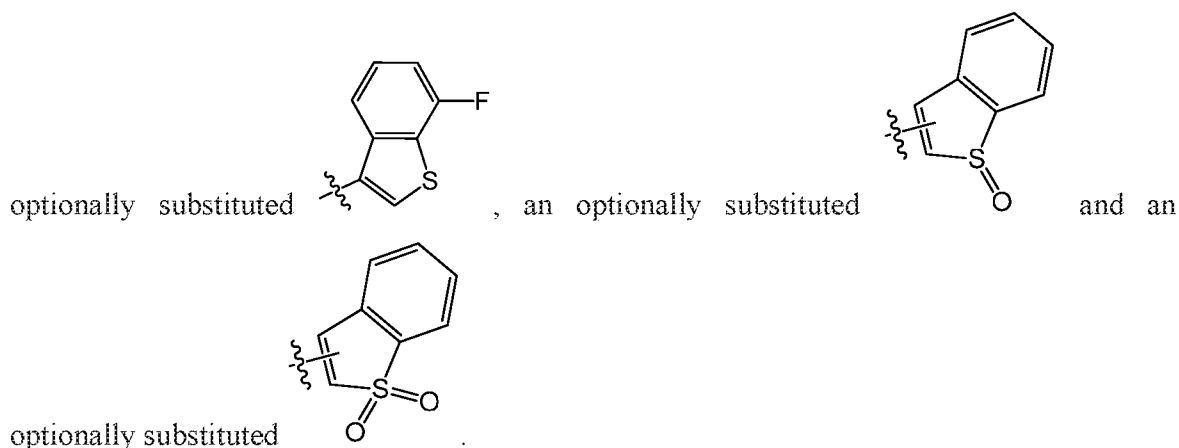
alkyl amine and/or

In other embodiments, when Y is an optionally substituted mono-cyclic heteroaryl, the mono-cyclic heteroaryl can be substituted 1, 2, 3 or more times with halo, an optionally substituted C_{1-4} alkyl, an optionally substituted phenyl and/or an unsubstituted acyl. In still other embodiments, when Y is an optionally substituted bi-cyclic heteroaryl, the bi-cyclic heteroaryl can be substituted 1, 2, 3 or more times with halo, an optionally substituted C_{1-4} alkyl, an optionally substituted phenyl, hydroxy, C_{1-4} alkoxy, an unsubstituted acyl, carbonyl, cyano, amino, mono- C_{1-4} alkyl amine and/or di- C_{1-4} alkyl amine.

[0140] In some embodiments, Y can be an optionally substituted benzothiophene. In some embodiments, Y can be a substituted benzothiophene. In other embodiments, Y can be an unsubstituted benzothiophene. In some embodiments, the benzothiophene can be substituted with one or more of the following: halogen (such as fluoro, chloro and/or bromo), carbonyl, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, NH_2 and/or mono-substituted amine. For



example, the benzothiophene can be an optionally substituted , such as an

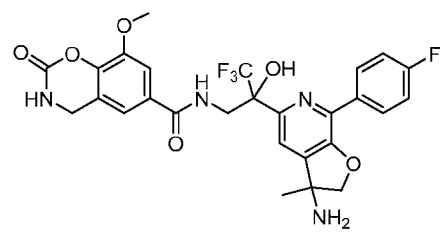
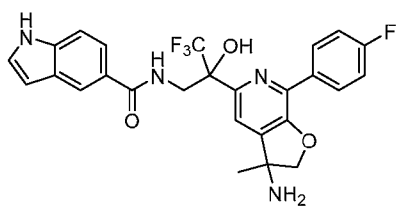
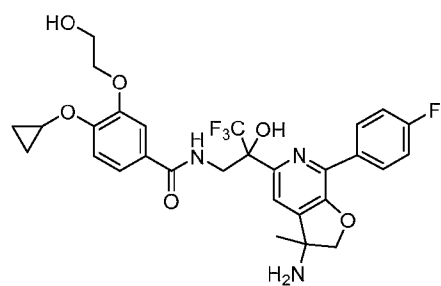
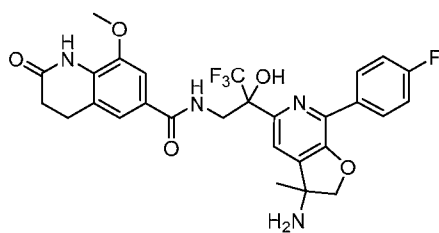
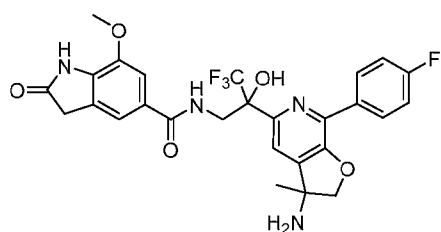
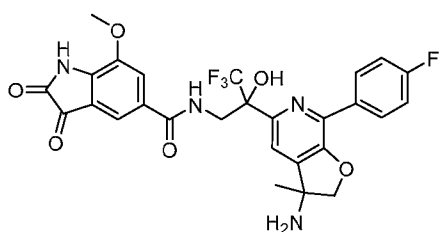
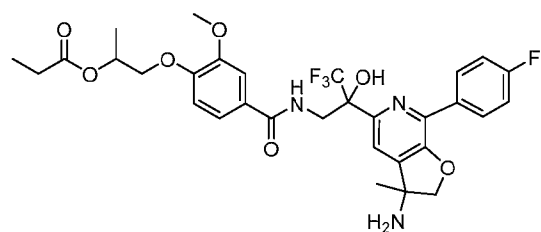
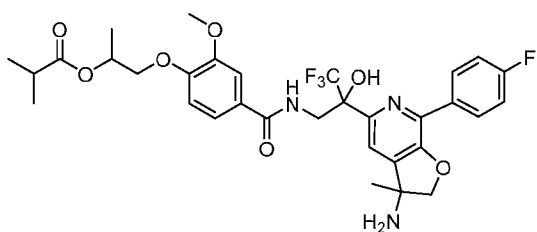
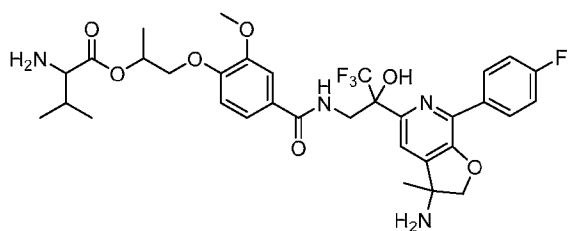
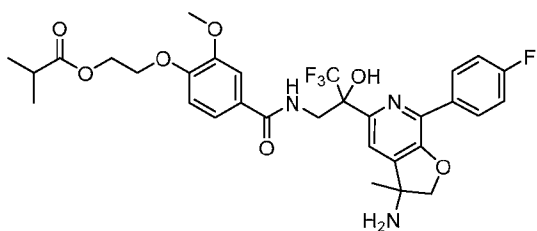
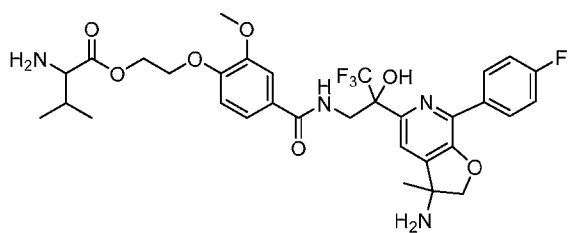
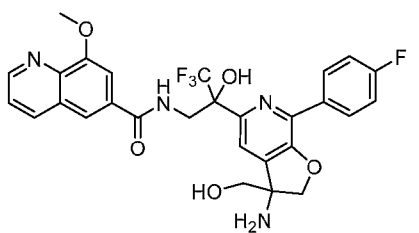


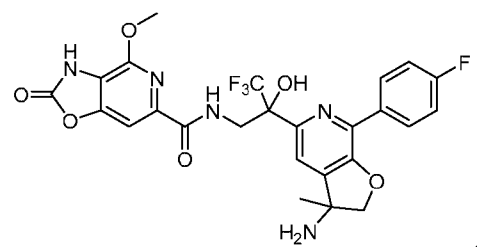
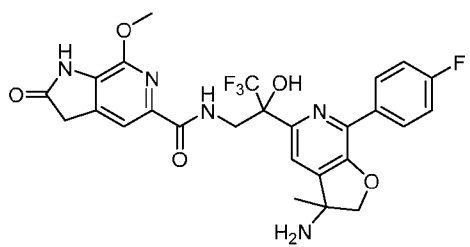
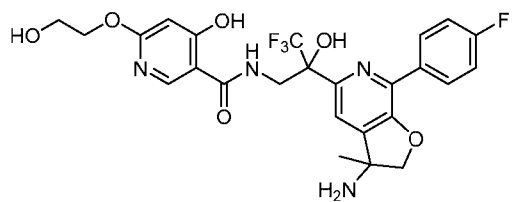
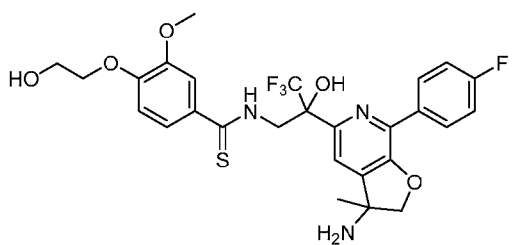
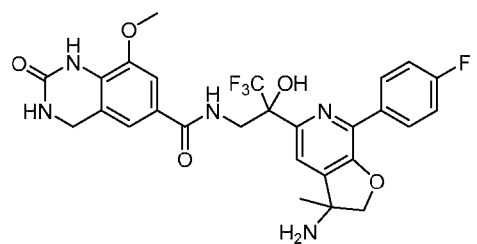
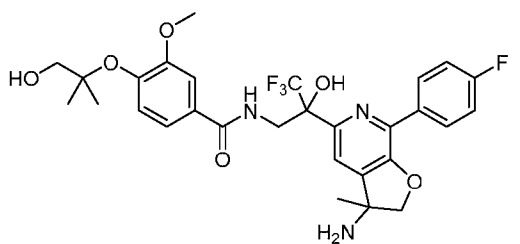
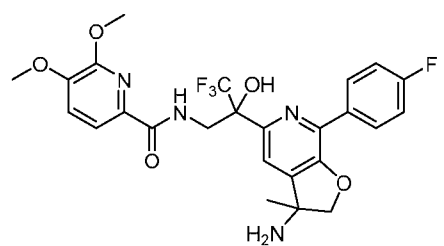
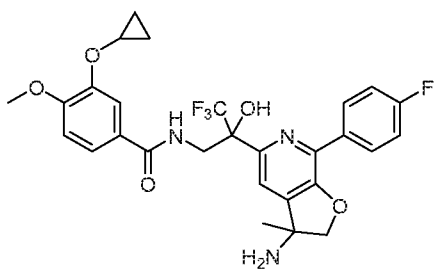
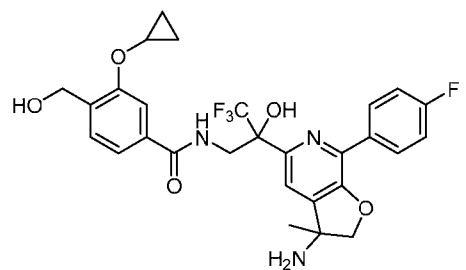
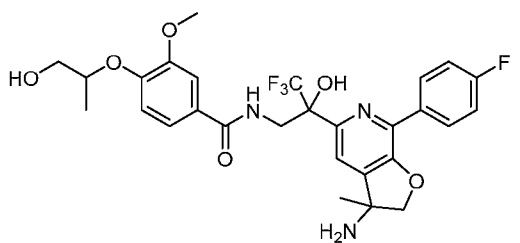
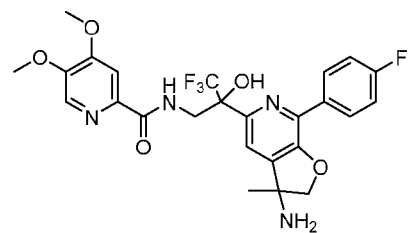
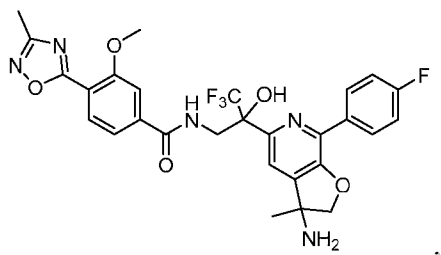
[0141] In some embodiments, Y can be an optionally substituted benzofuran.

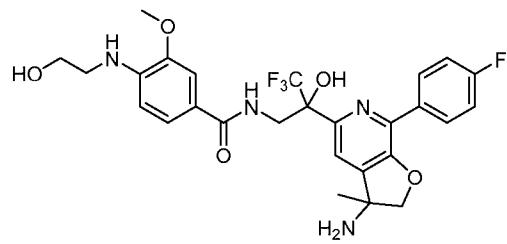
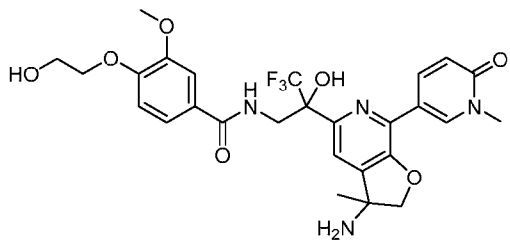
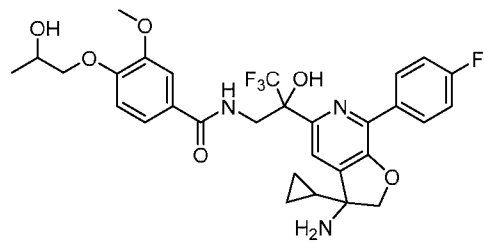
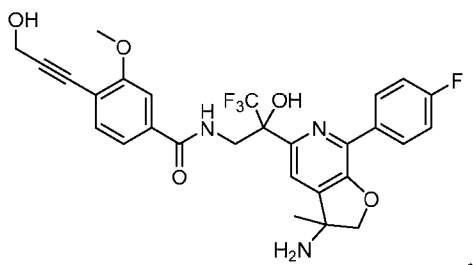
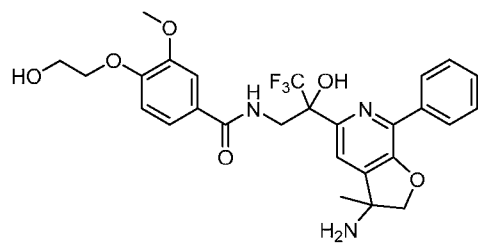
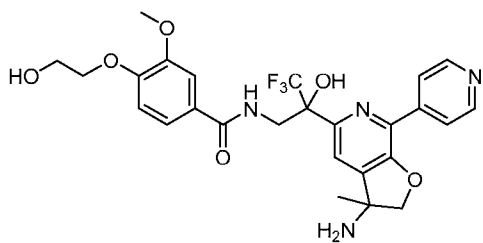
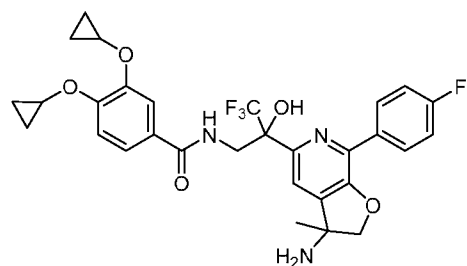
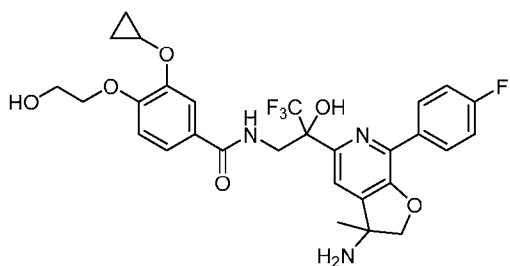
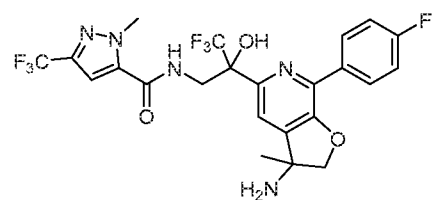
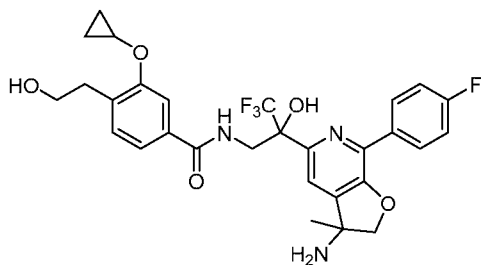
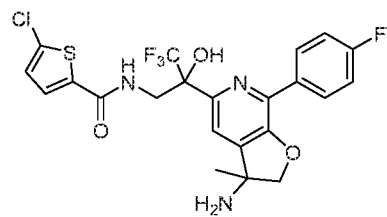
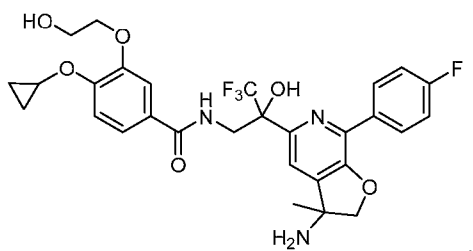
[0142] In some embodiments, Y can be an optionally substituted indole. In some embodiments, Y can be a substituted indole. In some embodiments, the indole can be substituted 1, 2, 3 or more time with phenyl (substituted or unsubstituted), C₁₋₄ alkyl and/or halo. In other embodiments, Y can be an unsubstituted indole.

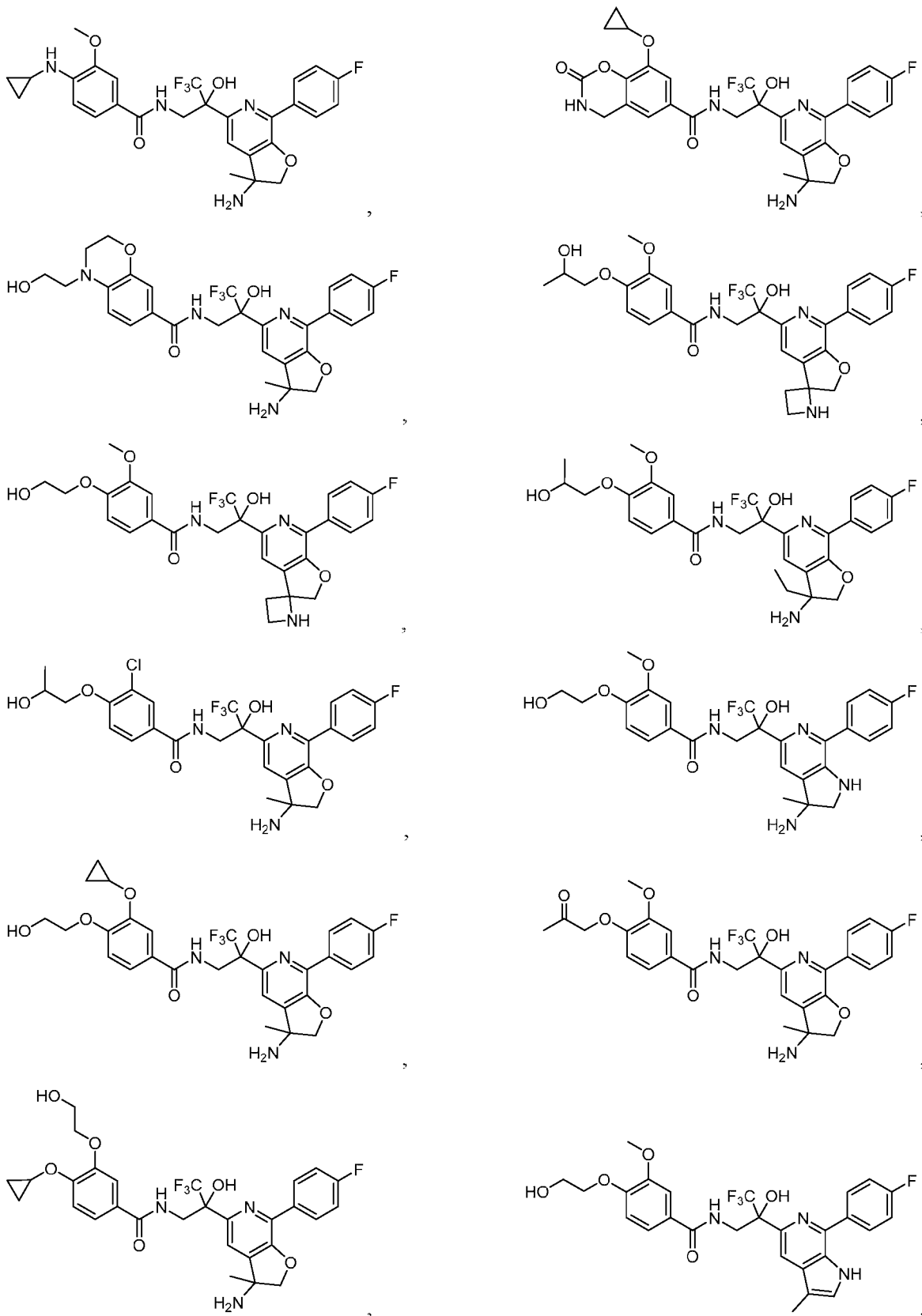
[0143] In some embodiments, Y can be substituted with one or more halogen. In some embodiments, Y can be substituted with one or more unsubstituted C₁₋₄ alkyl. In some embodiments, Y can be substituted with one or more hydroxy. In some embodiments, Y can be substituted with one or more optionally substituted phenyl. In some embodiments, Y can be substituted with one or more alkoxy. In some embodiments, Y can be substituted with one or more acyl. In some embodiments, Y can be substituted with one or more amino, mono-substituted amino, or di-substituted amino. In some embodiments, Y can be substituted with one or more haloalkyl. In some embodiments, Y can be substituted with one or more haloalkoxy. In some embodiments, Y can be substituted with one or more C-carboxy. In some embodiments, Y can be substituted with one or more C-amido. In some embodiments, Y can be substituted with one or more hydroxyalkyl.

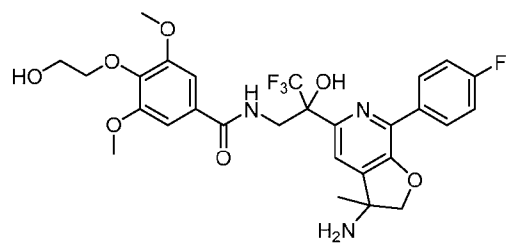
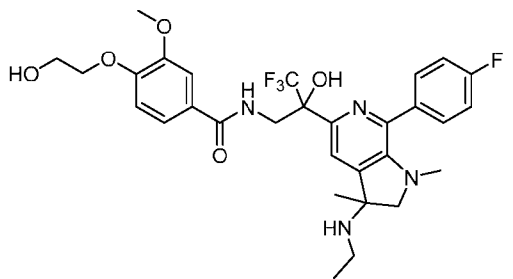
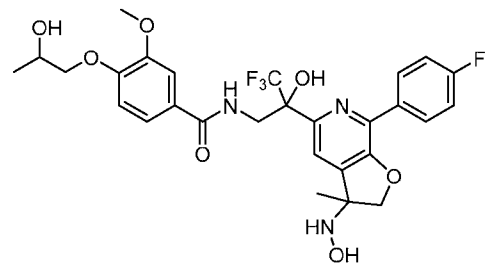
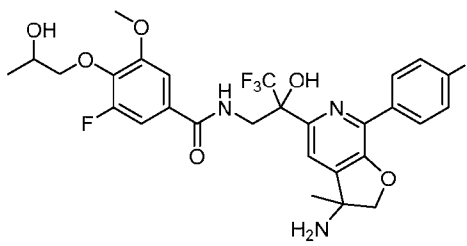
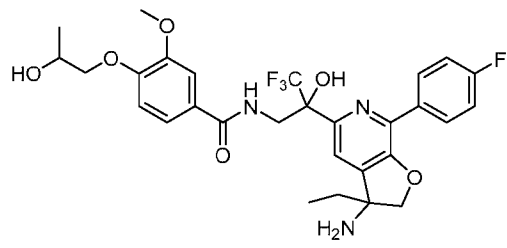
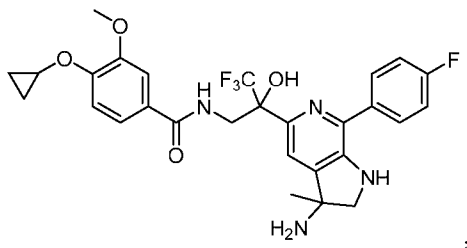
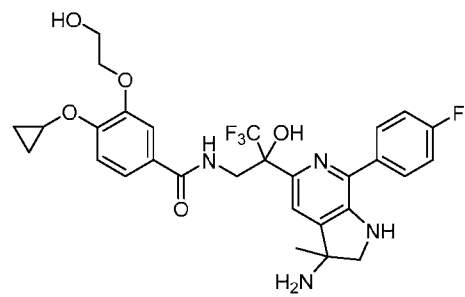
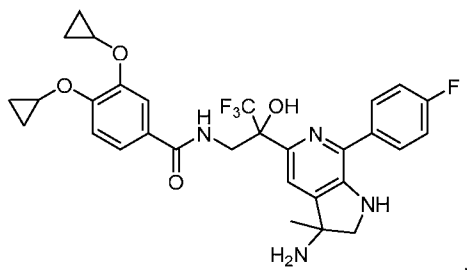
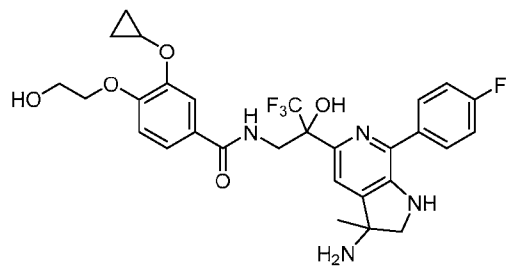
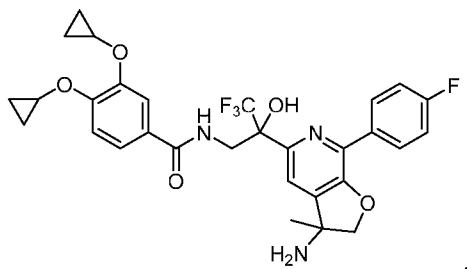
[0144] In some embodiments, a compound of Formula (I) can be selected from the following compounds:

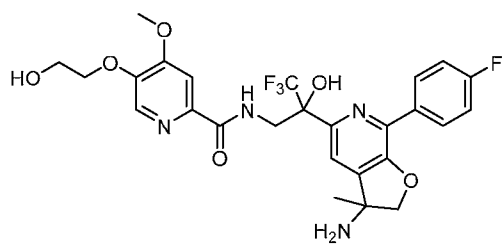
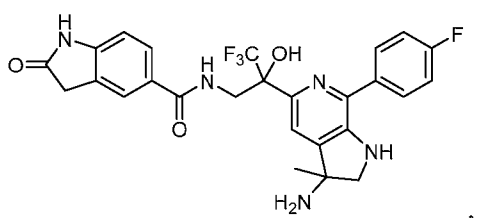
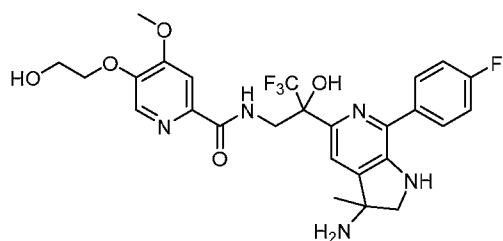
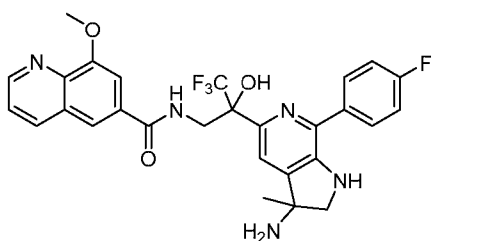
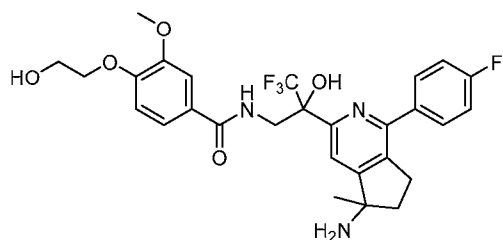
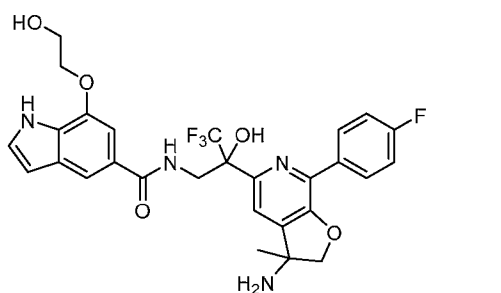
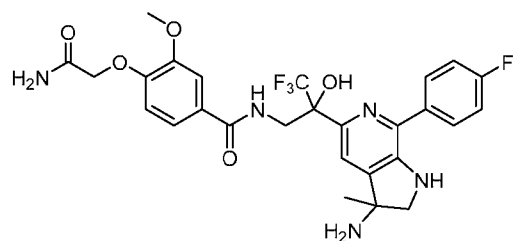
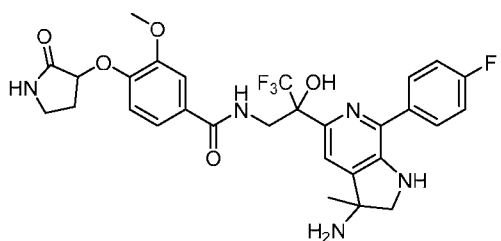
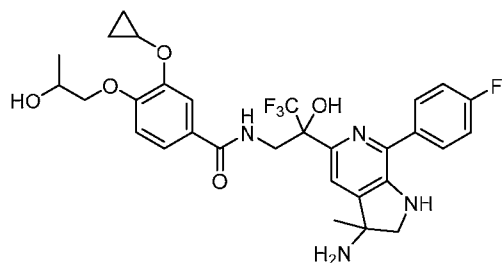
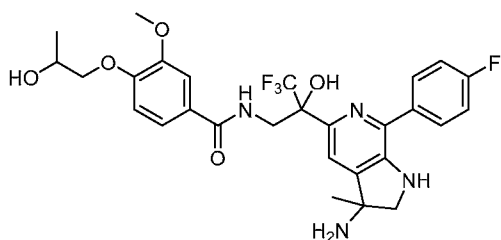
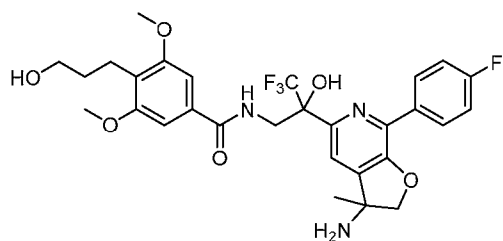
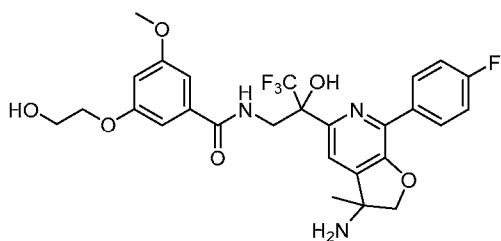


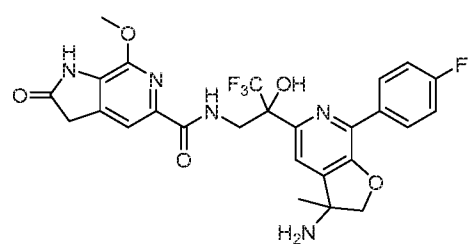
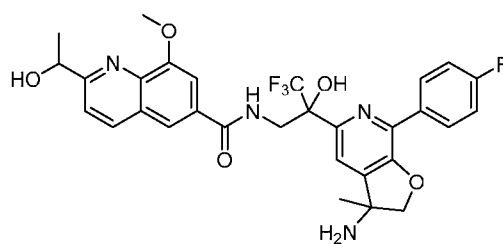
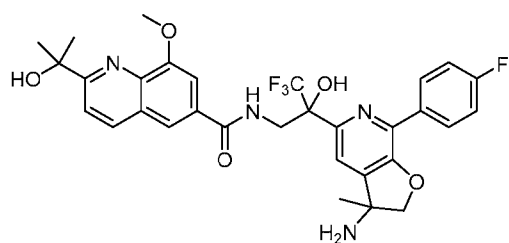
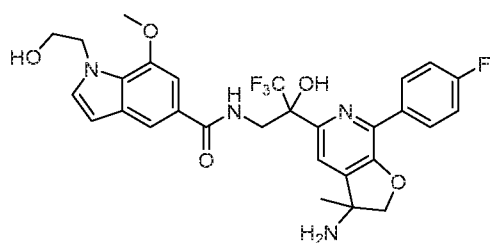
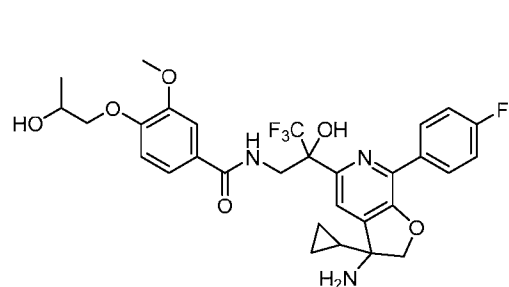
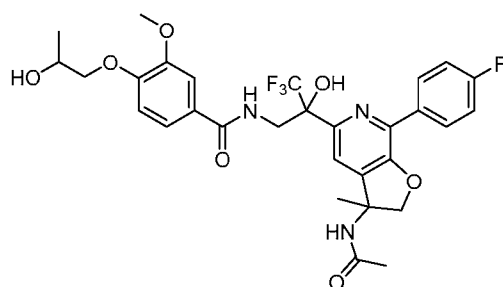
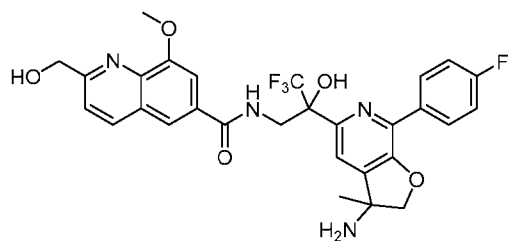
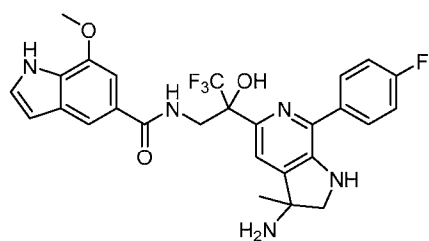
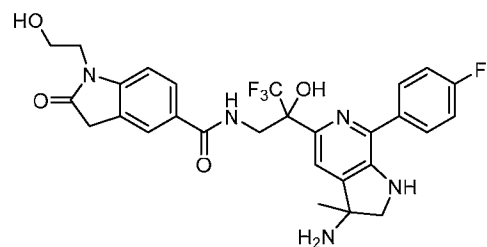
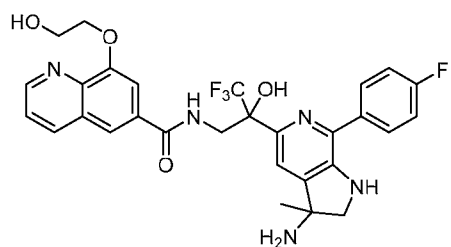
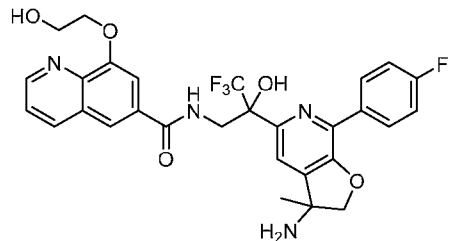
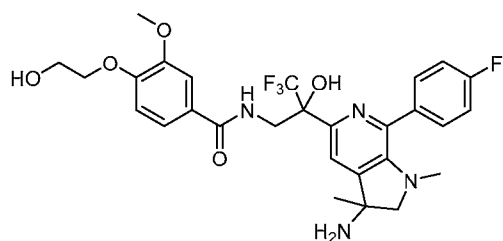


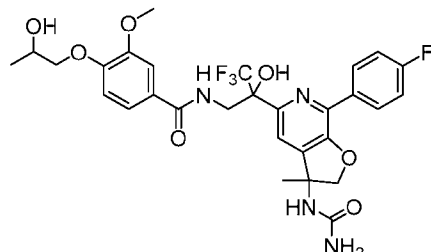
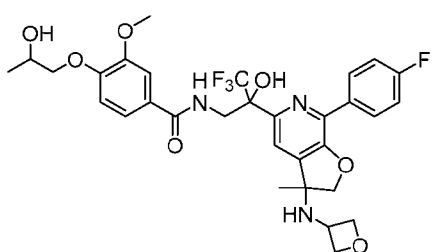
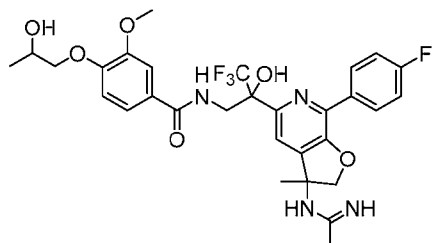
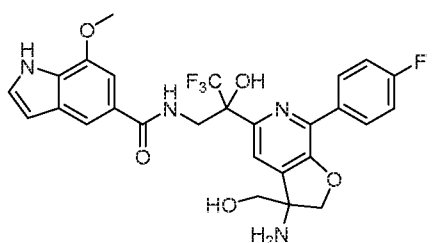
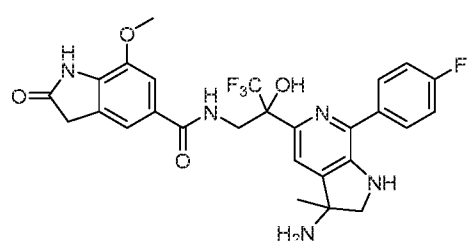
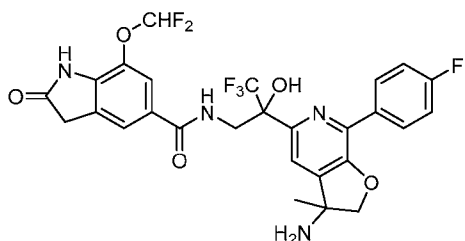
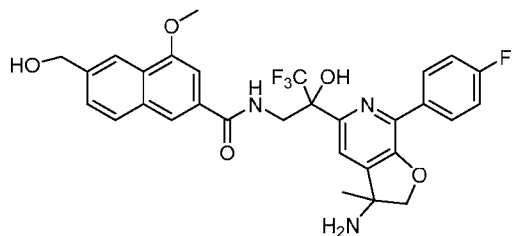
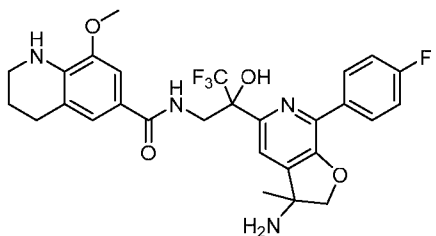
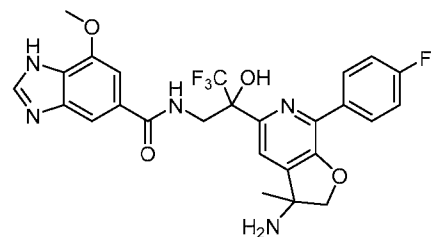
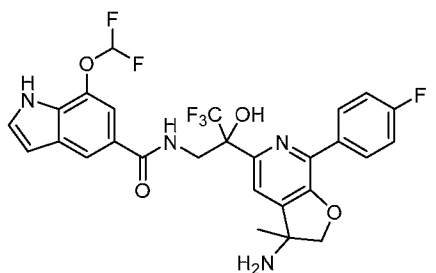










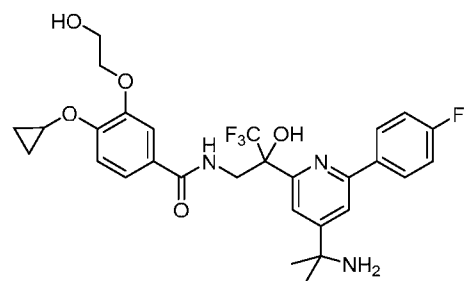
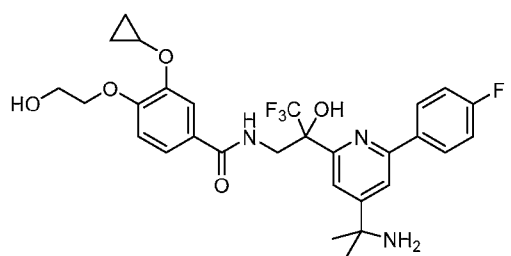
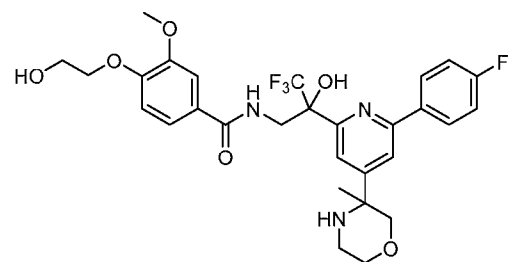
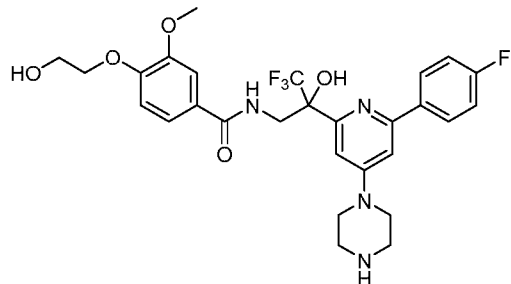
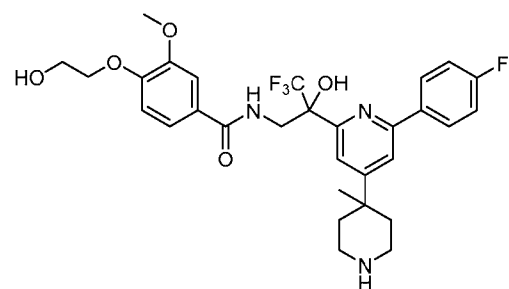
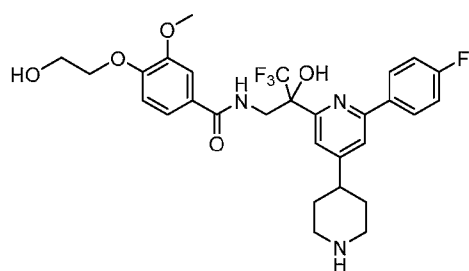
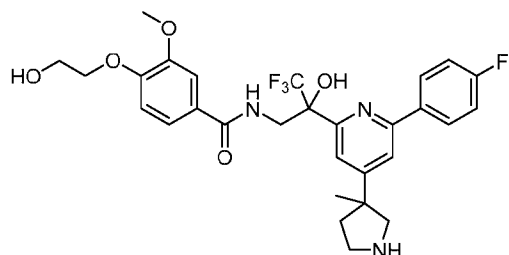
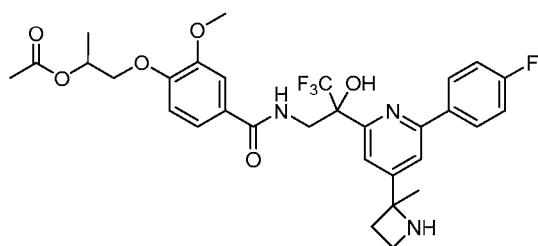
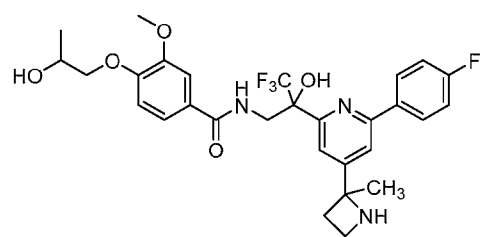
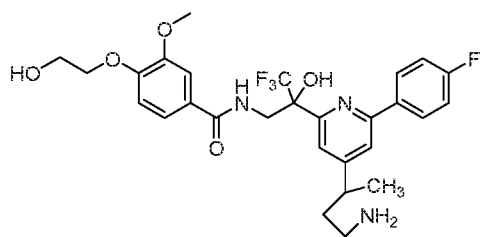


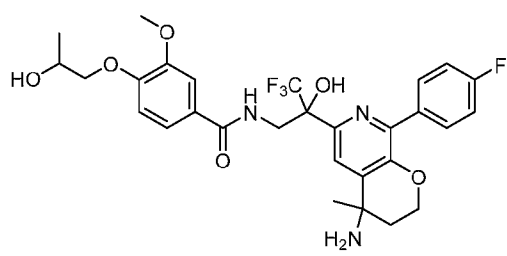
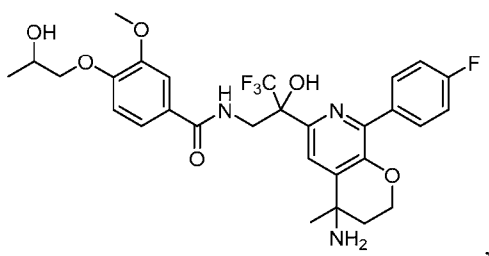
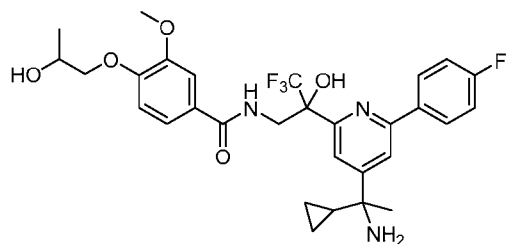
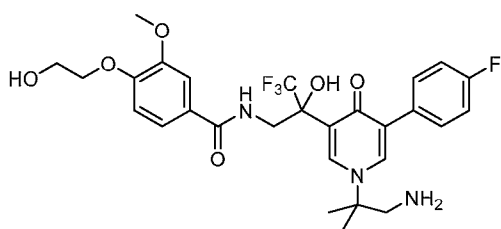
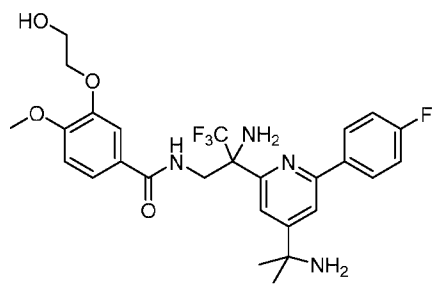
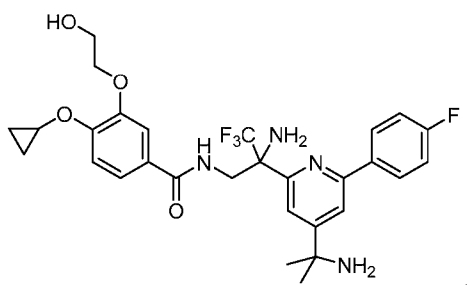
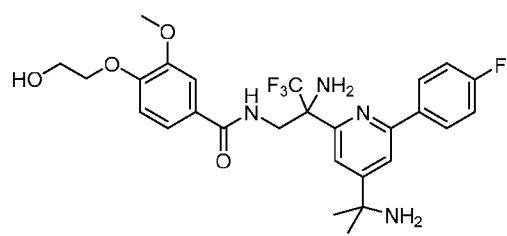
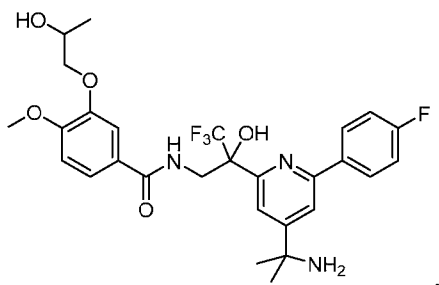
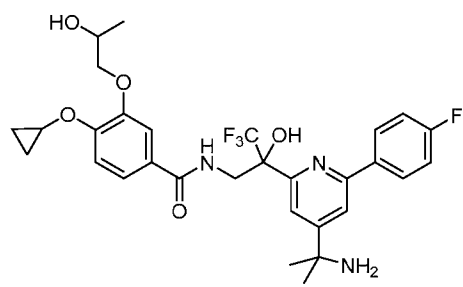
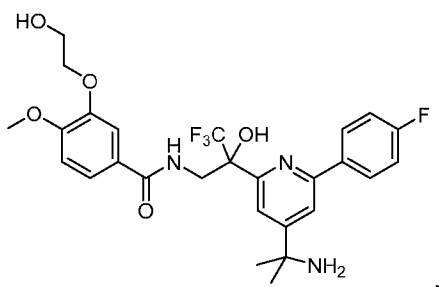
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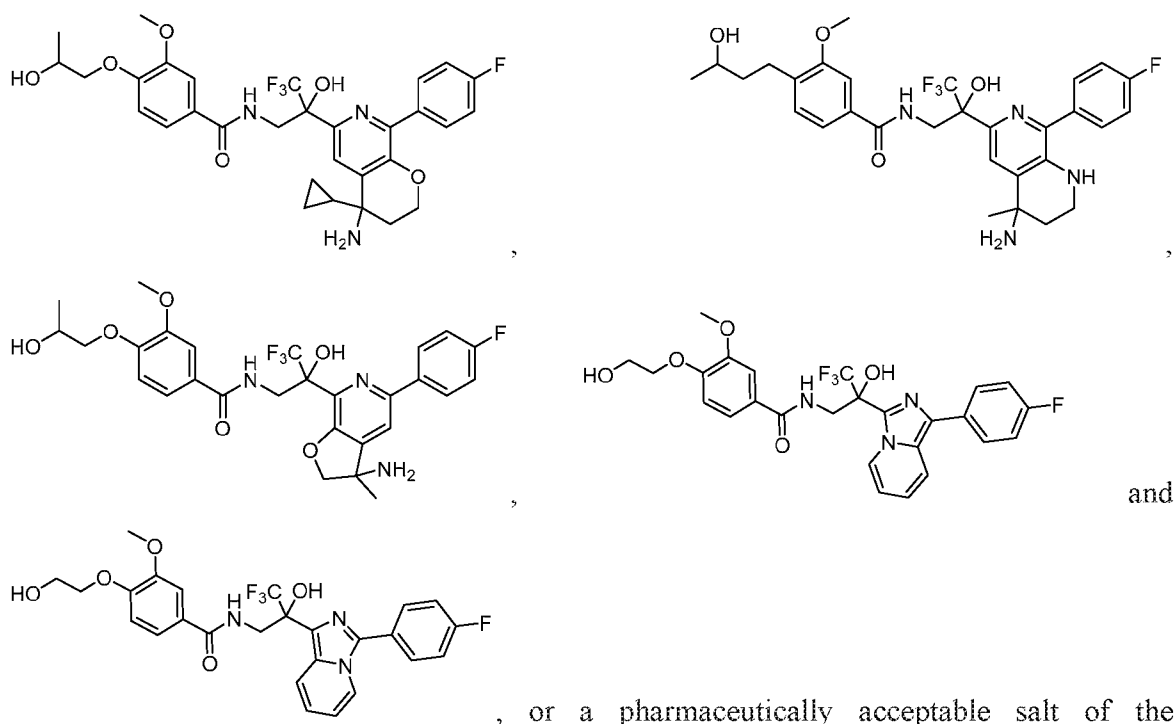
or a

pharmaceutically acceptable salt of the foregoing.

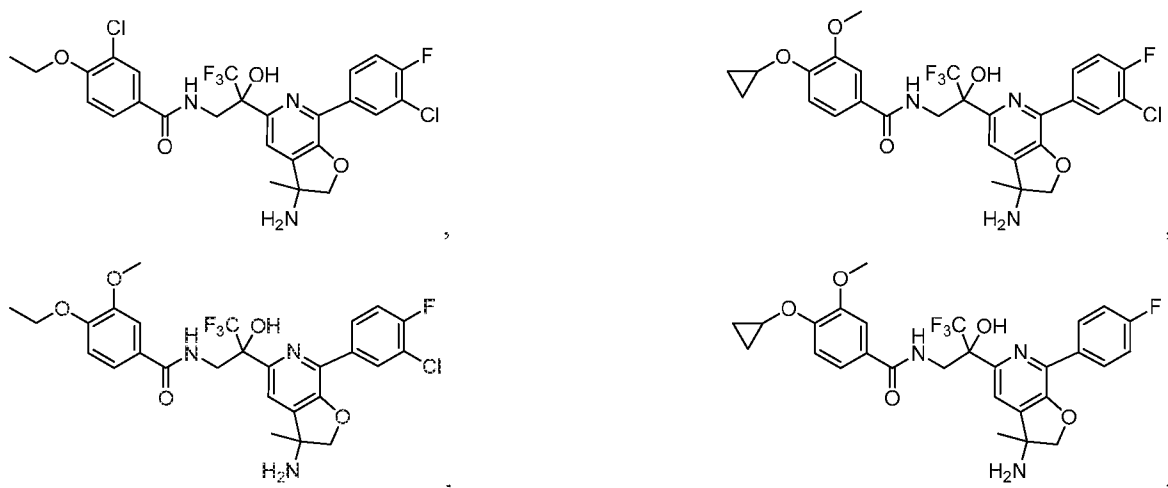
[0145] In some embodiments, a compound of Formula (I) can be selected from the following compounds:

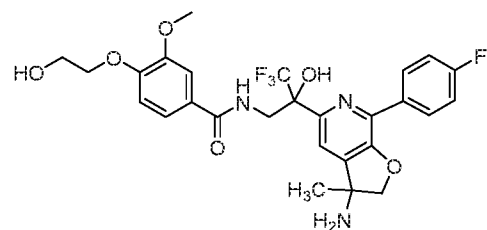
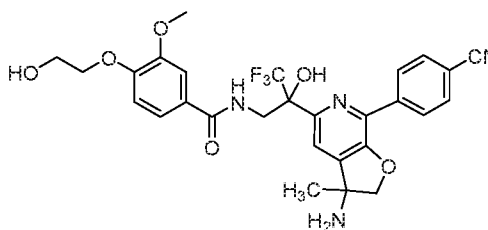
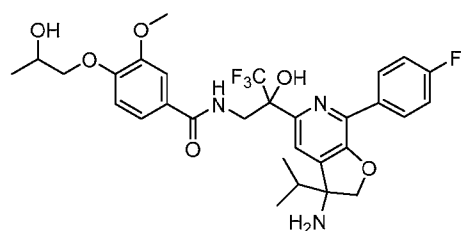
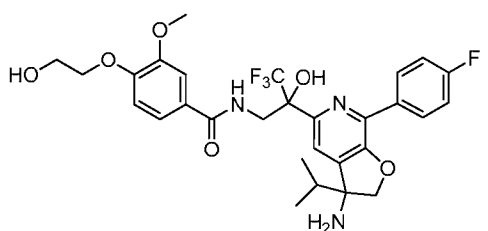
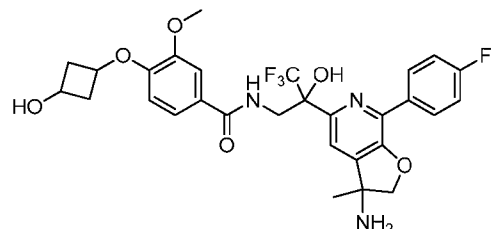
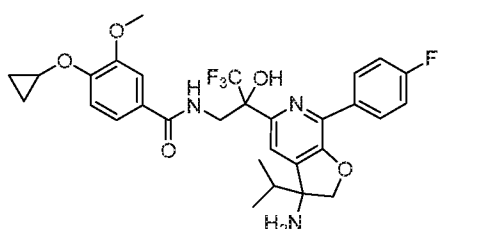
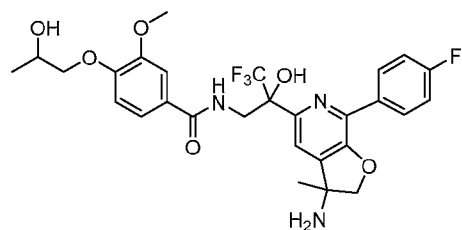
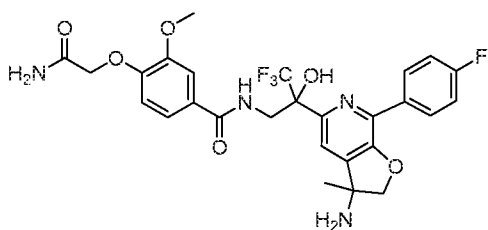
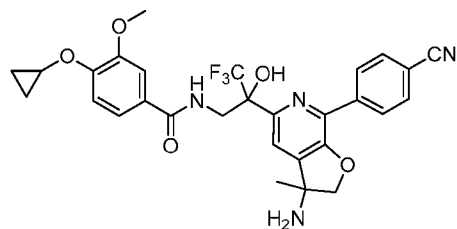
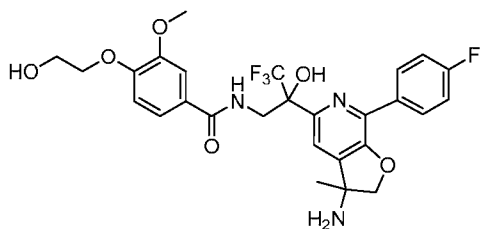
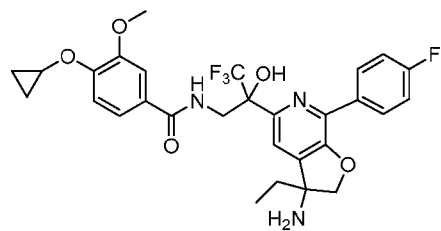
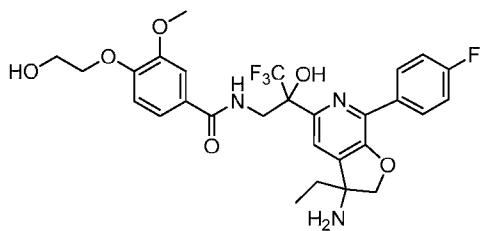


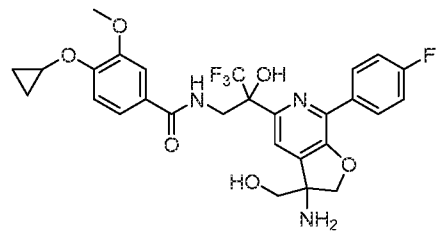
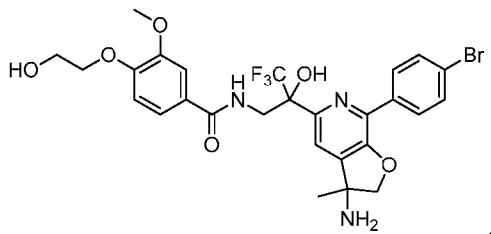
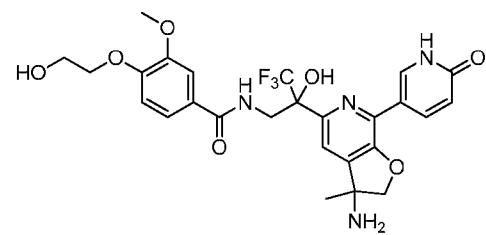
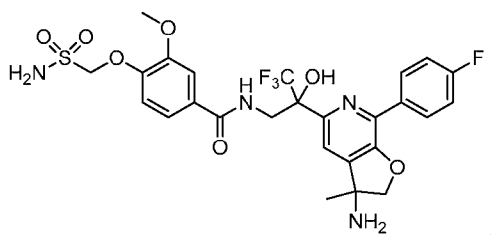
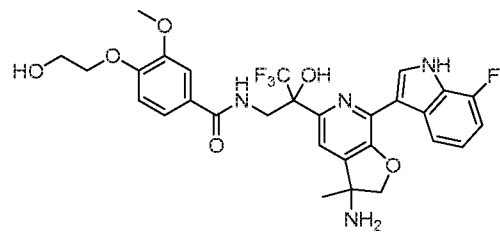
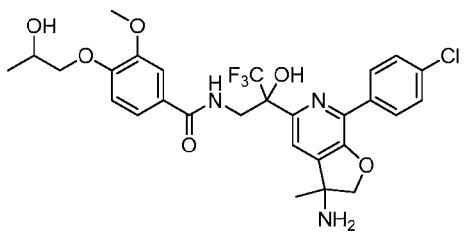
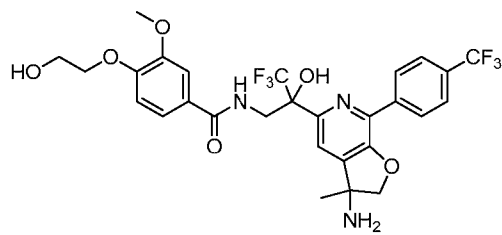
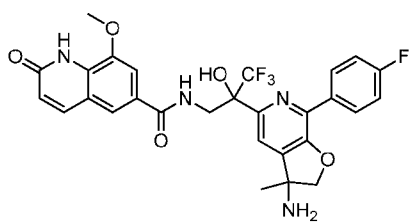
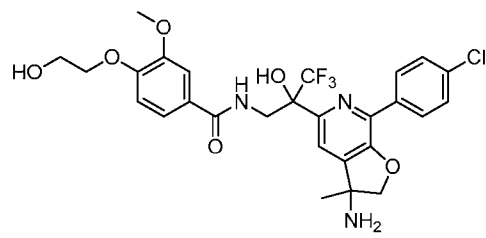
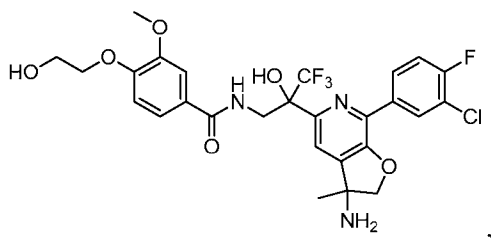
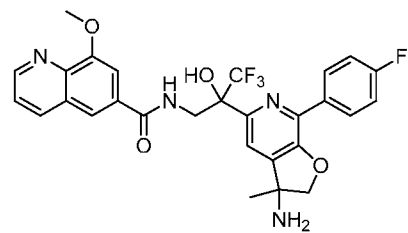
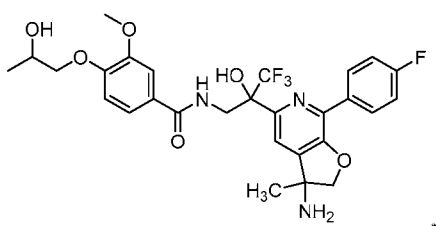


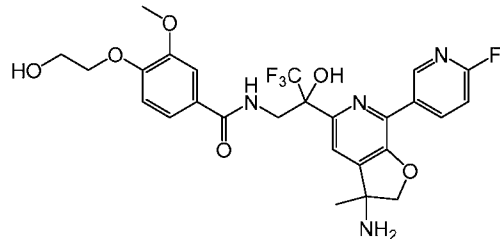
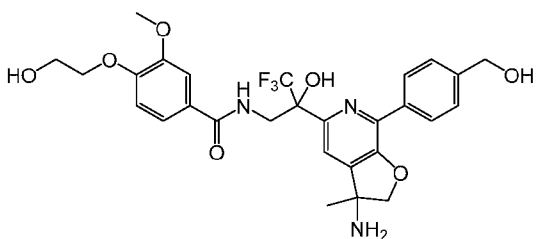
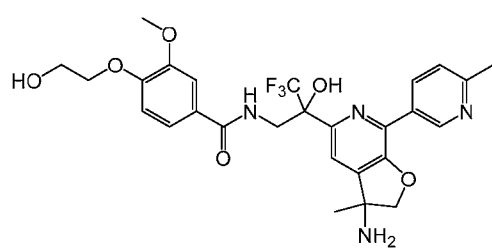
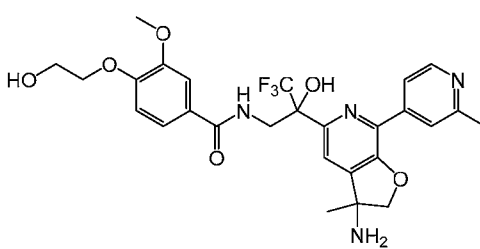
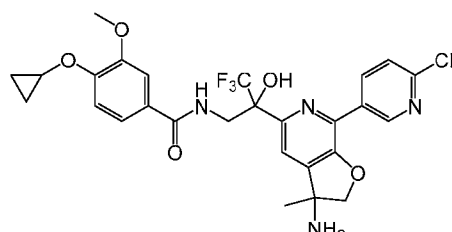
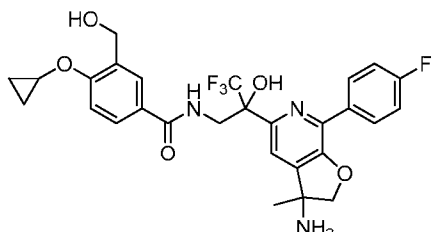
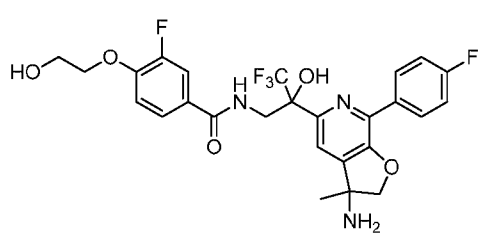
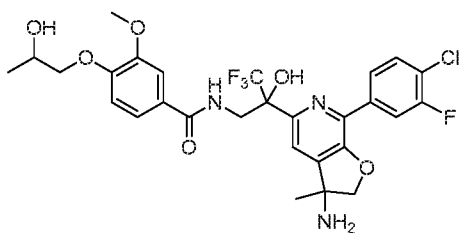
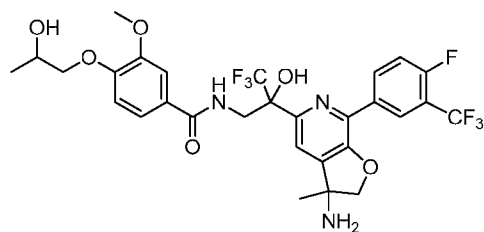
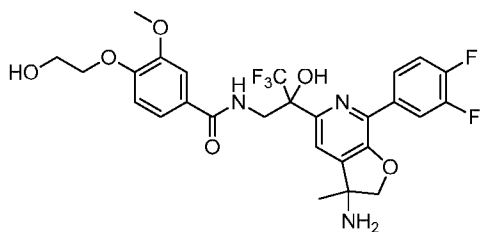
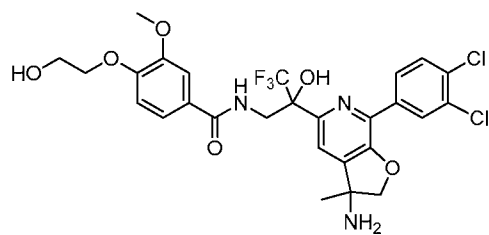
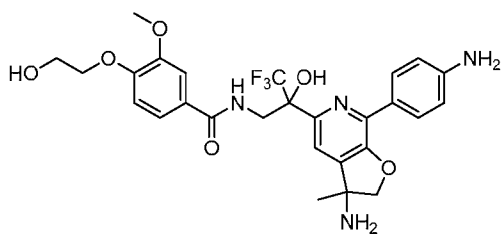


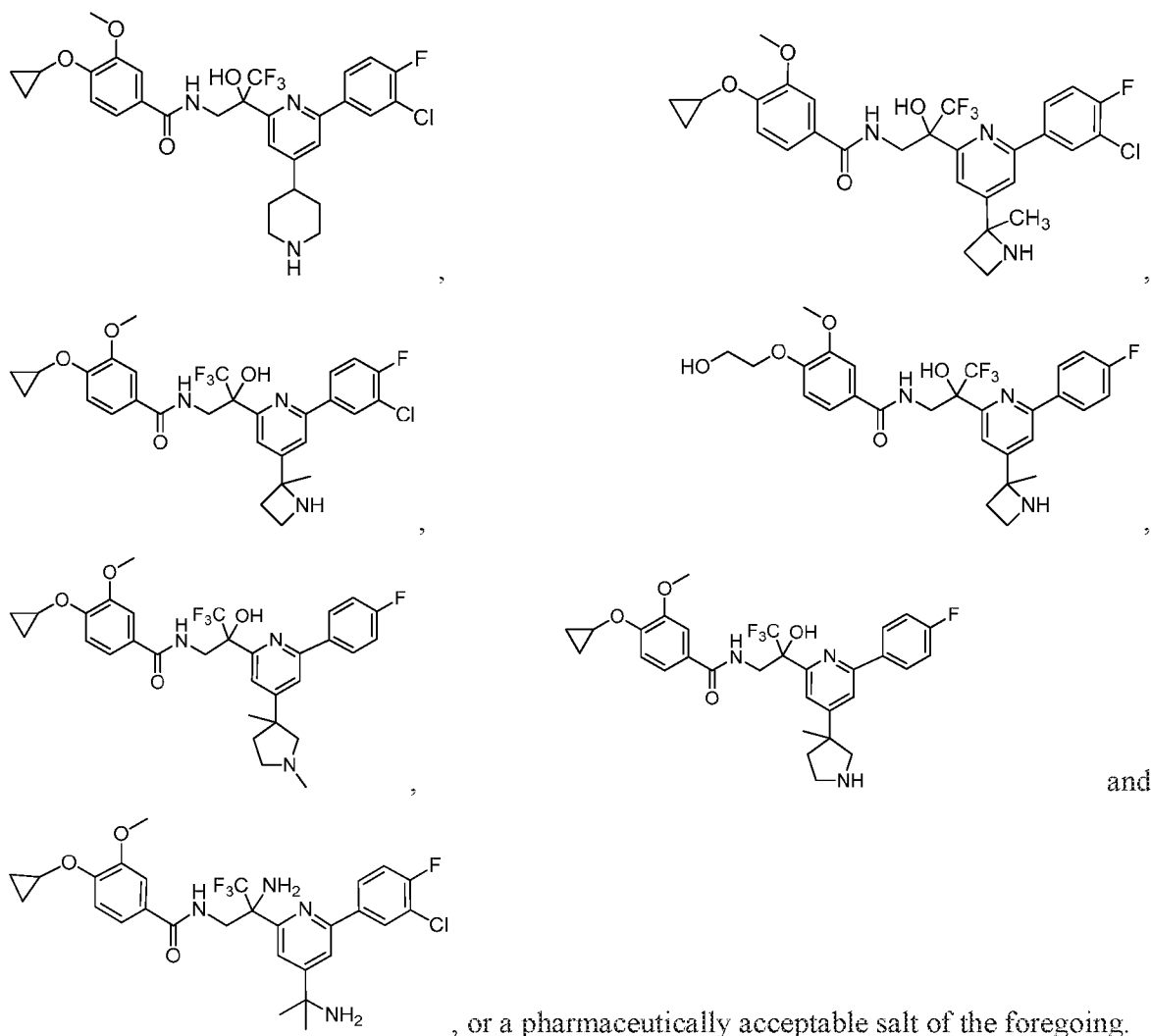
[0146] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, cannot be a compound provided in PCT Publication WO 2014/031784, published February 27, 2014. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, cannot be a compound provided in U.S. Publication No. 2015/0065504, published March 5, 2015. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, cannot be selected from:



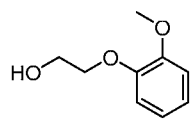




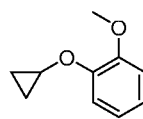




[0148] In some embodiments, A cannot be a mono-substituted phenyl. For example, A cannot be a mono-chloro-substituted phenyl, a mono-fluoro-substituted phenyl or a mono-hydroxyalkyl-substituted phenyl. In some embodiments, A cannot be



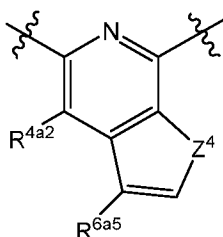
. In some embodiments, A cannot be



. In some embodiments, In

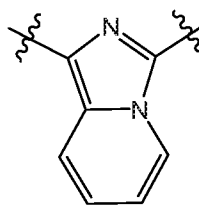
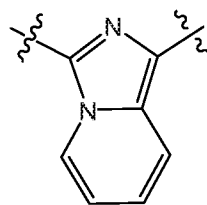
some embodiments, Y cannot be a mono-chloro-substituted phenyl or a mono-bromo-substituted phenyl. In some embodiments, Y cannot be an alkyl substituted phenyl (for example, C₁₋₄ alkyl substituted phenyl), a haloalkyl substituted phenyl (for example, CF₃ substituted phenyl), an amino substituted phenyl, a C-amido-substituted phenyl (such as a —C(=O)NH₂ substituted phenyl), a C-carboxy phenyl (for example, —C(=O)OH substituted phenyl) or a hydroalkyl-substituted phenyl (such as —CH(OH)CH₃ substituted phenyl). In

some embodiments, Y cannot be a di-substituted phenyl. For example, Y cannot be a di-halogen-substituted phenyl. In some embodiments, Y cannot be an optionally substituted heteroaryl (for example, an optionally substituted indole or an optionally substituted pyridine). In some embodiments, Y cannot be a mono-substituted heteroaryl (for example, a mono-substituted heteroaryl, wherein the substituent is a C_{1-4} alkyl, amino, haloalkyl (such as CF_3), C-amido (such as $-C(=O)NH_2$), C-carboxy (such as $-C(=O)OH$) or halogen). In other embodiments, Y cannot be an optionally substituted heterocyclyl (such as an optionally substituted pyridin-2-one). In some embodiments, Y cannot be a mono-substituted heterocyclyl. For example, Y cannot be a mono-substituted heteroaryl, wherein the substituent is a C_{1-4} alkyl, amino, haloalkyl (such as CF_3), C-amido (such as $-C(=O)NH_2$), C-carboxy (such as $-C(=O)OH$) or halogen. In some embodiments, Z^2 cannot be O. In some



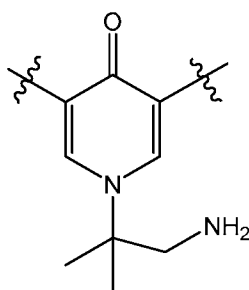
embodiments, L^1 cannot be

In some embodiments, L^1 cannot be



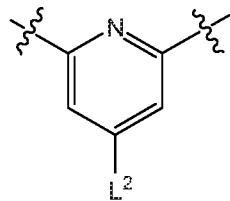
In some embodiments, L^1 cannot be

In some

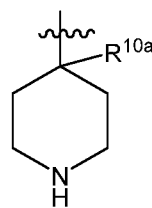


embodiments, L^1 cannot be

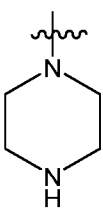
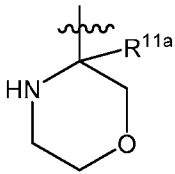
In some embodiments, L^1 cannot be

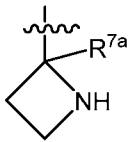
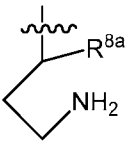


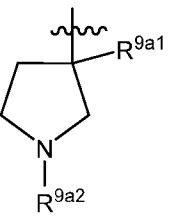
In some embodiments, L^2 cannot be

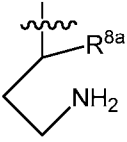
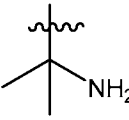


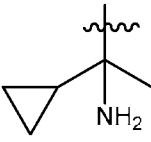
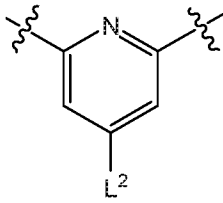
In some embodiments,

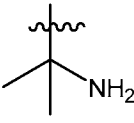
L^2 cannot be . In some embodiments, L^2 cannot be . In some

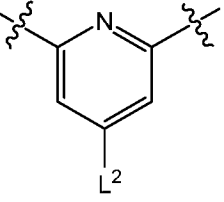
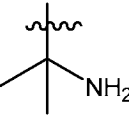
embodiments, L^2 cannot be . In some embodiments, L^2 cannot be . In

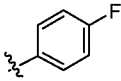
some embodiments, L^2 cannot be . In some embodiments, L^2 cannot be

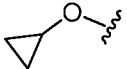
. In some embodiments, L^2 cannot be . In some embodiments, L^2

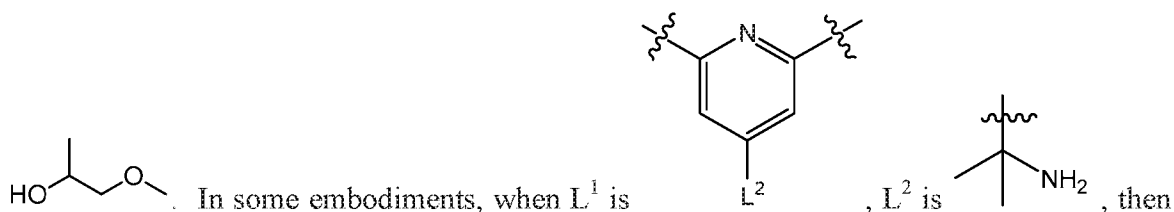
cannot be . In some embodiments, when L^1 is  and L^2 is

, then one of R^{3a} and R^{3a1} is NH_2 , and the other of R^{3a} and R^{3a1} is OH . In some

embodiments, when L^1 is , L^2 is , one of R^{3a} and R^{3a1} is CF_3 ,

and the other of R^{3a} and R^{3a1} is OH , then Y is  and A is a disubstituted phenyl

wherein one substituent is  and the other substituent is $-O-(CH_2)_{2-4}OH$ or



one of R^{3a} and R^{3a1} cannot be CF_3 , and the other of R^{3a} and R^{3a1} cannot be OH. In some embodiments, R^{9a1} cannot be hydrogen. In some embodiments, R^{9a2} cannot be hydrogen. In some embodiments, R^{10a} cannot be hydrogen. In some embodiments, R^{11a} cannot be hydrogen.

Pharmaceutical Compositions

[0149] Some embodiments described herein relate to a pharmaceutical composition, that can include an effective amount of one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0150] The term “pharmaceutical composition” refers to a mixture of one or more compounds disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid. Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0151] The term “physiologically acceptable” defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound nor cause appreciable damage or injury to an animal to which delivery of the composition is intended.

[0152] As used herein, a “carrier” refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0153] As used herein, a “diluent” refers to an ingredient in a pharmaceutical composition that lacks appreciable pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the pH and isotonicity of human blood.

[0154] As used herein, an “excipient” refers to an essentially inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. A “diluent” is a type of excipient.

[0155] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or carriers, diluents, excipients or combinations thereof. Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art.

[0156] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. Additionally, the active ingredients are contained in an amount effective to achieve its intended purpose. Many of the compounds used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically compatible counterions.

[0157] Multiple techniques of administering a compound exist in the art including, but not limited to, oral, rectal, pulmonary, topical, aerosol, injection and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections.

[0158] One may also administer the compound in a local rather than systemic manner, for example, via injection or implantation of the compound directly into the affected area, often in a depot or sustained release formulation. Furthermore, one may administer the

compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ. For example, intranasal or pulmonary delivery to target a respiratory infection may be desirable.

[0159] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Methods of Use

[0160] Some embodiments described herein relate to a method for ameliorating, treating and/or preventing a paramyxovirus viral infection, which can comprise administering an effective amount of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof).

[0161] Some embodiments described herein relate to a method for inhibiting viral replication of a paramyxovirus, which can comprise contacting a cell infected with the virus with an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof).

[0162] Some embodiments described herein relate to a method for contacting a cell infected with a paramyxovirus, which can comprise contacting a cell infected with the

virus with an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof).

[0163] In some embodiments, the paramyxovirus infection is a human respiratory syncytial virus infection.

[0164] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate a respiratory syncytial viral infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to prevent a respiratory syncytial viral infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the replication a respiratory syncytial virus. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the RSV polymerase complex. In some embodiments, the RSV can be RSV A. In some embodiments, the RSV can be RSV B.

[0165] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate a hendravirus infection and/or nipahvirus infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable

salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to prevent a hendraviral infection and/or nipahviral infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the replication a hendraviruses and/or nipahvirus. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the hendraviruses polymerase complex and/or nipahvirus polymerase complex.

[0166] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate a measles. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to prevent a measles. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the replication a measles virus. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the measles polymerase complex.

[0167] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical

composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate mumps. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to prevent mumps. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the replication a mumps virus. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the mumps polymerase complex.

[0168] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate a sendai viral infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to prevent a sendai viral infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the replication a sendai virus. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a

compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the sendai virus polymerase complex.

[0169] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate a HPIV-1 infection and/or HPIV-3 infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to prevent a HPIV-1 infection and/or HPIV-3 infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the replication of a HPIV-1 and/or HPIV-3. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the HPIV-1 polymerase complex and/or HPIV-3 polymerase complex.

[0170] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate a HPIV-2 infection and/or HPIV-4 infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to prevent a HPIV-2 infection and/or HPIV-4 infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes

one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the replication of a HPIV-2 and/or HPIV-4. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the HPIV-2 polymerase complex and/or HPIV-4 polymerase complex.

[0171] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate a human metapneumoviral infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to prevent a human metapneumoviral infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the replication of a human metapneumovirus. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to inhibit the human metapneumovirus polymerase complex.

[0172] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate an upper respiratory viral infection caused by a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus, a pneumovirus, and a metapneumovirus. In some embodiments, an effective amount of one or more compounds of Formula (I), or a

pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate a lower respiratory viral infection caused by a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus, a pneumovirus, and a metapneumovirus. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate one or more symptoms of an infection caused by a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus, a pneumovirus, and a metapneumovirus (such as those described herein).

[0173] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate an upper respiratory viral infection caused by RSV infection, measles, mumps, parainfluenza infection, and/or metapneumovirus. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate a lower respiratory viral infection caused by RSV infection, measles, mumps, parainfluenza infection, and/or metapneumovirus. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate one or more symptoms of an infection caused by RSV infection, measles, mumps, parainfluenza infection, and/or metapneumovirus (such as those described herein).

[0174] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of

Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate bronchiolitis and/or tracheobronchitis due to a RSV infection and/or human parainfluenza virus 3 (HPIV-3) infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate pneumonia due to a RSV infection and/or human parainfluenza virus 3 (HPIV-3) infection. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate croup due to a RSV infection and/or human parainfluenza virus 1 (HPIV-1) infection.

[0175] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate due to fever, cough, runny nose, red eyes, a generalized rash, pneumonia, an ear infection and/or bronchitis due to measles. In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used treat and/or ameliorate due to swelling of the salivary glands, fever, loss of appetite and/or fatigue due to mumps.

[0176] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to prevent a human parainfluenza viral infection. In some embodiments, the human parainfluenza viral infection can be a human parainfluenza virus 1 (HPIV-1). In other embodiments, the human parainfluenza viral infection can be a human parainfluenza virus 2 (HPIV-2). In other

embodiments, the human parainfluenza viral infection can be a human parainfluenza virus 3 (HPIV-3). In other embodiments, the human parainfluenza viral infection can be a human parainfluenza virus 4 (HPIV-4). In some embodiments, one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, can be used to treat and/or ameliorate one or more subtypes of human parainfluenza virus. For example, one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, can be used to treat HPIV-1 and/or HPIV-3.

[0177] The one or more compounds of Formula (I) or a pharmaceutically acceptable salt thereof, that can be used to treat, ameliorate and/or prevent a paramyxovirus viral infection can be a compound of Formula (I), or pharmaceutically acceptable salt thereof, provided in any of the embodiments described in paragraphs [0078]-[0148].

[0178] As used herein, a “subject” refers to an animal that is the object of treatment, observation or experiment. “Animal” includes cold- and warm-blooded vertebrates and invertebrates such as fish, shellfish, reptiles and, in particular, mammals. “Mammal” includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject is human.

[0179] As used herein, the terms “prevent” and “preventing,” mean lowering the efficiency of viral replication and/or inhibiting viral replication to a greater degree in a subject who receives the compound compared to a subject who does not receive the compound. Examples of forms of prevention include prophylactic administration to a subject who has been or may be exposed to an infectious agent, such as a paramyxovirus (e.g., RSV).

[0180] As used herein, the terms “treat,” “treating,” “treatment,” “therapeutic,” and “therapy” do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of a disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the subject’s overall feeling of well-being or appearance, and may positively affect one or more symptoms or aspects of the disease while having effects on other aspects of the disease or on unrelated systems that may be considered undesirable.

[0181] The terms “therapeutically effective amount” and “effective amount” are used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the

biological or medicinal response indicated. For example, a therapeutically effective amount of compound can be the amount needed to prevent, treat, alleviate or ameliorate one or more symptoms or conditions of disease or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0182] Various indicators for determining the effectiveness of a method for treating a viral infection, such as a paramyxovirus, are known to those skilled in the art. Example of suitable indicators include, but are not limited to, a reduction in viral load, a reduction in viral replication, a reduction in viral RNA, a reduction in time to seroconversion (virus undetectable in patient serum), a reduction of morbidity or mortality in clinical outcomes, and/or other indicator of disease response.

[0183] In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to reduce viral titers to essentially undetectable or very low levels, for example, to less than $1.7 \log_{10}$ plaque forming units equivalents (PFUe)/mL, or less than $0.3 \log_{10}$ plaque forming units equivalents (PFUe)/mL. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can reduce the viral load compared to the viral load before administration of the combination (for example, 60 hours after receiving the initial dosage of the combination). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, described herein can reduce the viral load to lower than $1.7 \log_{10}$ (PFUe)/mL, or lower than $0.3 \log_{10}$ (PFUe)/mL. In some embodiments, a combination of compounds described herein can achieve a reduction in viral titer in the serum of the subject in the range of about 1.5-log to about a 2.5-log reduction, about a 3-log to about a 4-log reduction, or a greater than about 5-log reduction compared to the viral load before

administration of the combination. For example, the viral load is measure before administration of the combination, and several hours after receiving the initial dosage of the combination (for example, 60 hours after receiving the initial dosage of the combination).

[0184] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in at least a 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, 75, 100-fold or more reduction in the replication of a paramyxovirus relative to pre-treatment levels in a subject, as determined several hours after receiving the initial dosage of the combination (for example, 60 hours after receiving the initial dosage of the combination). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, described herein can result in a reduction of the replication of a paramyxovirus relative to pre-treatment levels in the range of about 2 to about 5 fold, about 10 to about 20 fold, about 15 to about 40 fold, or about 50 to about 100 fold. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in a reduction of a paramyxovirus replication in the range of 1 to 1.5 log, 1.5 log to 2 log, 2 log to 2.5 log, 2.5 to 3 log, 3 log to 3.5 log or 3.5 to 4 log more reduction of a paramyxovirus replication compared to the reduction of a paramyxovirus reduction achieved by ribavirin (Virazole®), or may achieve the same reduction as that of ribavirin (Virazole®) therapy in a shorter period of time, for example, in one day, two days, three days, four days, or five days, as compared to the reduction achieved after 5 days of ribavirin (Virazole®) therapy.

[0185] After a period of time, infectious agents can develop resistance to one or more therapeutic agents. The term “resistance” as used herein refers to a viral strain displaying a delayed, lessened and/or null response to a therapeutic agent(s). For example, after treatment with an antiviral agent, the viral load of a subject infected with a resistant virus may be reduced to a lesser degree compared to the amount in viral load reduction exhibited by a subject infected with a non-resistant strain. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered to a subject infected with RSV that is resistant to one or more different anti-RSV agents (for example, ribavirin). In some embodiments, development of resistant RSV strains is delayed when subjects are treated with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, compared to the development of RSV strains resistant to other RSV drugs.

[0186] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can decrease the percentage of subjects that experience complications from a RSV viral infection compared to the percentage of subjects that experience complication being treated with ribavirin. For example, the percentage of subjects being treated with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that experience complications can be 10% , 25%, 40%, 50%, 60%, 70%, 80% and 90% less compared to subjects being treated with ribavirin.

[0187] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound described herein, can be used in combination with one or more additional agent(s). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with one or more agents currently used in a conventional standard of care for treating RSV. For example, the additional agent can be ribavirin, palivizumab, and RSV-IGIV. For the treatment of RSV, additional anti-RSV agents include but are not limited to an anti-RSV antibody, a fusion protein inhibitor, an N-protein inhibitor, a RSV polymerase inhibitor, an IMPDH inhibitor, an interferon and an other compound that inhibits the RSV virus, or a pharmaceutically acceptable salt of any of the foregoing. A non-limiting list of examples of additional agents is provided herein.

anti-RSV antibodies	RSV-IGIV (RespiGam®) palivizumab (Synagis®, a chimeric humanized IgG monoclonal antibody) motavizumab (MEDI-524, humanized monoclonal antibody)
fusion protein inhibitors	1-cyclopropyl-3-[[1-(4-hydroxybutyl)benzimidazol-2-yl]methyl]imidazo[4,5-c]pyridin-2-one (BMS-433771) 4,4"-bis- {4,6-bis-[3-(bis-carbamoylmethyl-sulfamoyl)-phenylamino]-(1,3,5)triazin-2-ylamino}-biphenyl-2,2"-disulfonic-acid (RFI-641) 4,4'-Bis[4,6-di[3-aminophenyl-N,N-bis(2-carbamoylethyl)-sulfonilimino]-1,3,5-triazine-2-ylamino]-biphenyl-2,2'-disulfonic acid, disodium salt (CL387626) 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-4-methyl-1H-benzimidazol-1-yl]-6-methyl-3-pyridinol (JNJ-2408068) 2-[[6-[[[2-(3-Hydroxypropyl)-5-methylphenyl]amino]methyl]-2-[[3-(morpholin-4-yl)propyl]amino]benzimidazol-1-yl]methyl]-6-methylpyridin-3-ol (TMC-353121) 5,5'-bis[1-(((5-amino-1H-tetrazolyl)imino)methyl)]2,2',4''-methylidynetrisphenol (VP-14637, MDT-637)

	N-(2-hydroxyethyl)-4-methoxy-N-methyl-3-(6-methyl-[1,2,4]triazolo[3,4-a]phthalazin-3-yl)benzenesulfonamide (P13) 2-((2-((1-(2-aminoethyl)piperidin-4-yl)amino)-4-methyl-1H-benzo[d]imidazol-1-yl)methyl)-6-methylpyridin-3-ol (R170591) 1,4-bis(3-methylpyridin-4-yl)-1,4-diazepane (C15) (R)-9b-(4-chlorophenyl)-1-(4-fluorobenzoyl)-2,3-dihydro-1H-imidazo[1',2':1,2]pyrrolo[3,4-c]pyridin-5(9bH)-one (BTA9981) [2,2-bis(docosyloxy-oxymethyl)propyl-5-acetamido-3,5-dideoxy-4,7,8,9-tetra-O-(sodium-oxysulfonyl)-D-glycero-D-galacto-2-nonulopyranosid]onate (MBX-300) BTA-C286 N-(2-((S)-2-(5-((S)-3-aminopyrrolidin-1-yl)-6-methylpyrazolo[1,5-a]pyrimidin-2-yl)piperidine-1-carbonyl)-4-chlorophenyl)methanesulfonamide (GS-5806) an anti-RSV nanobody (e.g., ALX-0171 (a trivalent nanobody, Ablynx) a peptide fusion inhibitor (such as a peptide having the sequence DEFDAISQVNEKINQSLAFIRKSDELL (T-67) a peptide having the sequence FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST (T-118)
N-protein inhibitors	(S)-1-(2-fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)urea (RSV-604) STP-92 (siRNA delivered through nanoparticle based delivery systems, Sirnaomics) iKT-041 (Inhibikase)

RSV polymerase inhibitors	6-{4-[(biphenyl-2-ylcarbonyl) amino]benzoyl}-N-cyclopropyl-5,6-dihydro-4H-thieno[3,2-d][1]benzazepine-2-carboxamide (YM-53403) N-cyclopropyl-5-(4-(2-(pyrrolidin-1-yl)benzamido)benzoyl)-5,6,7,10-tetrahydrobenzo[b]cyclopenta[d]azepine-9-carboxamide 6-(4-(2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)nicotinamido)benzoyl)-N-cyclopropyl-5,6-dihydro-4H-benzo[b]thieno[2,3-d]azepine-2-carboxamide 4-amino-8-(3-{[2-(3,4-dimethoxyphenyl)ethyl]amino}propyl)-6,6-dimethyl-2-(4-methyl-3-nitrophenyl)-1H-imidazo[4,5-h]-isoquinoline-7,9(6H,8H)-dione (CAS Reg. No. 851658-10-1) 6-(4-(2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)nicotinamido)benzoyl)-N-cyclopropyl-5,6-dihydro-4H-benzo[b]thieno[2,3-d]azepine-2-carboxamide (AZ27) (2R,3R,4R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(chloromethyl)-4-fluoro-2-((isobutyryloxy)methyl)tetrahydrofuran-3-yl isobutyrate (2R,3R,4R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(chloromethyl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl isobutyrate 4-amino-1-((2R,3R,4R,5R)-5-(chloromethyl)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one ((2R,3R,4R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(chloromethyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methyl triphosphate
IMPDH inhibitors	ribavirin 5-ethynyl-1-beta-D-ribofuranosylimidazole-4-carboxamide (EICAR) 4-hydroxy-3-beta-D-ribofuranosylpyrazole-5-carboxamide (pyrazofurin) 1-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1H-1,2,4-triazole-3-carboximidamide (Taribavirin, viramidine) 1,3,4-thiadiazol-2-ylcyanamide (LY253963) tetrahydrofuran-3-yl-3-(3-(3-methoxy-4-(oxazol-5-yl)phenyl)ureido)benzylcarbamate (VX-497) (4E)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-2-benzofuran-5-yl)-4-methylhex-4-enoic acid (Mycophenolic acid) 2-morpholin-4-ylethyl-(E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1H-2-benzofuran-5-yl)-4-methylhex-4-enoate (Mycophenolate Mofetil)

Interferons	Type 1 interferon Type 2 interferon Type 3 interferon an alpha-interferon (IFN- α) Pegylated interferon-alpha-2a (PEGASYS®) Pegylated interferon-alpha-2b (PEG-INTRON®) interferon alfacon-1 (INFERGEN®) beta-interferon (IFN- β) lambda-interferon (IFN- λ)
other compounds	a double stranded RNA oligonucleotide 5-methyl-N-[4-(trifluoromethyl) phenyl]-isoxazole-4-carboxamide (leflumomide) N-(2-chloro-4-methylphenyl)-2-((1-(4-methoxyphenyl)-1H-benzo[d]imidazol-2-yl)thio)propanamide (JMN3-003) an intratracheal formulation of recombinant human CC10 (CG-100) high titer, human immunoglobulin (RI-001, ADMA Biologics Inc.) a non-neutralizing mAb against the G protein (mAb 131-2G) ALN-RSV01 (an siRNA agent with the sense strand sequence (5' to 3') GGCUCUUAGCAAAGUCAAGdTdT (SEQ ID NO. 3) and the antisense strand sequence (5' to 3') CUUGACUUUGC AAGAGCCdTdT (SEQ ID NO. 4) ALN-RSV02
	Medi-559 Medi-534 Medi-557

ALN-RSV01 and/or ALN-RSV02 can be found in U.S. Publication No. 2009/0238772, filed Dec. 15, 2008 (Alnylam Pharmaceuticals).

ALX-0171 described in U.S. Publication No. 2012/0128669, filed June 7, 2010.

T-67, SEQ ID NO: 1, U.S. Patent No. 6,623,741, filed Feb. 29, 2000.

T-118, SEQ ID NO: 2, U.S. Patent No. 6,623,741, filed Feb. 29, 2000.

[0188] Other examples of compounds that can be used in combination with a compound of Formula (I), or a pharmaceutically acceptable salt, include those provided in WO 2013/186333, published December 19, 2013; WO 2013/186332, published December 19, 2013; WO 2013/186335, published December 19, 2013; WO 2013/186334, published December 19, 2013; WO 2012/080447, published June 21, 2012; WO 2012/080449, published June 21, 2012; WO 2012/080450, published June 21, 2012; WO 2012/080451, published June 21, 2012; WO 2012/080446, published June 21, 2012; WO 2010/103306, published September 16, 2010; WO 2012/068622, published May 31, 2012; WO 2005/042530, published May 12, 2005; WO 2006/136561, published December 28, 2006; WO 2005/058869, published June 30, 2005; U.S. 2013/0090328, published April 11, 2013;

WO 2014/009302, published January 16, 2014; WO 2011/005842, published January 13, 2011; U.S. 2013/0273037, published October 17, 2013; U.S. 2013/0164280, published June 27, 2013; U.S. 2014/0072554, published March 13, 2014; WO 2014/031784, published February 27, 2014 and WO 2015/026792, published February 26, 2015, all of which are hereby incorporated by reference.

[0189] In combination therapy, the additional agents can be administered in amounts that have been shown to be effective for those additional agents. Such amounts are known in the art; alternatively, they can be derived from viral load or replication studies using the parameters for “effective amount” set forth above. Alternatively, the amount used can be less than the effective monotherapy amount for such additional agents. For example, the amount used could be between 90% and 5% of such amount, e.g., 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, or 5%, or intermediate values between those points.

[0190] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered with one or more additional agent(s) together in a single pharmaceutical composition. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered with one or more additional agent(s) as two or more separate pharmaceutical compositions. For example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered in one pharmaceutical composition, and at least one of the additional agents can be administered in a second pharmaceutical composition. If there are at least two additional agents, one or more of the additional agents can be in a first pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one of the other additional agent(s) can be in a second pharmaceutical composition.

[0191] The order of administration of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with one or more additional agent(s) can vary. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered prior to all additional agents. In other embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered prior to at least one additional agent. In still other embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered concomitantly with one or more additional agent(s). In yet still other embodiments, a compound of Formula (I), or a

pharmaceutically acceptable salt thereof, can be administered subsequent to the administration of at least one additional agent. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered subsequent to the administration of all additional agents.

[0192] A potential advantage of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) described in paragraphs [0187]-[0188] (including the table), including pharmaceutically acceptable salts and prodrugs thereof, may be a reduction in the required amount(s) of one or more compounds of paragraphs [0187]-[0188] (including the table) (including pharmaceutically acceptable salts and prodrugs thereof) that is effective in treating a disease condition disclosed herein (for example, RSV), as compared to the amount required to achieve same therapeutic result when one or more compounds described in paragraphs [0187]-[0188] (including the table), including pharmaceutically acceptable salts thereof, are administered without a compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, the amount of a compound described in paragraphs [0187]-[0188] (including the table), including a pharmaceutically acceptable salt and prodrug thereof, can be less compared to the amount of the compound described in paragraphs [0187]-[0188] (including the table), including a pharmaceutically acceptable salt and prodrug thereof, needed to achieve the same viral load reduction when administered as a monotherapy. Another potential advantage of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) described in paragraphs [0187]-[0188] (including the table), including pharmaceutically acceptable salts and prodrugs thereof, is that the use of two or more compounds having different mechanism of actions can create a higher barrier to the development of resistant viral strains compared to the barrier when a compound is administered as monotherapy.

[0193] Additional advantages of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) described in paragraphs [0187]-[0188] (including the table), including pharmaceutically acceptable salts and prodrugs thereof, may include little to no cross resistance between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) described in paragraphs [0187]-[0188] (including the table) (including

pharmaceutically acceptable salts and prodrugs thereof); different routes for elimination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) described in paragraphs [0187]-[0188] (including the table) (including pharmaceutically acceptable salts and prodrugs thereof); little to no overlapping toxicities between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) described in paragraphs [0187]-[0188] (including the table) (including pharmaceutically acceptable salts and prodrugs thereof); little to no significant effects on cytochrome P450; and/or little to no pharmacokinetic interactions between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) described in paragraphs [0187]-[0188] (including the table), including pharmaceutically acceptable salts and prodrugs thereof).

[0194] As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight, the severity of the affliction, and mammalian species treated, the particular compounds employed, and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine methods, for example, human clinical trials and *in vitro* studies.

[0195] The dosage may range broadly, depending upon the desired effects and the therapeutic indication. Alternatively dosages may be based and calculated upon the surface area of the patient, as understood by those of skill in the art. Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral dose of between 0.01 mg and 3000 mg of each active ingredient, preferably between 1 mg and 700 mg, e.g. 5 to 200 mg. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the subject. In some embodiments, the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years.

[0196] In instances where human dosages for compounds have been established for at least some condition, those same dosages may be used, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established

human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compositions, a suitable human dosage can be inferred from ED₅₀ or ID₅₀ values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0197] In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the above-stated, preferred dosage range in order to effectively and aggressively treat particularly aggressive diseases or infections.

[0198] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0199] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0200] Compounds disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset

of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, or monkeys, may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, route of administration and/or regime.

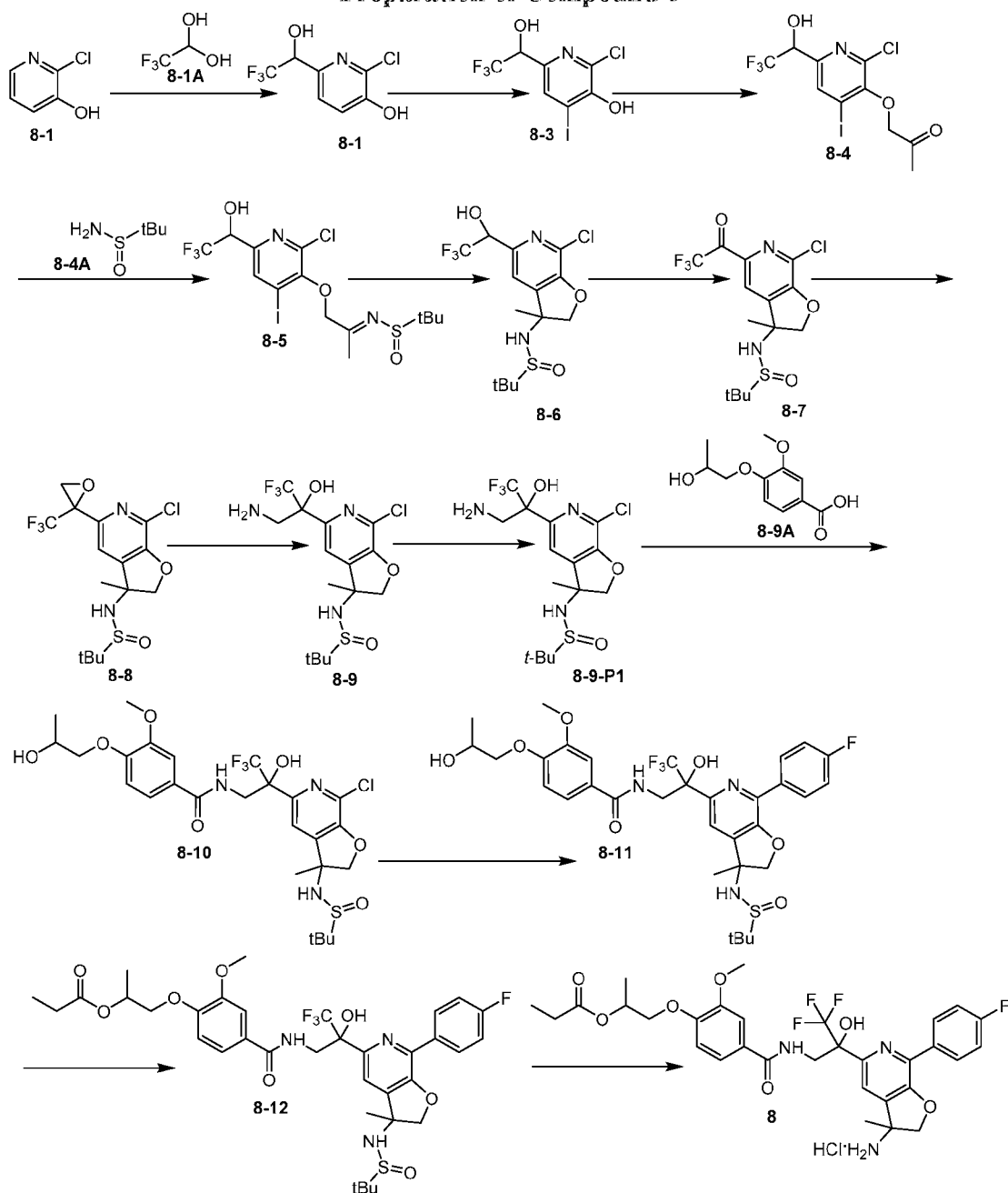
Synthesis

[0201] Compounds of Formula (I), and those described herein may be prepared in various ways. Some compounds of Formula (I) can be obtained commercially and/or prepared utilizing known synthetic procedures. General synthetic routes to the compounds of Formula (I), and some examples of starting materials used to synthesize the compounds of Formula (I) are shown and described herein. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

EXAMPLES

[0202] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

EXAMPLE 1
Preparation of Compound 8



[0203] An internal metal surface autoclave (2 L) was charged with **8-1** (200 g, 1.54 mol), **8-1A** (538 g, 4.63 mol) and K_2CO_3 (427 g, 3.09 mol) in H_2O (0.8 L). The vessel was sealed and heated to 120 °C for 20 H. The mixture was cooled to room temperature (RT), diluted with water (500 mL) and acidified to pH=3~4 using a 6.0 M HCl solution. A

white precipitate formed and was collected by filtration. The solid was dried under vacuum to give **8-2** as a white solid (312 g, 89%).

[0204] To a stirring solution of **8-2** (300 g, 1.32 mol) and Na₂CO₃ (280 g, 2.64 mol) in H₂O (2 L) was added I₂ (436 g, 1.72 mol) in portions. The mixture was stirred at 25 °C for 48 h. The reaction was monitored by LCMS. After **8-2** was consumed, a sat. sodium sulfite solution (2 L) was used to quench the reaction. The mixture was acidified with 3.0 M HCl solution and diluted with EA (1 L). The organic phase was separated, and the aqueous phase was extracted with EA (3 X 500 mL). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was solidified to give **8-3** (416 g, 89.3%) as a yellow solid.

[0205] To a solution of **8-3** (397 g, 1.12 mol) and 1-chloropropan-2-one (258 g, 2.8 mol) in DMF (1.5 L) was added NaHCO₃ (282 g, 3.36 mmol) in portions at RT under N₂. The mixture was stirred at 25 °C for 25 h. After **8-3** was consumed, the solid was removed by filtration. The filtrate was concentrated to dryness under reduced pressure, and the residue was washed by DCM (1 L). The white solid was collected with filtration and dried under vacuum to give **8-4** (402 g, 87%).

[0206] A mixture of **8-4** (41 g, 100 mmol), **8-4A** (S-configuration, 12.74 g, 105 mmol) and titanium(IV) ethoxide (48 g, 210 mmol) in anhydrous THF (160 mL) was heated to 80°C under N₂ and stirred for 1 h. The reaction was monitored by TLC (DCM:EA=8:1). After **8-4** was consumed, the mixture was concentrated to dryness. The residue was dissolved in EA (400 mL). The solution was poured into sat. aq. NaHCO₃ (500 mL), and the mixture was stirred for 2 mins. The mixture was filtered through a pad of celite, and the cake was washed with EA (2 X 400 mL). The combined organic phase was removed under reduced pressure, and the residue was purified by column chromatography using 10% EA in DCM as the eluent to give **8-5** (~39 g, 76%) as a yellow oil. **8-5** was used for next step immediately.

[0207] To a solution of EtMgBr (25.4 mL, 76.2 mmol, 3 M in ether) in dry THF (400 mL) was added *n*-BuLi (61 mL, 152.5 mmol, 2.5 M in hexane), and the mixture was stirred at 0°C. After stirring for 10 mins, the mixture was cooled to -78 °C. A solution of **8-5** (39 g, 76 mmol) in dry THF (100 mL) was added dropwise, and the mixture was stirred at -78 °C for 30 mins. The reaction was quenched with H₂O (100 mL) and extracted with EA (2

X 400 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 0~10% EA in DCM) to afford **8-6** (17 g, 58%).

[0208] To a stirring solution of **8-6** (6.8 g, 17.6 mmol) in DCM (50 mL) was added Dess-Martin reagent (8.95 g, 21.1 mmol), and the mixture stirred at RT under N₂ atmosphere for 1 h. The reaction was quenched with a sat. aq. Na₂SO₃ solution and a sat. aq. NaHCO₃ solution. After 30 mins of vigorous stirring, the organic layers were separated. The aqueous layer was extracted with EA (2 X 100 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 0~10% EA in DCM) to afford **8-7** (5.1 g, 75.4%).

[0209] To a solution of *t*-BuOK (1.64 g, 14.58 mmol) in CH₃CN (150 mL) was added Me₃SOI (3.21 g, 14.58 mmol). The mixture was degassed and stirred at RT for 30 mins. The solution containing the ylide was filtered, and the filtrate was treated with a solution of **8-7** (5.1 g, 13.25 mmol, previously degassed) in CH₃CN (150 mL). The mixture was stirred at RT for 1 h. The volatiles were removed under reduced pressure, and the residue was purified by column chromatography using DCM:EA=9:1 as the eluent to give **8-8** (3.2 g, 60.5%).

[0210] **8-8** (3.2 g, 8.02 mmol) was dissolved in NH₃-MeOH (7.0 M, 80 mL). The solution was stirred at 25 °C for 18 h. The volatiles were removed under reduced pressure to afford the crude **8-9** (3.1 g, 93%). **8-9** (~100 g) was submitted for prep-HPLC (TFA condition). The separated solution was neutralized by NaHCO₃, and extracted with EA. The organic phase was concentrated to give **8-9-P1** (~17 g, 17%).

[0211] To a solution of **8-9A** (0.8 g, 3.5 mmol) in DMF (10.0 mL) was added HATU (1.35 g, 3.5 mmol) and DIEA (0.92 g, 7.1 mmol). The mixture was stirred at 25 °C for 10 mins, and **8-9-P1** (1.47 g, 3.5 mmol) was added. The mixture was stirred for 1 h. LCMS trace showed that **8-9-P1** was consumed. The mixture was partitioned between water (10 mL) and EA (30 mL). The organic phase was separated, washed with brine (2 X 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue

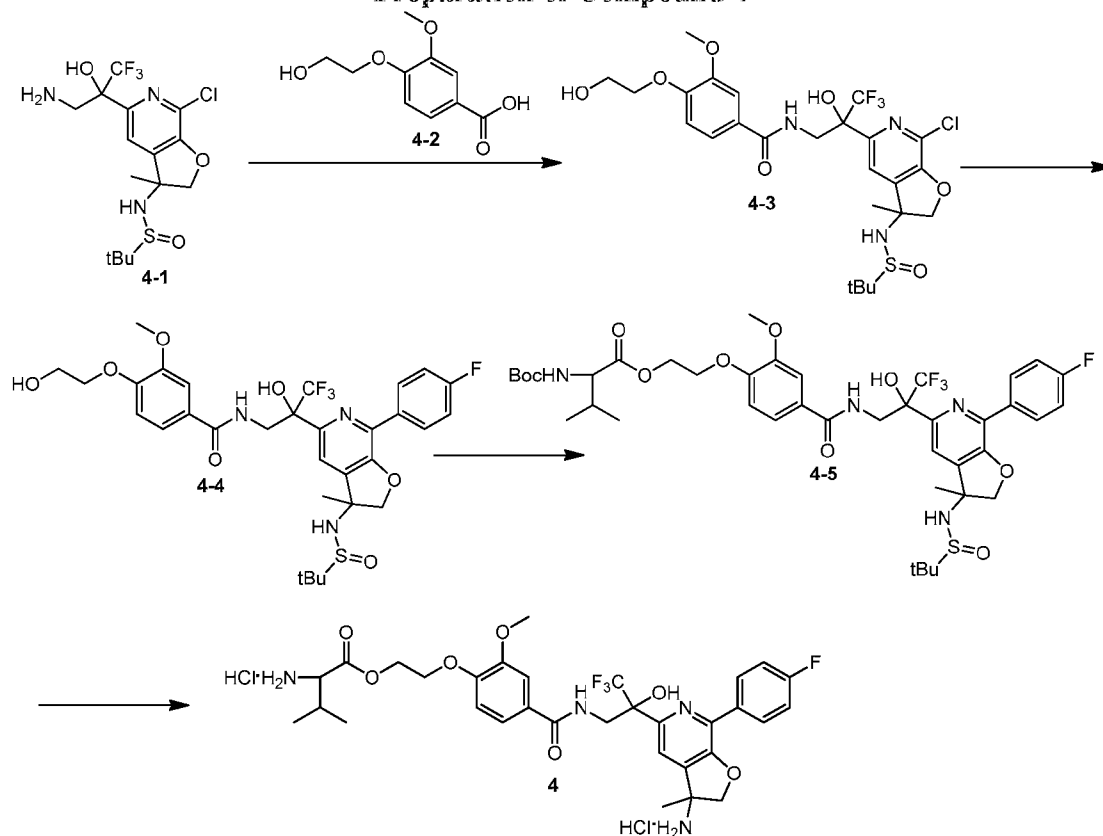
was purified by column chromatography using 10% EA in DCM as the eluent to give **8-10** (2.10 g, 95.1%) as a colorless oil. +ESI-MS: m/z 624.0 $[M+H]^+$.

[0212] A 100 mL round bottom flask was charged with a mixture of **8-10** (2.1 g, 3.36 mmol), 4-fluorophenyl-boronic acid (0.94 g, 6.72 mmol), Na_2CO_3 (1.07 g, 10.1 mmol) and $Pd(PPh_3)_4$ (0.25 g, 0.35 μ mol, 0.10 eq.) in dioxane (13.0 mL) and H_2O (3 mL). The mixture was degassed *3x) and refilled with N_2 . The mixture was heated to 90 °C overnight. The mixture was partitioned between water (20 mL) and EA (35 mL). The organic phase was separated, washed with brine (2 X 10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography using 10% EA in DCM as THE eluent to give **8-11** (1.95 g, 85%) as a pale yellow oil. +ESI-MS: m/z 684.2 $[M+H]^+$.

[0213] To a mixture of **8-11** (500 mg, 731.0 μ mol) and propionic acid (163 mg, 2.2 mmol) in THF (20.0 mL) was added DCC (453 mg, 2.2 mmol) and DMAP (4.5 mg, 36.6 μ mol) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. LCMS trace showed that the reaction was completed. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified by column chromatography using 5~50% EA in PE as the eluent to give **8-12** (450 mg, 83%) as a light yellow solid. +ESI-MS: m/z 740.1 $[M+H]^+$.

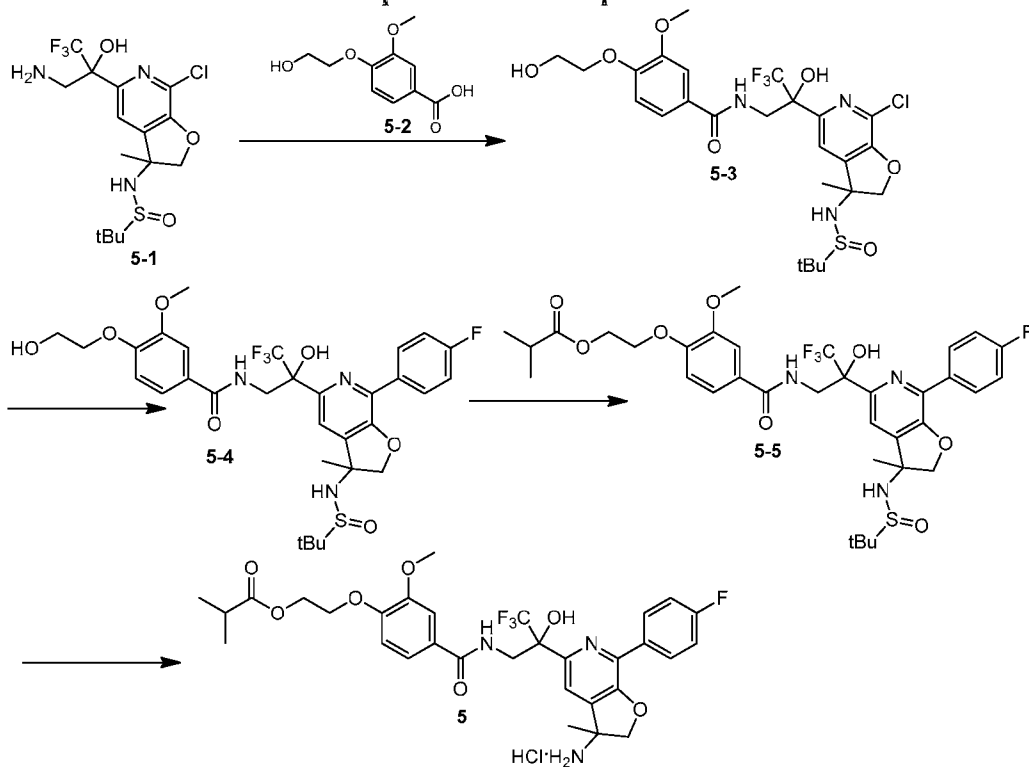
[0214] To a solution of **8-12** (450 mg, 608 μ mol) in dioxane (5.0 mL) was added HCl/dioxane (4 M, 1 mL) dropwise at 25°C. The mixture was stirred at 25 °C for 30 mins. LCMS trace showed that the reaction was completed. The mixture was concentrated under reduced pressure to dryness. The residue was purified by prep-HPLC (HCOOH) and lyophilized to give a white solid. The white solid was dissolved in CH_3CN (5.0 mL) and H_2O (20.0 mL). HCl (1 M, 0.6 mL) was added dropwise with stirring. The mixture was lyophilized to give **8** (220 mg, 52%) as a white solid. +ESI-MS: m/z 636.1 $[M+H]^+$; 658.1 $[M+Na]^+$.

EXAMPLE 2
Preparation of Compound 4



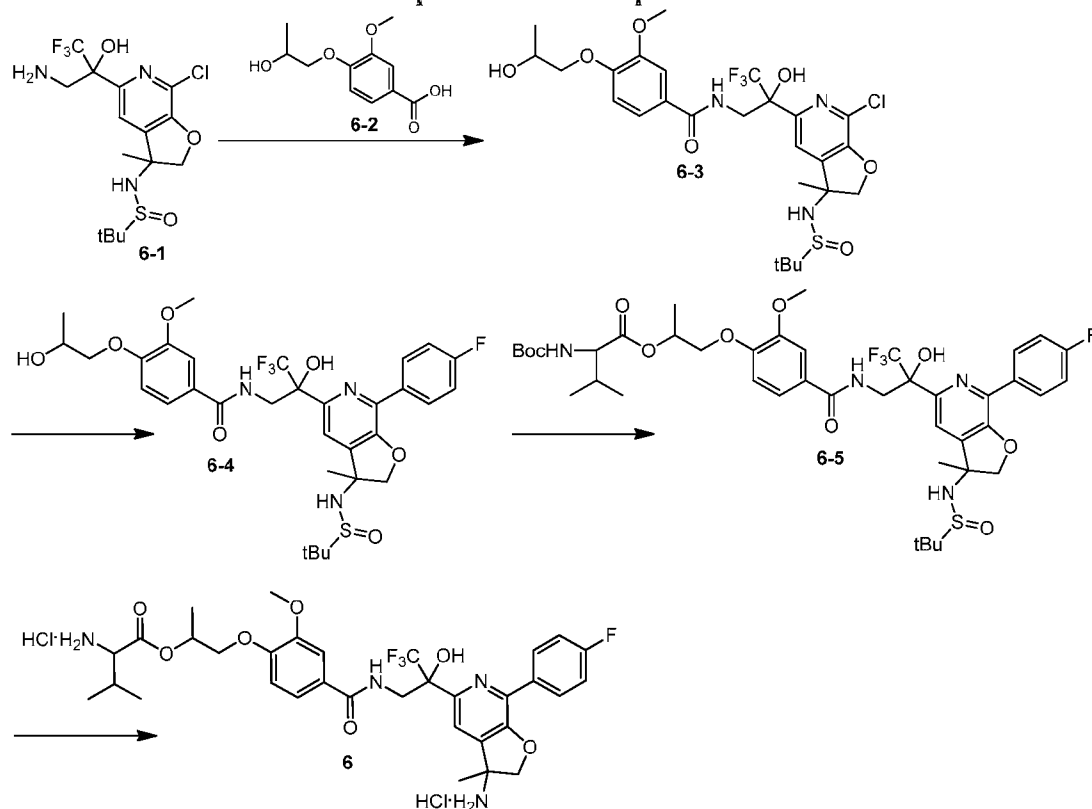
[0215] Compound 4 (432 mg, white solid) was using procedures similar to those used for preparing **8** using **4-1** and **4-2**. +ESI-MS: m/z 665.1 $[M+H]^+$; 687.2 $[M+Na]^+$.

EXAMPLE 3
Preparation of Compound 5



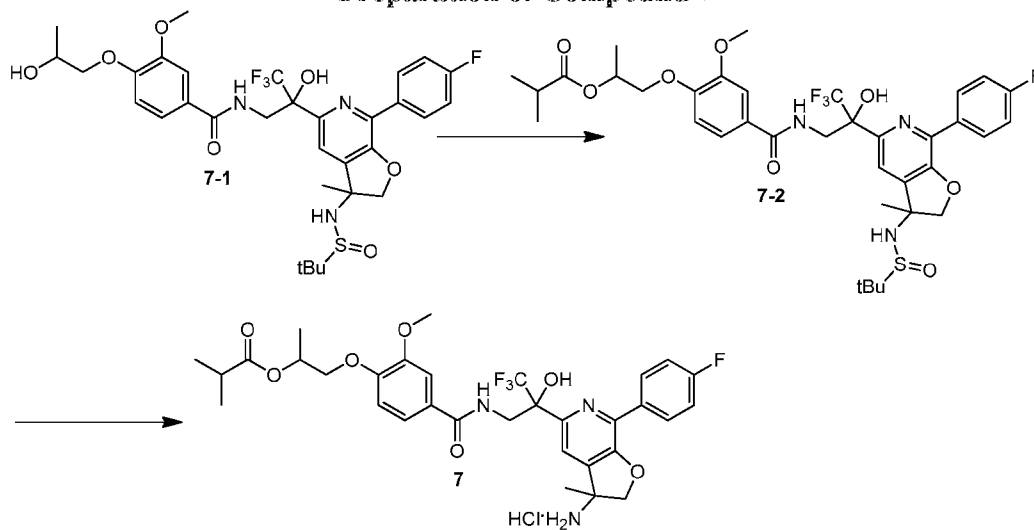
[0216] Compound **5** (350 mg, white solid) was using procedures similar to those used for preparing **8** using **5-2** and **5-1**. +ESI-MS: m/z 636.1 $[\text{M}+\text{H}]^+$; 658.2 $[\text{M}+\text{Na}]^+$.

EXAMPLE 4
Preparation of Compound 6



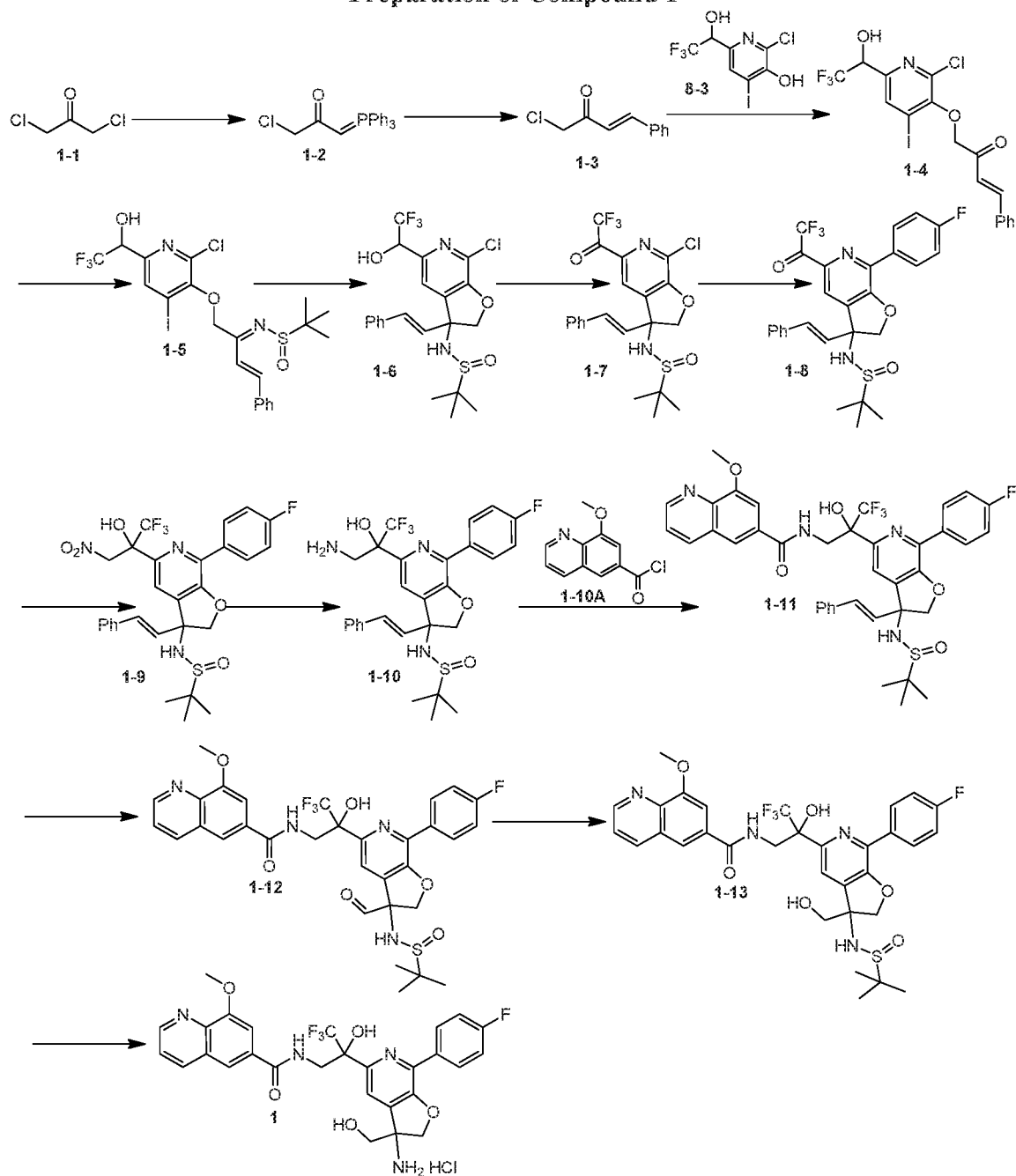
[0217] Compound **6** (210 mg, white solid) was using procedures similar to those used for preparing **8** using **6-2** and **6-1**. +ESI-MS: m/z 679.2[M+H]⁺.

EXAMPLE 5
Preparation of Compound 7



[0218] Compound 7 (306 mg, white solid) was using procedures similar to those used for preparing 8 using 7-1 and isobutyl acid. +ESI-MS: m/z 650.1[M+H]⁺, 672.2[M+Na]⁺.

EXAMPLE 6 Preparation of Compound 1



[0219] 1-3 was prepared according to procedures provided in Hénichart, J. et al., Journal of Heterocyclic Chemistry (1986) 23(5):1531-3.

[0220] To a solution of **8-3** (16 g, 45.3 mmol) in CH₃CN (150 mL) was added K₂CO₃ (12.5 g, 90.5 mmol) in one portion. After stirring at RT for 5 mins, a solution of **1-3** (9.8 g, 54.3 mmol) in CH₃CN (10 mL) was added slowly under N₂. The mixture was stirred at 90 °C for 1 h in a pre-heated oil bath. TLC showed that the reaction was completed. After cooling to RT, the mixture was poured into water (150 mL) and stirred for 5 mins. The mixture was extracted with EA (2 X 150 mL). The combined organic phase was washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography using 2~5% EA in PE as the eluent to afford **1-4** (10.9 g, 49%) as a yellow solid.

[0221] **1-8** was prepared from **1-4** using procedures similar to those used for preparing **8**. To a solution of **1-8** (5.1 g, 9.6 mmol) in CH₃NO₂ (15 mL) was added TEA (2.0 mL) in one portion at RT. The mixture was stirred for 2 h and concentrated under reduced pressure. The residue was purified by column chromatography using 10~20% EA in PE as the eluent to afford **1-9** (2 g, 35%) as a yellow solid. +ESI-MS: m/z 593.9 [M+H]⁺.

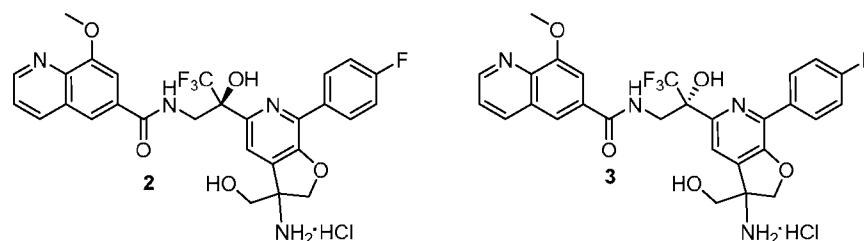
[0222] To a solution of **1-9** (2.0 g, 3.4 mmol) in EtOH (20 mL) and H₂O (10 mL) was added Fe (753 mg, 13.5 mmol) and NH₄Cl (721 mg, 13.5 mmol) in one portion. The mixture was stirred at 80 °C for 2 h. After cooling to RT, the mixture was poured into water (20 mL) and extracted with EA (3 X 20 mL). The combined organic phase was washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography using EA as the eluent to afford the **1-10** (950 mg, 50%) as a yellow solid. +ESI-MS: m/z 564.1 [M+H]⁺.

[0223] To a solution of **1-10A** (349 mg, 1.7 mmol) in THF (10 mL) was added DMF (0.5 mL) and SOCl₂ (2.1 g, 17.2 mmol), and the mixture was stirred at 80 °C for 1 h. The mixture was concentrated in vacuum to give crude 8-methoxyquinoline-6-carbonyl chloride. Crude 8-methoxyquinoline-6-carbonyl chloride was dissolved in DCM (12 mL), and **1-10** (950 mg, 1.7 mmol) and TEA (2.1 g, 20.6 mmol) was added at 30°C. The mixture was stirred at 30 °C for 1 h. The mixture was washed with NaHCO₃ solution (40 mL) and extracted with EA (3 X 60 mL). The combined organic phase was washed with sat. brine (2 X 20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography using 50~100% EA in PE as the eluent to give **1-11** (560 mg, 34%) as a yellow solid. +ESI-MS: m/z 749.3 [M+H]⁺.

[0224] To a solution of **1-11** (500 mg, 0.67 mmol) in acetone (20.0 mL) and H₂O (4.0 mL) was added NMO (94 mg, 0.8 mmol) in one portion at 30 °C. OsO₄ (5.1 mg, 0.02 mmol) was added. The mixture was stirred at 30 °C for 20 mins, and concentrated under reduced pressure. The residue was dissolved in THF (15 mL), and the solution was treated with NaIO₄ (286 mg, 1.3 mmol) in one portion. The mixture was stirred at 30 °C for 12 h. The mixture was washed with Na₂SO₃ solution (50 mL) and extracted with EA (3 X 50 mL). The combined organic phase was washed with sat. brine (2 X 50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to dryness. The residue was purified by column chromatography using EA as the eluent to give **1-12** (381 mg, 77.8%) as a yellow oil. +ESI-MS: m/z 674.1 [M+H]⁺.

[0225] To a solution of **1-12** (381 mg, 0.56 mmol) in MeOH (10 mL) was added NaBH₄ (107 mg, 2.8 mmol) in one portion at 25 °C. The mixture was stirred at 25 °C for 30 mins. The reaction was quenched with water (10 mL). The aqueous phase was extracted with EA (3 X 30 mL). The combined organic phase was washed with sat. brine (2 X 20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to dryness. The residue was purified by column chromatography using EA as the eluent to give **1-13** (347 mg, 84%) as a yellow solid. +ESI-MS: m/z 677.0 [M+H]⁺.

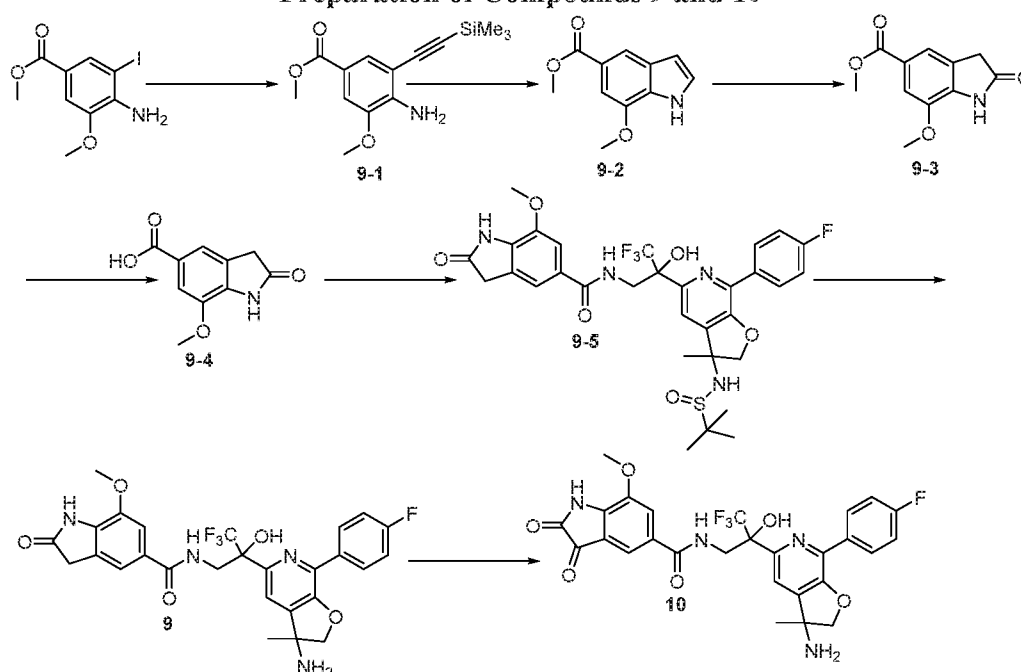
[0226] To a solution of **1-13** (347 mg, 0.51 mmol) in dioxane (15 mL) was added HCl/dioxane (4 M, 1 mL) in one portion at 30 °C. The mixture was stirred at 30 °C for 0.5 h. The mixture was concentrated to dryness. The residue was purified by prep-HPLC (neutral condition) to afford a yellow solid. The yellow solid was dissolved in CH₃CN (8 mL) and H₂O (10 mL). HCl (3 M, 0.4 mL) was added in one portion at 0 °C with stirring. The mixture was lyophilized to give **1** (135 mg) as a yellow solid. +ESI-MS: m/z 573.1 [M+H]⁺.



[0227] Compound **1** (126 mg) was separated by SFC to give two isomers. The two isomers were dissolved in CH₃CN (5 mL), and then 3 M HCl was added. The solution

was lyophilized to give **2** (40 mg, white solid) and **3** (62 mg, white solid). **2**: +ESI-MS: m/z 573.1 $[M+H]^+$; **3**: +ESI-MS: m/z 573.1 $[M+H]^+$. Compounds **2** and **3** are shown above with relative stereochemistry arbitrarily assigned.

EXAMPLE 7 Preparation of Compounds 9 and 10



[0228] Methyl 3-iodo-4-amino-5-methoxybenzoate (1.0 g, 3.25 mmol) was dissolved in triethylamine (6 mL). 1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.11 g, 0.16 mmol) and cuprous chloride (16 mg, 0.16 mmol) were added, and the mixture was cooled to 0 °C. Trimethylsilylacetylene (0.55 mL, 3.9 mmol) was added dropwise. The mixture was warmed to RT and stirred for 1.5 h. The mixture was concentrated, then re-dissolved in EA, washed with brine, dried and concentrated. The crude material was purified by chromatography on silica gel (hexane:EA) to give **9-1** (0.27 g, 30 %).

[0229] John-Phos AuMeCNBF₄ (120 mg, 0.15 mmol) was added to **9-1** (0.21 g, 0.76 mmol) in toluene (2 mL). The mixture was heated at 60 °C for 2h. The mixture was purified by silica gel chromatography (hexane:EA) to give **9-2** (57 mg, 27 %). LC/MS: 206.05 $[M+H]^+$.

[0230] A solution of lithium bromide (33 mg, 0.39 mmol) and bromine (19 μ L, 0.38 mmol) in acetic acid (0.4 mL) was added dropwise to a solution of **9-2** (24 mg, 0.12

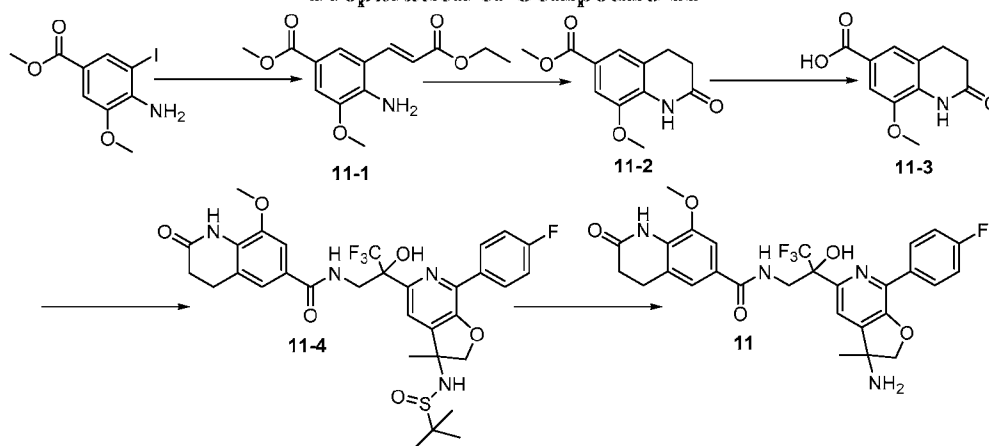
mmol) in EtOH (0.5 mL) and acetic acid (0.5 mL) at 0 °C. The mixture was slowly warmed to RT and stirred for 2 h total. Zinc (76 mg, 1.2 mmol) and acetic acid (0.5 mL) were added, and the mixture was stirred for 2 h. The mixture was concentrated, then re-dissolved in EA. The organic layer was washed with sodium bicarbonate and brine, dried and concentrated. The crude material was purified by chromatography (hexane:EA) to give **9-3** (6 mg, 25%). LC/MS: 222.05 [M+H]⁺.

[0231] **9-3** (30 mg, 0.13 mmol) was dissolved in conc. HCl (0.5 mL) and 4N HCl in dioxane (0.5 mL). The mixture was heated at 95 °C for 1 h. The mixture was concentrated and the resulting **9-4** was used without further purification. LC/MS: 206.15 [M-H].

[0232] DIEA (20 µL, 0.11 mmol) was added to a solution of N-(5-(3-amino-1,1,1-trifluoro-2-hydroxypropan-2-yl)-7-(4-fluorophenyl-3-methyl-2,3-dihydrofuro[2,3-c]pyridine-3-yl)-2-methylpropane-2-sulfinamide (13 mg, 0.027 mmol), **9-4** (0.13 mmol) and HATU (23 mg, 0.06 mmol). The mixture was stirred at RT for 2 h. The mixture was purified by reverse-phase HPLC to provide **9-5** (12 mg, 70 %). LCMS: 665.20 [M+H]⁺.

[0233] HCl (4N in dioxane, 0.2 mL) was added to a solution of **9-5** (32 mg, 0.049 mmol) in CH₂Cl₂ (1 mL). The mixture was stirred at RT for 5 h. The mixture was concentrated, and the crude product purified by HPLC to give **9**. LC/MS: 561.15 [M+H]⁺. **9** air oxidizes to **10**. LC/MS: 576.05 [M+H]⁺.

EXAMPLE 8 Preparation of Compound 11



[0234] Palladium acetate (73 mg, 0.22 mmol) was added to a solution of 3-iodo-4-amino-5-methoxybenzoate (1.0 g, 3.25 mmol), methyl acrylate (0.32 mL, 3.6 mmol),

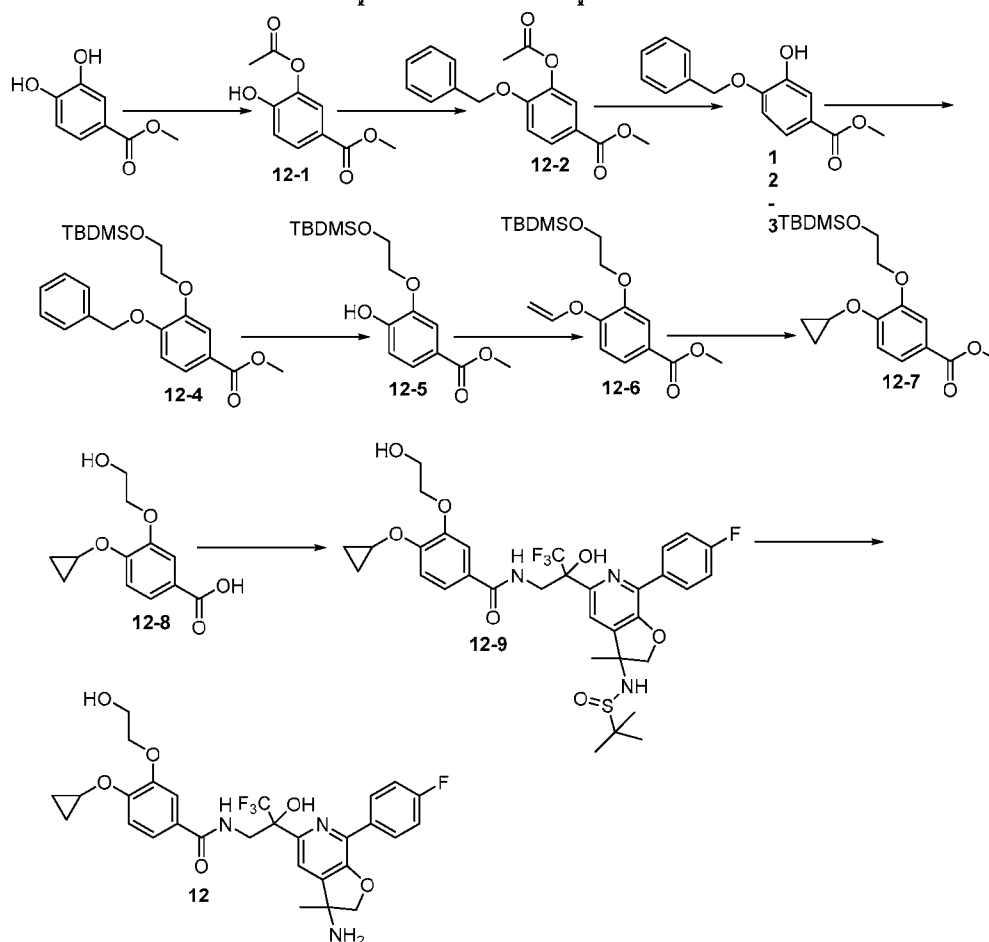
triphenylphosphine (0.17 g, 0.65 mmol), and triethylamine (0.9 mL, 6.5 mmol) in CH₃CN (10 mL). The mixture was flushed with Ar and heated at 80 °C in a sealed tube for 90 mins. The mixture was diluted with EA, and washed with 1N HCl and brine. The organic layers were dried and concentrated. Crude **11-1** was chromatographed (hexane:EA) to give **11-1** (0.52 g, 57 %). LC/MS: 280.05 [M+H]⁺.

[0235] **11-1** (0.52 g, 1.9 mmol) was hydrogenated over 10% Pd/C (250 mg) in acetic acid (5 mL) at 60 psi for 2 h. The catalyst was removed by filtration, and the solvent was evaporated to provide crude **11-2**, which was purified by chromatography (hexane:EA) to give **11-2** (0.40 g, 89 %). LC/MS: 236.05 [M+H]⁺.

[0236] 2N NaOH (4 mL, 8.0 mmol) was added to a solution of **11-2** (0.40 g, 1.7 mmol) in MeOH (20 mL), and the mixture was stirred at RT for 1 h. The mixture was acidified with 1N HCl, and **11-3** was extracted with EA. The organic extracts were washed with brine, dried, concentrated and the obtained **11-3** was used without further purification.

[0237] **11-4** was prepared using similar procedures as **9-5**. LC/MS: 665.20 [M+H]⁺. Compound **11** using similar procedures as **9**. LC/MS: 575.15 [M+H]⁺.

EXAMPLE 9
Preparation of Compound 12



[0238] Potassium t-butoxide (210 mg, 1.9 mmol) was added to 3,4-dihydroxybenzoic acid methyl ester (0.55 g, 3.3 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred for 15 minutes. Acetic anhydride (0.31 mL, 3.3 mmol) was added, and the mixture was stirred for 20 mins. The reaction was diluted with EA, and washed with water and brine. The product was purified by chromatography (hexane:EA) to give **12-1** (0.56 g, 78 %).

[0239] Benzyl bromide (0.62 mL, 5.2 mmol) was added to a solution of **12-1** (91.1 g, 5.2 mmol) and potassium carbonate (1.1 g, 7.9 mmol) in DMF (5 mL), and the mixture was stirred at RT overnight. The mixture reaction was diluted with EA, and washed with water and brine. The product was purified by chromatography (hexane:EA) to give **12-2** (1.26 g, 81 %).

[0240] Potassium carbonate (16 mg, 0.12 mmol) was added to a solution of **12-2** (1.26 g, 4.2 mmol) in MeOH (100 mL). The mixture was heated at reflux for 30 mins and then stirred at RT overnight. The mixture was concentrated, and the product purified by chromatography (hexane:EA) to give **12-3** (0.91 g, 88 %).

[0241] Potassium carbonate (0.78 g, 5.7 mmol) was added to a solution of **12-3** (0.91 g, 3.7 mmol) and (2-bromoethoxy)(tert-butyl)dimethylsilane (0.87 mL, 4.0 mmol) in DMF (5 mL). The mixture was heated at 60 °C for 1 h. The mixture was diluted with EA, and washed with water and brine. The product was chromatographed (hexane:EA) to give **12-4** (0.91 g, 57 %).

[0242] **12-4** (0.91 g, 2.2 mmol) was hydrogenated over 10% Pd/C (93 mg) in EtOH (10 mL). The catalyst was removed by filtration, and the crude product was chromatographed (hexane:EA) to give **12-5** (0.50 g, 55 %).

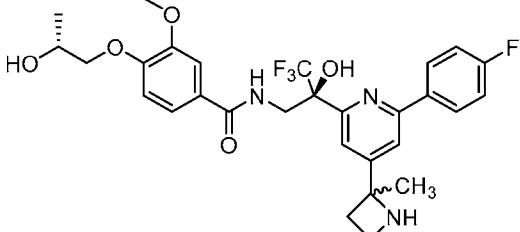
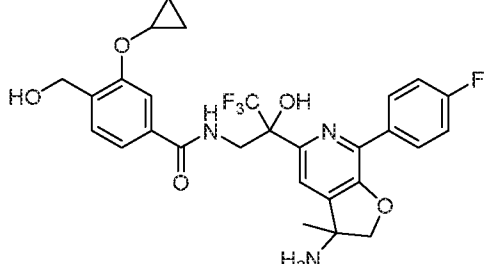
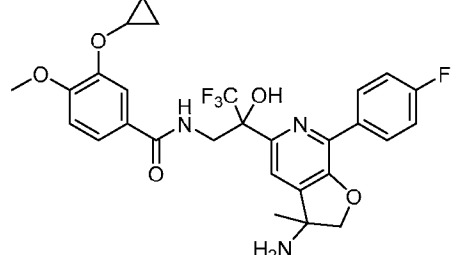
[0243] 1,5-Cyclooctadiene-iridium (I) chloride dimer (12 mg, 0.018 mmol) and sodium carbonate (69 mg, 0.65 mmol) were pre-mixed in toluene (1.2 mL). **12-5** (0.60 g, 1.8 mmol) and vinyl acetate (0.33 mL, 3.6 mmol) were added. The mixture was flushed with Ar and then stirred at 100 °C 2 h. The crude material was purified by chromatography (hexane:EA) to give **12-6** (0.23 g, 35 %).

[0244] Diethylzinc (5.1 mL, 1M in hexane) was added dropwise to a solution of **12-6** (0.23 g, 0.64 mmol) and diiodoethane (0.41 mL, 5.1 mmol) in dichloroethane (2 mL) at 0 °C. The mixture was stirred at RT overnight. The reaction was quenched with 1N HCl, and extracted with dichloromethane. The product was purified by chromatography (hexane:EA) to give **12-7** (80 mg, 32 %).

[0245] Compound **12-8** was prepared using similar procedures as **11-3**. Compound **12-9** was prepared using similar procedures as **9-5**. LC/MS: 696.25 [M+H]⁺. Compound **12** was prepared using similar procedures as **10**. LC/MS: 592.70 [M+H]⁺.

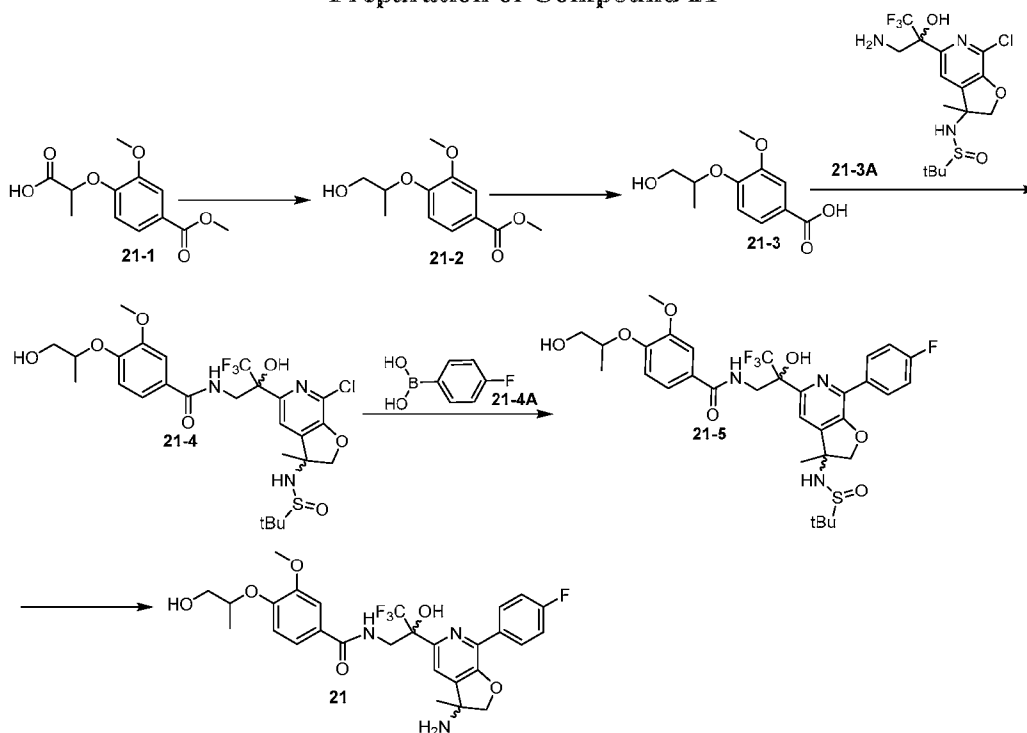
EXAMPLE 10

[0246] The following compounds were prepared following one or more of the methods provided herein.

No.	Structure	MS [M+1] ⁺
15		578.1
22		562.0
23		583.9 [M+1+Na] ⁺

*Compound 15 is individual isomer with relative stereochemistry arbitrarily assigned

EXAMPLE 11
Preparation of Compound 21



[0247] Compound **21-1** was prepared according to the procedures provided US 2007/287730 A1, and compound **21-3A** can be prepared according to procedures provided in WO 2016/26792 A1.

[0248] To a solution of **21-1** (673 mg, 2.65 mmol) in anhydrous THF (15 mL) was added $\text{BH}_3\text{-Me}_2\text{S}$ (10 M, 0.8 mL) dropwise at 0 °C with stirring. The mixture was stirring at 50 °C for 1 h. The reaction was quenched with MeOH (2 mL), acidified with HCl (2M, 1 mL) and extracted with EA (3 X 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 5~10% EA in PE to give **21-2** (351 mg, 55.1%). MS: m/z 240.8 $[\text{M}+\text{H}]^+$.

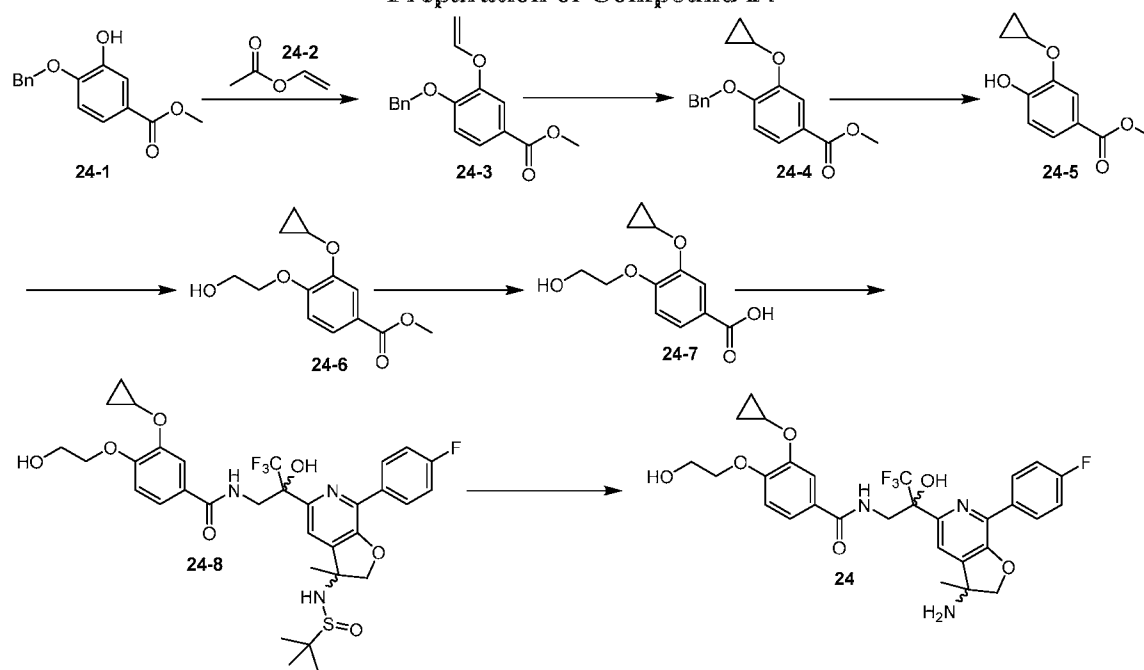
[0249] To a solution of **21-2** (351 mg, 1.46 mmol) in MeOH (4 mL) was added aqueous NaOH (4 M, 2 mL). The mixture was stirred at 70 °C for 1 h. The MeOH was evaporated. The aqueous solution was acidified with 1 M HCl to pH 3~4 and extracted with EA (3 X 10 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to give **21-3** (280 mg, 84.8%). MS: m/z 226.9 $[\text{M}+\text{H}]^+$.

[0250] To a solution of **21-3** (145 mg, 0.64 mmol) in DMF (10 mL) was added HATU (244 mg, 0.64 mmol) and DIEA (204 mg, 1.58 mmol) with stirring at 25 °C. After 10 mins, **21-3A** (240 mg, 0.58 mmol) was added. The mixture was stirred for 1 h. The mixture was partitioned between water (10 mL) and EA (30 mL). The organic phase was separated, washed with brine (2 X 10 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 25~50% EA in PE as eluent to give **21-4** (332 mg, 92%) as yellow oil. MS: m/z 623.9 [M+H]⁺.

[0251] To a mixture of **21-4** (280 mg, 0.45 mmol), **21-4A** (250 mg, 1.79 mmol) in dioxane:H₂O (8 mL:2 mL) was added K₂CO₃ (124 mg, 0.9 mmol) and Pd(dppf)Cl₂ (33 mg, 0.045 mmol) under N₂. The mixture was stirring at 130 °C under microwave for 50 mins. The reaction was diluted with EA (20 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography using 3~8% MeOH in DCM as eluent to give **21-5** (51 mg, 16.7%). MS: m/z 684.1 [M+H]⁺.

[0252] To a solution of **21-5** (51 mg, 73 μmol) in THF (1 mL) was added HCl/dioxane (4 M, 0.5 mL). The mixture was stirred at 25 °C for 10 mins, concentrated and purified by prep-HPLC (HCl condition) to give **21** (11 mg, 25.8%) as a white solid. MS: m/z 580.1 [M+H]⁺.

EXAMPLE 12
Preparation of Compound 24



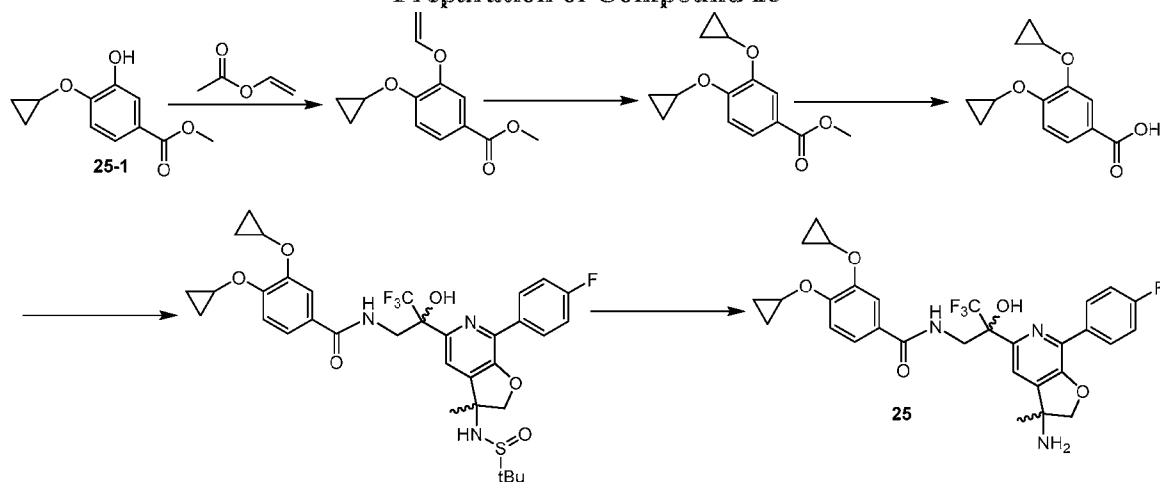
[0253] Compound **24-1** was prepared according to the procedures provided in Desroses et al., *Organic Preparations and Procedures International* (2004) 36(5):445-452. Compound **24-4** was prepared according to a similar procedure for preparing **23** starting with **24-1** and **24-2**.

[0254] To a solution of **24-4** (236 mg, 0.79 mmol) in DCM (5 mL) was added BBr_3 (238 mg, 0.95 mmol) at -20°C , and the mixture was stirred for 10 mins. The solution was poured into ice and extracted with EA (2 X 10 mL). The organic phase was concentrated and purified by column chromatography using 15~25% DCM in PE to give **24-5** (122 mg, 74.1%) as a yellow solid. MS: m/z 209.1 $[\text{M}+\text{H}]^+$.

[0255] To a solution of **24-5** (122 mg, 0.59 mmol) in DMF (2 mL) was added NaH (24 mg, 0.59 mmol) at 0°C . After stirring for 0.5 h, 2-bromoethanol (146 mg, 1.18 mmol) was added, and the mixture was stirred at RT overnight. The mixture was poured into water (10 mL) and extracted with EA (2 X 20 mL). The organic phase was dried over Na_2SO_4 and concentrated to give **24-6** (150 mg, crude) as a yellow solid. MS: m/z 253.1 $[\text{M}+\text{H}]^+$.

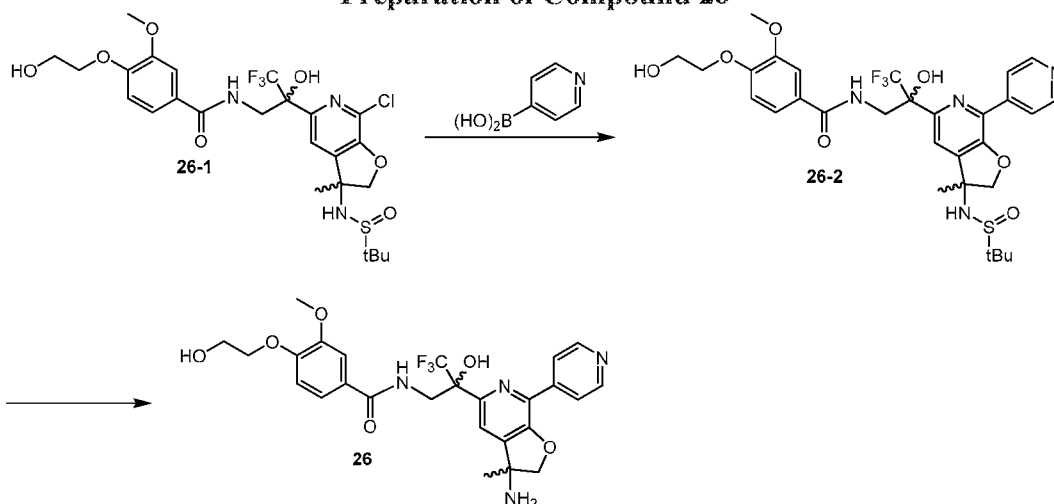
[0256] Compound **24** (49 mg, white solid) was obtained from **24-6** using a similar procedure for preparing **21**. MS: m/z 614.0 $[M+Na]^+$.

EXAMPLE 13
Preparation of Compound 25



[0257] Compound **25** (5 mg, white solid) was obtained from **25-1** using a similar procedure for preparing **23**. MS: m/z 588.1 $[M+H]^+$.

EXAMPLE 14
Preparation of Compound 26

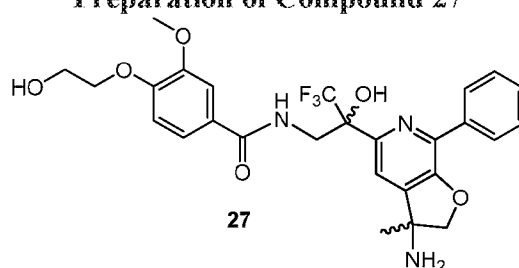


[0258] Compound **26-1** was prepared according to a similar procedure as provided in PCT Publication No. WO 2015/26792 A1.

[0259] A mixture of **26-1** (267 mg, 0.44 mmol), 4-pyridylboronic acid (108 mg, 0.88 mmol), Pd(dppf)Cl₂ (32 mg, 0.044 mmol) and K₂CO₃ (242 mg, 1.75 mmol) in dioxane (3.00 mL) and H₂O (1.00 mL) was heated at 130 °C for 1 h under microwave. The mixture was diluted with water (10 mL), and extracted with EA (2 X 10 mL). The organic phase was washed with brine, dried over Na₂SO₄, and concentrated to give **26-2** (250 mg, crude) as a yellow liquid.

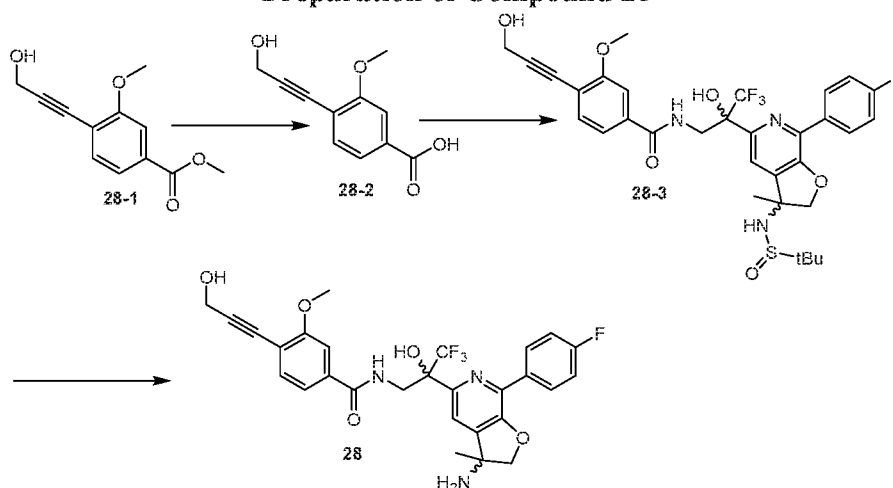
[0260] To a solution of **26-2** (250 mg, crude) in MeOH (5 mL) was added HCl/MeOH (4 M, 0.3 mL). The mixture was stirred at 25 °C for 10 mins and concentrated. The residue was purified by purified by prep-HPLC (HCl condition) to give **26** (98.7 mg, 46%) as a white solid. MS: m/z 549.0 [M+H]⁺.

EXAMPLE 15 Preparation of Compound 27



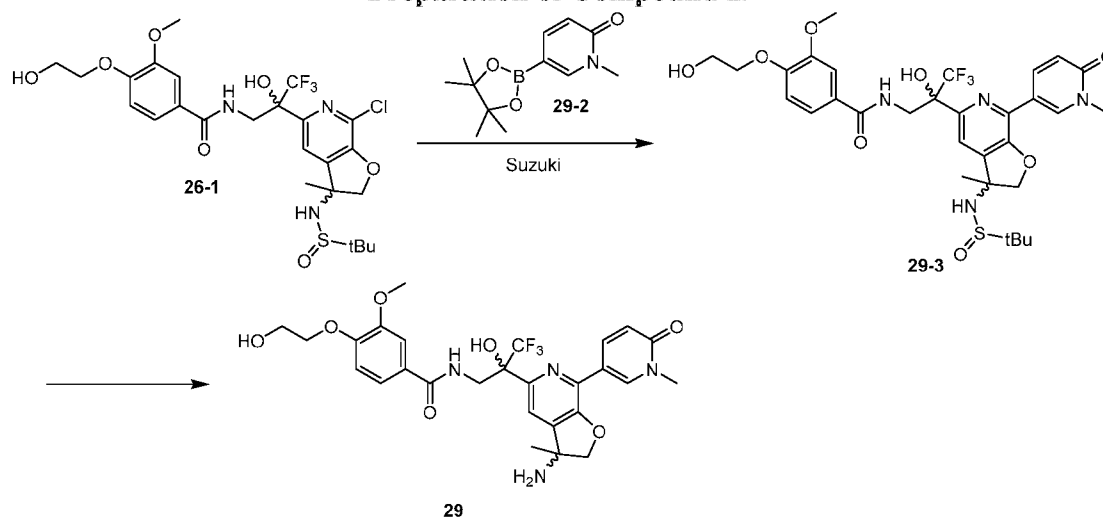
[0261] Compound **27** (23 mg, pale yellow solid) was obtained from **26-2** using a similar procedure for preparing **26**. MS: m/z 548.0 [M+H]⁺.

EXAMPLE 16 Preparation of Compound 28



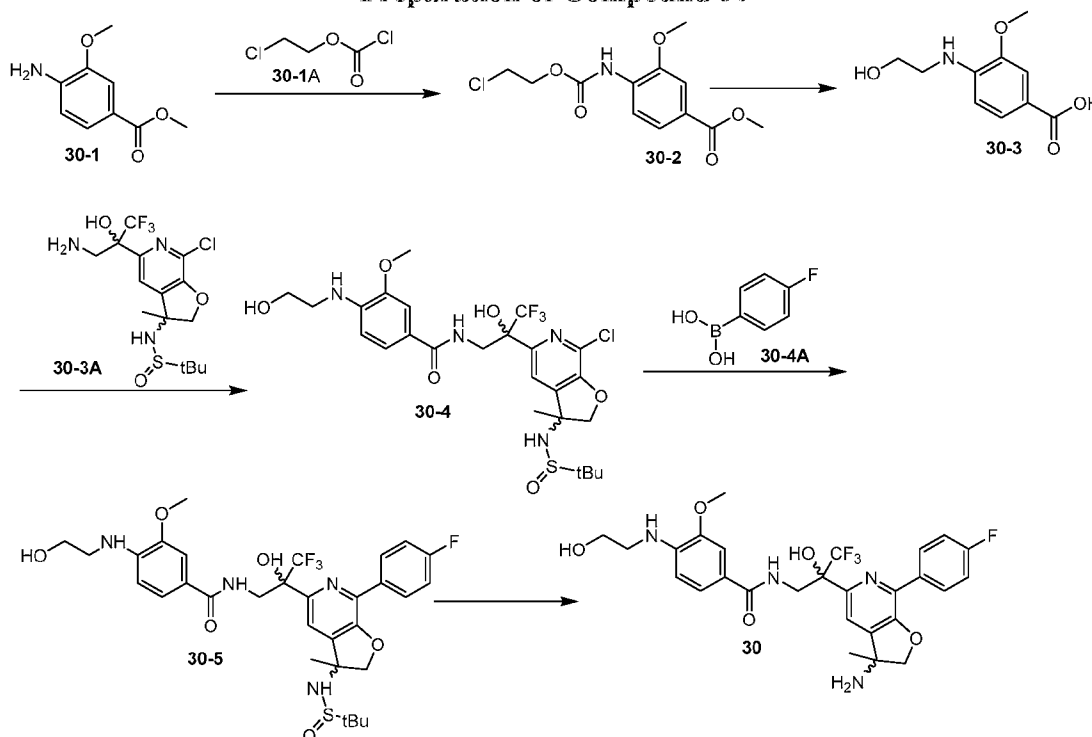
[0262] Compound **28-1** was prepared according to a similar procedure as provided in PCT Publication No. WO 2015/26792 A1. Compound **28** (68 mg, white solid) was obtained from **28-1** using a similar procedure for preparing **21**. m/z 560.1 $[M+H]^+$.

EXAMPLE 17
Preparation of Compound 29



[0263] Compound **29-2** was prepared according to similar procedure as provided in U.S. Publication No. 2015/111885 A1. Compound **29** (108 mg, white solid) was obtained from **26-1** and **29-2** using a similar procedure for preparing **26**. MS: m/z 579.0 $[M+H]^+$.

EXAMPLE 18
Preparation of Compound 30

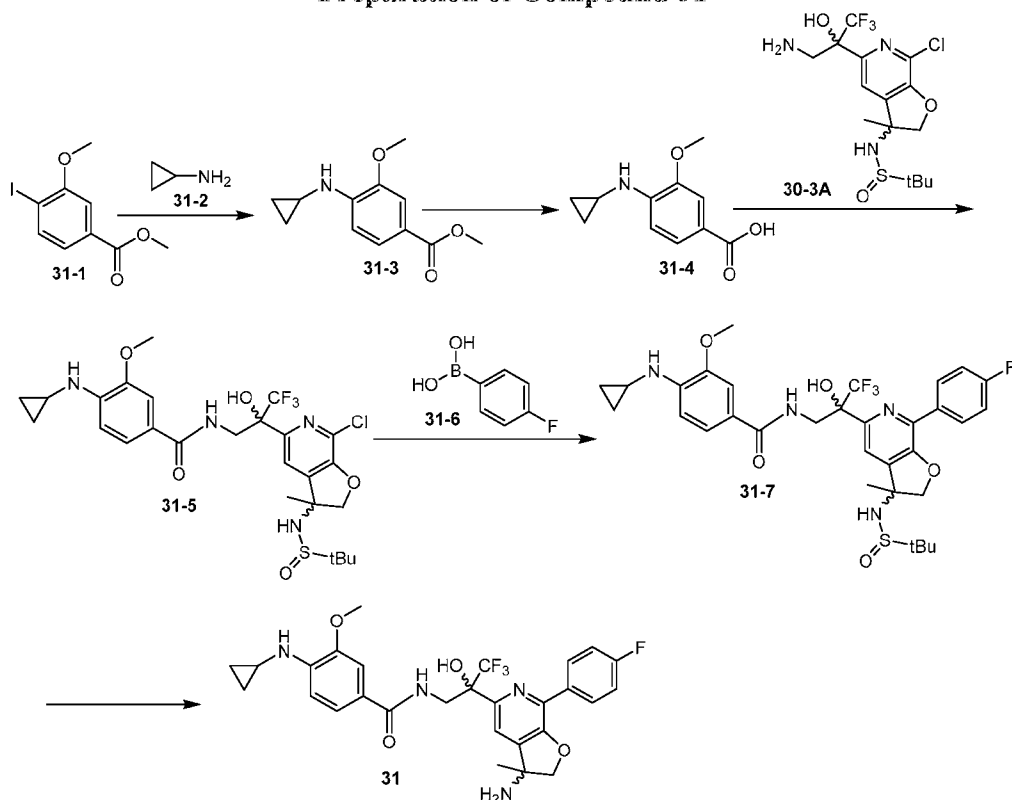


[0264] Compound **30-3A** was prepared according to a similar procedure as provided in PCT Publication No. WO 2015/26792 A1. To a mixture of **30-1** (350 mg, 1.93 mmol) and pyridine (458 mg, 5.79 mmol) in DCM (5 mL) was added **30-1A** (276 mg, 1.93 mmol) dropwise at 0 °C. The mixture was stirred for 2 h. The mixture was diluted with water (10 mL) and EA (10 mL). The organic phase was isolated and washed with brine (10 mL), dried over Na₂SO₄, and concentrated to give **30-2** (521 mg, crude) as a colorless oil. MS: m/z 288.0 [M+H]⁺.

[0265] To a solution of **30-2** (520 mg crude) in EtOH (10 mL) was added KOH (304 mg, 5.42 mmol). The mixture was heated to 80 °C and stirred for 0.5 h. The reaction was cooled to RT, acidified to pH 3~4 by 3 M HCl, and concentrated to give **30-3** (192 mg, crude) as a brown solid. MS: m/z 212.0 [M+H]⁺.

[0266] Compound **30** (62 mg, yellow solid) was obtained from **30-3** and **30-3A** using a similar procedure for preparing **21**. MS: m/z 565.1 [M+H]⁺.

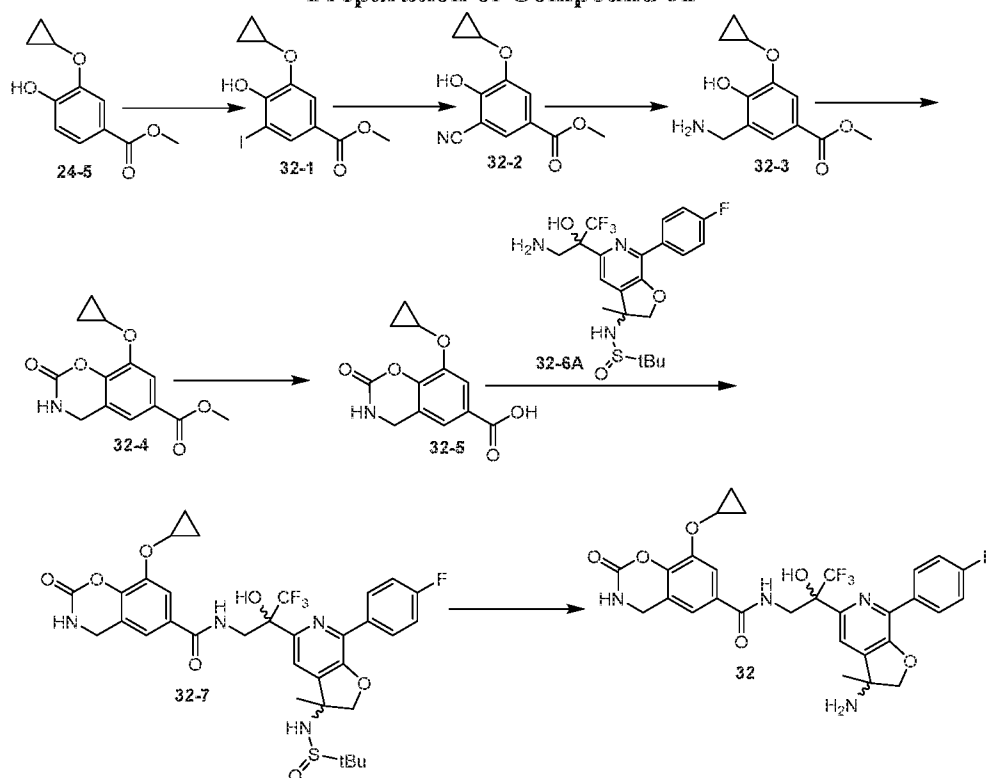
EXAMPLE 19
Preparation of Compound 31



[0267] Compound **31-1** was prepared according to a similar procedure as provided in PCT Publication No. WO 2010/56722 A1. A mixture of **31-1** (1.0 g, 3.42 mmol), **31-2** (293 mg, 5.13 mmol), Cs₂CO₃ (4.46 g, 13.68 mmol), Pd₂(dba)₃ (326 mg, 0.68 mmol), and X-phos (313 mg, 0.34 mmol) in DMF (15 mL) was stirred at 100 °C for 12 h under N₂. The mixture was cooled to RT, diluted with H₂O (20 mL) and extracted with EA (2 X 20 mL). The organic phase was washed with brine, dried over Na₂SO₄, concentrated and purified by column chromatography using 10% EA in PE to give **31-4** (251 mg, 33%) as a light yellow oil. MS: m/z 221.9 [M+H]⁺.

[0268] Compound **31** (18 mg, yellow solid) was obtained from **31-3** and **30-3A** using a similar procedure for preparing **21**. MS: m/z 561.2 [M+H]⁺.

EXAMPLE 20
Preparation of Compound 32



[0269] Compound **32-6A** was prepared according to a similar procedure as provided in PCT Publication No. WO 2015/26792 A1.

[0270] To a mixture of **24-5** (1.0 g, 4.8 mmol) and Na_2CO_3 (1.02 g, 9.6 mmol) in DCM (20 mL) and H_2O (1 mL) was added I_2 (2.44 g, 9.6 mmol). The mixture was stirred at RT for 1 h. The reaction was quenched with aq. Na_2SO_3 (50 mL), extracted with EA (50 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column using 0~25% EA in PE to give **32-1** (920 mg, 57.4%) as a white solid. MS: m/z 334.9 $[\text{M}+\text{H}]^+$.

[0271] A mixture of **32-1** (920 mg, 2.75 mmol) and CuCN (985 mg, 11.00 mmol) in NMP (8 mL) was heated to 140 °C and stirred for 1 h under microwave. The mixture was cooled to RT, poured into water (30 mL) and extracted with EA (2 X 60 mL). The organic phase was concentrated and purified by column chromatography using 10~100% EA in PE to give the **32-3** (618 mg, 96.7%) as a yellow oil. MS: m/z 233.9 $[\text{M}+\text{H}]^+$.

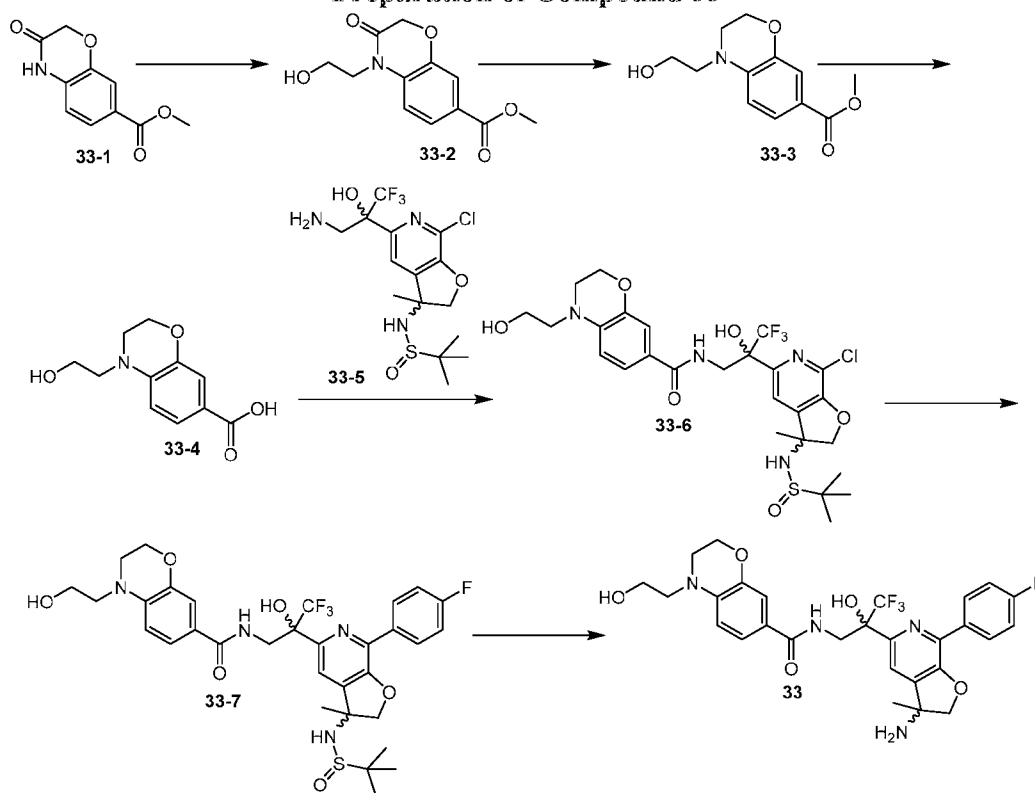
[0272] To a solution of **32-2** (618 mg, 2.66 mmol) in THF (5 mL) was added $\text{BH}_3\cdot\text{THF}$ (1 M, 5.0 mL). The solution was heated to 70 °C and stirred for 0.5 h. The

reaction was quenched by water (30 mL) and extracted with EA (3 X 30 mL). The organic phase was concentrated to give **32-3** (432 mg, crude) as a yellow oil. MS: m/z 237.9 [M+H]⁺.

[0273] To a solution of **32-3** (430 mg, crude) in THF (10 mL) was added CDI (587 mg, 3.62 mmol). The solution was stirred at RT for 15 h. The mixture was then diluted with EA (20 mL) and water (10 mL). The organic phase was isolated and washed with brine, dried over Na₂SO₄, concentrated purified by prep-TLC (EA) to give **32-4** (212 mg, 44.1%). MS: m/z 264.1 [M+H]⁺.

[0274] A solution of **32-4** (50 mg, 0.19 mmol) in HCl/dioxane (4M, 1.0 mL) and conc. HCl (12 M, 1.0 mL) was heated to 100 °C and stirred for 0.5 h. The solution was cooled to RT, poured into water (10 mL) and extracted with EA (2 X 20 mL). The organic phase was concentrated and purified by prep-HPLC (FA condition) to give **32-5** (31 mg) as a white solid. MS: m/z 250.1 [M+H]⁺.

[0275] Compound **32** (6.4 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **32-5** and **32-6A**. MS: m/z 603.2 [M+H]⁺.

EXAMPLE 21**Preparation of Compound 33**

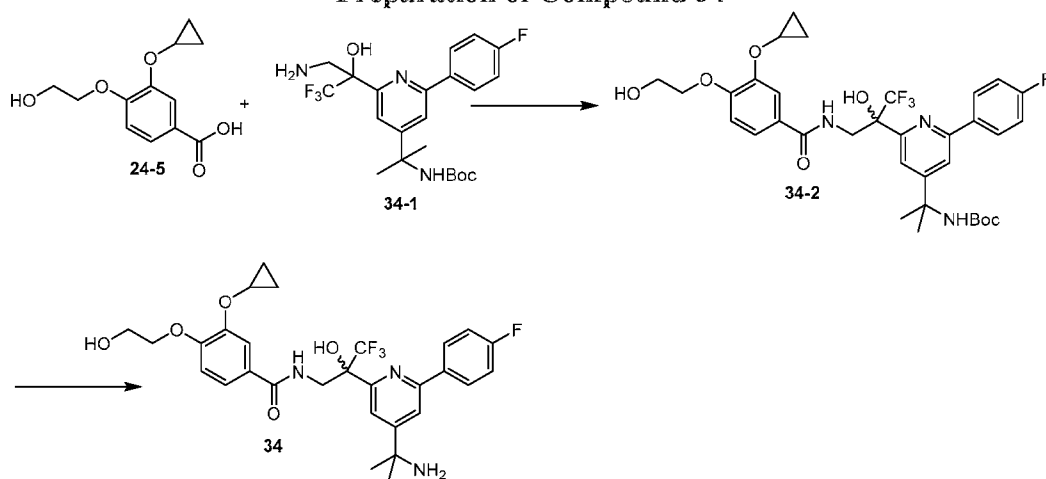
[0276] Compound **33-1** was prepared according to a similar procedure as provided in Ramesh et al., Tetrahedron (2011) 67(6):1187-1192. Compound **33-5** was prepared according to a similar procedure as provided in WO 2015/26792 A1.

[0277] To a solution of **33-1** (810 mg, 3.9 mmol) in DMF (10 mL) was added NaH (313 mg, 7.8 mmol) at RT. After stirring for 5 mins, 2-bromoethanol (489 mg, 3.9 mmol) was added, heated to 80 °C and stirred for 0.5 h. The reaction was cooled to RT, poured into water (50 mL) and extracted with EA (2 X 50 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to give **33-2** (520 mg, crude) as a brown solid. MS: m/z 251.8 [M+H]⁺.

[0278] To a solution of **33-2** (200 mg, crude) in THF (1.0 mL) was added BH₃-THF (1 M, 2.0 mL) at RT. The solution was heated to 70 °C and stirred for 1 h. The reaction was quenched with water (2 mL), and extracted with EA (2 X 5 mL). The organic phase was concentrated to give **33-3** (182 mg, crude) as a yellow oil. MS: m/z 237.9 [M+H]⁺.

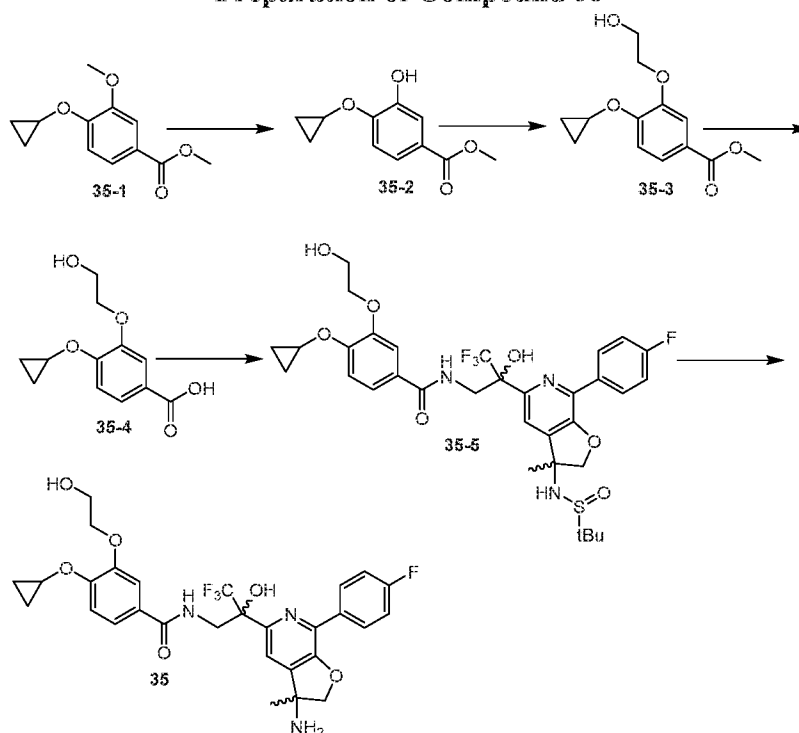
[0279] Compound **33** (14 mg, a white solid) was prepared using methods similar to those for preparing **21** from **33-5** and **33-5**. MS: m/z 577.0 $[M+H]^+$.

EXAMPLE 22
Preparation of Compound 34



[0280] Compound **34-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound **34** (46 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **24-5** and **34-1**. MS: m/z 578.0 $[M+H]^+$.

EXAMPLE 23
Preparation of Compound 35



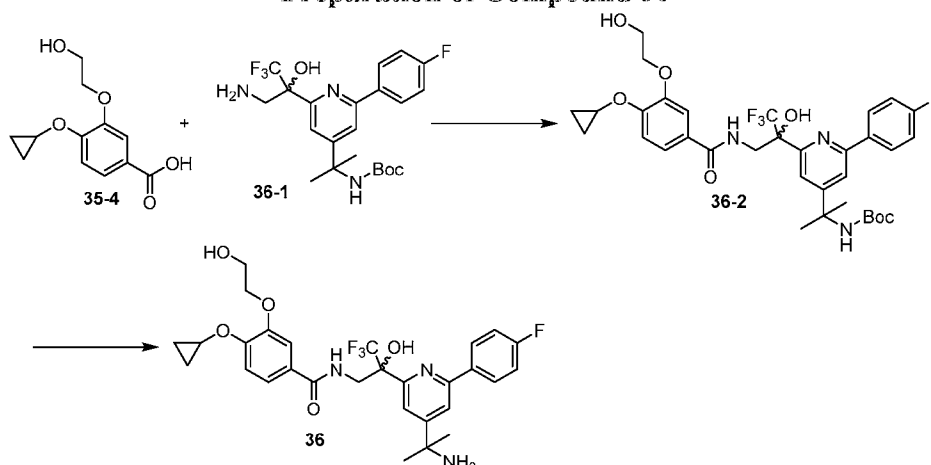
[0281] Compound **35-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1.

[0282] To a solution of **35-1** (1.0 g, 4.5 mmol) in CH_2Cl_2 (4 mL) was added BBr_3 (0.4 g, 1.57 mmol) with stirring at -78°C . The mixture was stirred for 1 h then warmed to 10°C in 2 h. The reaction was quenched with aqueous Na_2CO_3 , extracted with EA (3 X 20 mL). The organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography using 10~20% EA in PE to give **35-2** (0.78 g, 83.2%).

[0283] A mixture of **35-2** (0.4 g, 1.92 mmol), 2-bromoethanol (0.48 g, 3.84 mmol) and K_2CO_3 (0.8 g, 5.76 mmol) in CH_3CN (4 mL) was heated to 80°C and stirred for 12 h. The mixture was cooled to RT, filtered and concentrated. The residue was purified by column chromatography using 10~20% EA in PE to give **35-3** (412 mg, 85%).

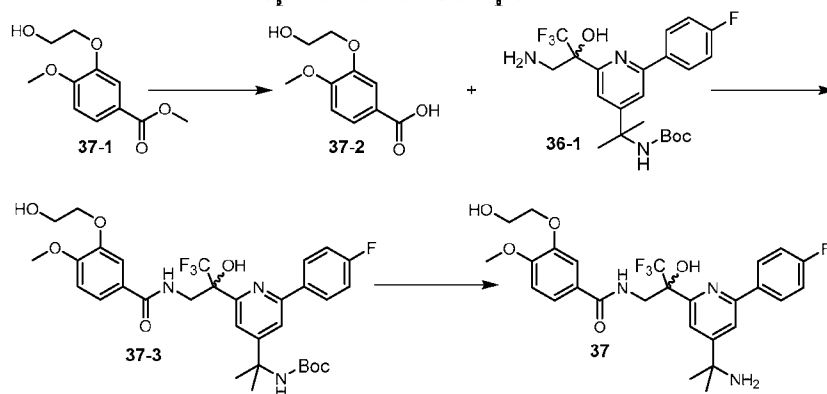
[0284] Compound **35** (31 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **35-3**. MS: m/z 578.0 $[\text{M}+\text{H}]^+$. MS: m/z 592.1 $[\text{M}+\text{H}]^+$.

EXAMPLE 24
Preparation of Compound 36



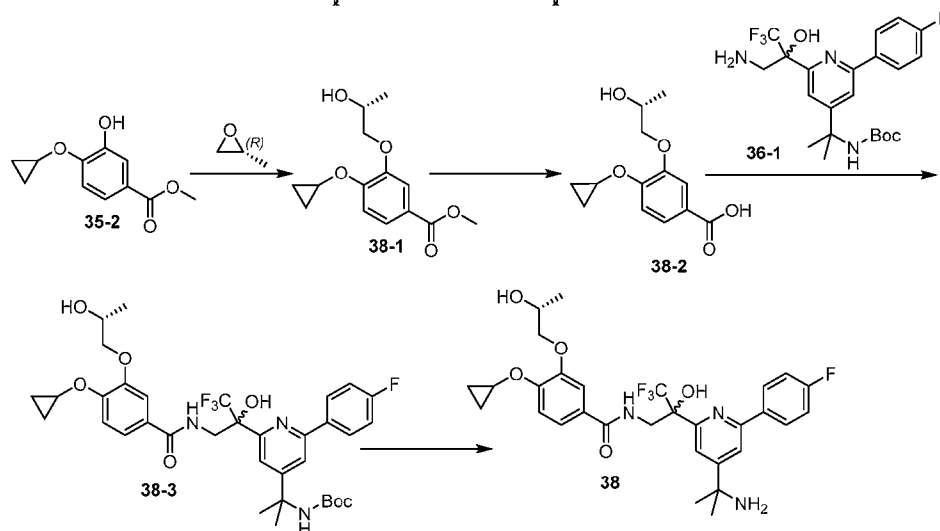
[0285] Compound 36-1 was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound 36 (77 mg, a white solid) was prepared using methods similar to those for preparing 21 from 35-4 and 36-1. MS: m/z 578.1 $[M+H]^+$.

EXAMPLE 25
Preparation of Compound 37



[0286] Compound 37-1 was prepared according to a similar procedure as provided in Uto et al., Bioorganic and Medicinal Chemistry Letters (2009) 19(15):4151-4158. Compound 37 (42 mg, a white solid) was prepared using methods similar to those for preparing 21 from 36-1 and 37-1. MS: m/z 552.2 $[M+H]^+$.

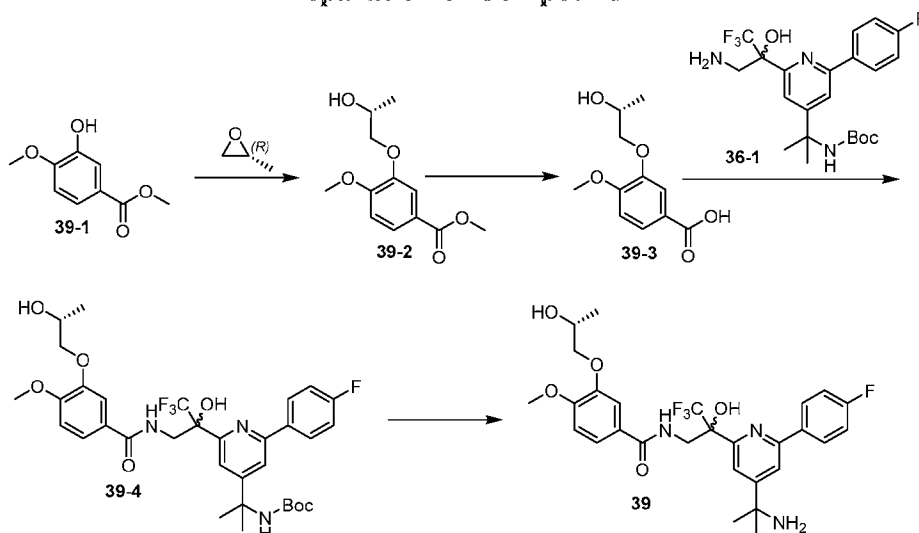
EXAMPLE 26
Preparation of Compound 38



[0287] A mixture of **35-2** (700 mg, 3.36 mmol), (2R)-2-methyloxirane (1.95 g, 33.6 mmol) and K_2CO_3 (550 mg, 4.0 mmol) in acetone (10 mL) was heated to 80 °C in a sealed tube and stirred for 18 h. The mixture was cooled to RT and filtered. The filtrate was concentrated, and the residue was purified by column chromatography using 5~10% EA in PE to give **38-1** (813 mg, 90.7%) as a colorless oil. MS: m/z 226.9 $[M+H]^+$.

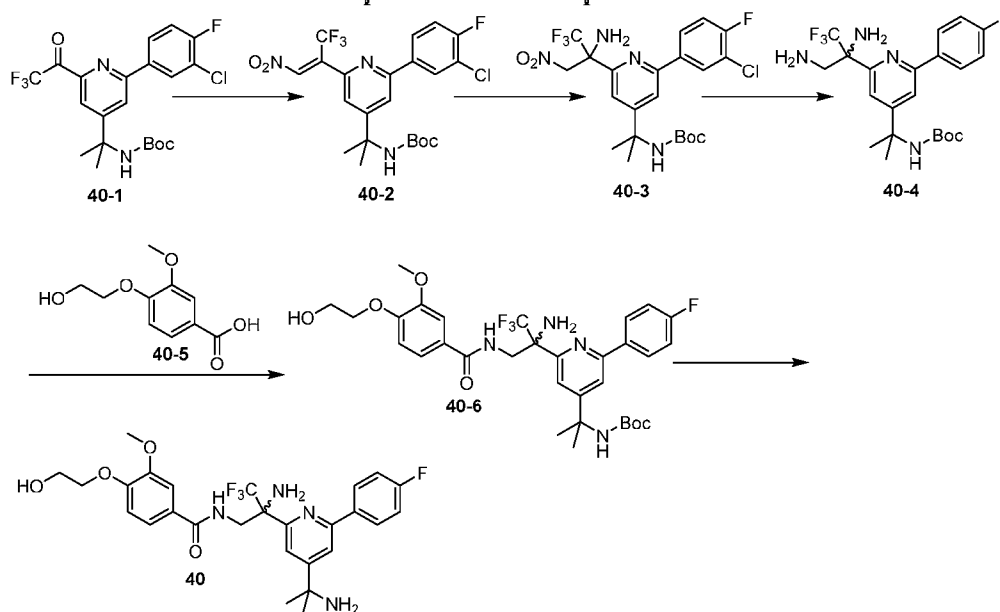
[0288] Compound **38** (39 mg, a white solid) was prepared using methods similar to those for preparing **21** from **38-1**. MS: m/z 592.1 $[M+H]^+$.

EXAMPLE 27
Preparation of Compound 39



[0289] Compound **39-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound **39** (68 mg, a white solid) was prepared using methods similar to those for preparing **21** from **39-1**. MS: m/z 566.1 $[M+H]^+$.

EXAMPLE 28
Preparation of Compound 40



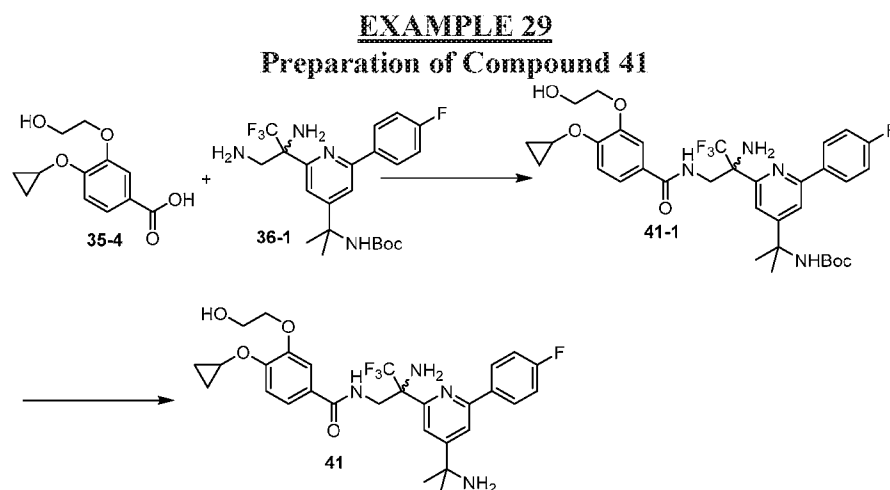
[0290] Compound **40-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1, and compound **40-5** was prepared according to a similar procedure as provided in WO 2013/31784 A1.

[0291] A mixture of **40-1** (821 mg, 1.78 mmol) and K_2CO_3 (542 mg, 3.92 mmol) in CH_3NO_2 (10 mL) was stirred at RT for 3 h, diluted with H_2O (20 mL) and extracted with EA (2 X 10 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue (815 mg, crude) and pyridine (370 mg, 4.68 mmol) were dissolved in toluene (10 mL) and stirred at 0 °C for 10 mins. $SOCl_2$ (0.28 mL 3.90 mmol) was added slowly at 0 °C. The mixture was stirred at 0 °C for 30 mins, quenched by water (20 mL), extracted with EA (2 X 20 mL). The organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using ~20% EA in PE to give **40-2** (721 mg, 73.1%) as a white solid. MS: m/z 503.9 $[M+H]^+$.

[0292] A mixture of **40-2** (721 mg, 1.43 mmol) and ammonia water (1 mL, 14 M) in DMSO (6 mL) was stirred at 0 °C for 1 h. The mixture was diluted with H₂O (50 mL), and extracted with EA (3 X 30 mL). The organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 20% EA in PE to give **40-3** (651 mg, 87.4%) as a yellow oil. MS: m/z 521.1 [M+H]⁺.

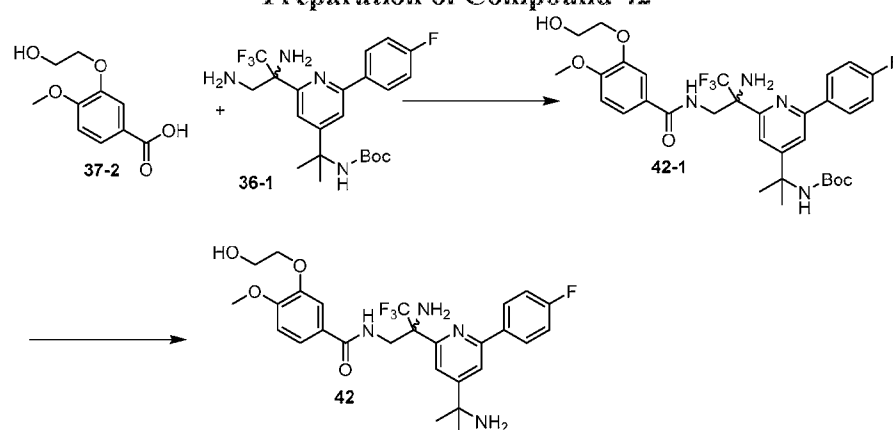
[0293] A mixture of **40-3** (650 mg, 1.25 mmol) and Raney-Ni (0.2 g) in MeOH (20 mL) was stirred under hydrogen (45 Psi) at RT for 16 h. The mixture was filtered through a pad of celite and Pd/C (65 mg, 10%) was added. The mixture was stirred under hydrogen (45 Psi) at RT for 16 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated to give **40-4** (382 mg 38.8%). MS: m/z 457.1 [M+H]⁺.

[0294] Compound **40** (29 mg, a white solid) was prepared using methods similar to those for preparing **21** from **40-4** and **40-5**. MS: m/z 551.1 [M+H]⁺.



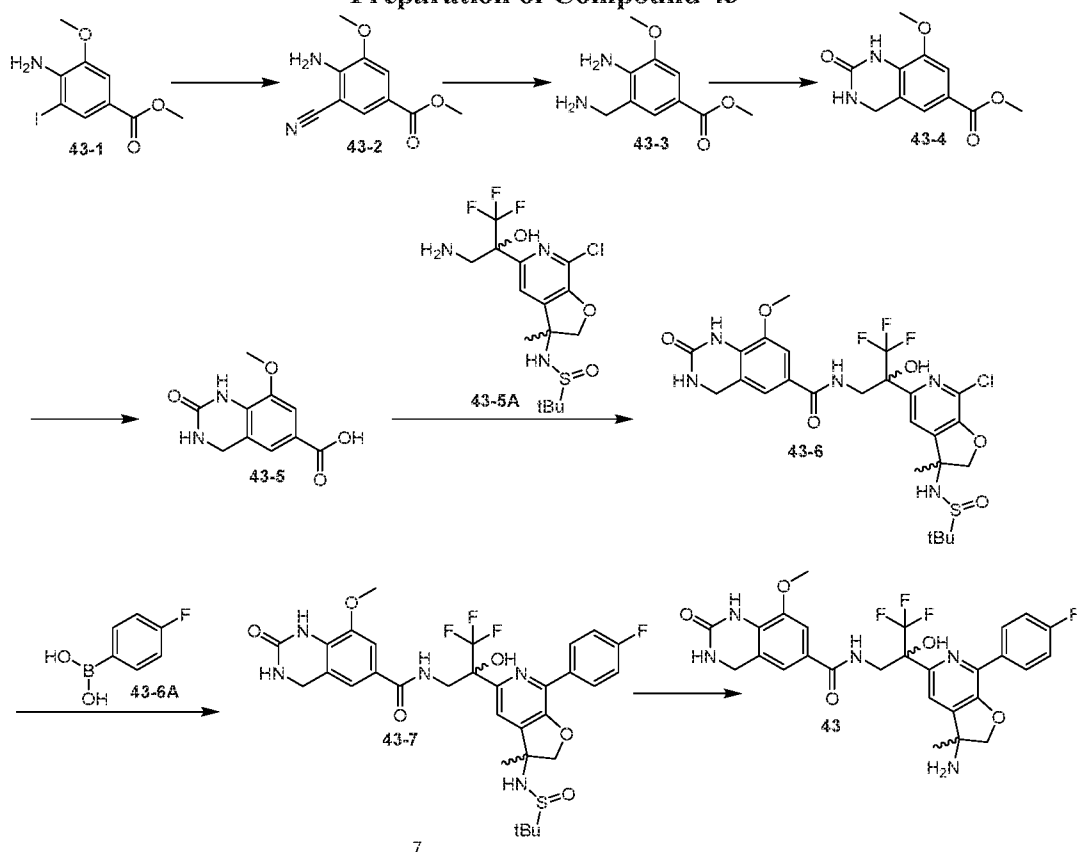
[0295] Compound **41** (23 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **35-4** and **36-1**. MS: m/z 577.1 [M+H]⁺.

EXAMPLE 30
Preparation of Compound 42



[0296] Compound **42** (39 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **37-2** and **36-1**. MS: m/z 551.1 $[M+H]^+$.

EXAMPLE 31
Preparation of Compound 43



[0297] Compound **43-1** was prepared according to a similar procedure as provided in Ezquerro et al., Journal of Organic Chemistry (1996) 61(17):5804-5812, and compound **43-5A** was prepared according to a similar procedure as provided in WO 2015/26792 A1.

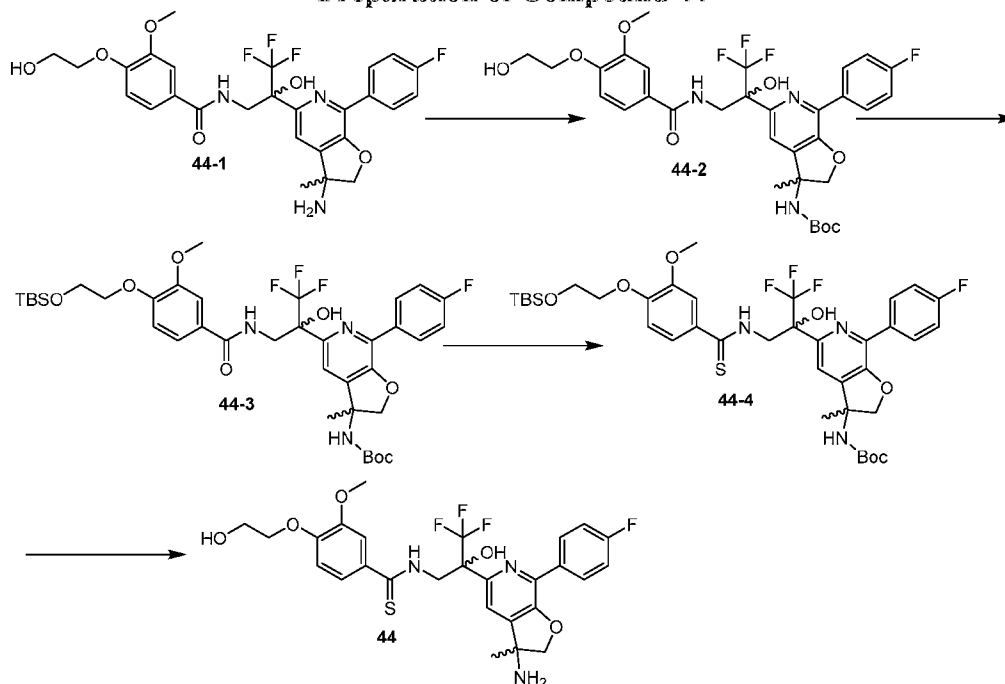
[0298] A mixture of **43-1** (2.5 g, 4.1 mmol), CuCN (1.46 g, 8.2 mmol) in DMF (15 mL*2) was heated to 120 °C and stirred for 1 h under microwave irradiation. The mixture was poured into water (50 mL) and extracted with EA (2 X 50 mL). The organic phase was concentrated, and the residue was purified by column chromatography using 5~20% EA in PE to give **43-2** (1.6 g, 95.3%) as a yellow solid. MS: m/z 206.9 [M+H]⁺.

[0299] A mixture **43-2** (1.1 g, 5.3 mmol) in BH₃-THF (1 M, 20 mL) was heated to 70 °C and stirred for 2 h. The solution was quenched with water, basified by aqueous K₂CO₃ to pH 11~12, and extracted with EA (2 X 30 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to give **43-3** (1.02 g, crude) as a brown oil. MS: m/z 193.9 [M-NH₂]⁺.

[0300] To a solution of **43-3** (1.0 g, 4.7 mmol) in THF (20 mL) was added CDI (1.6 g, 9.5 mmol) at 20 °C. The mixture was stirred overnight. The mixture was then poured into water (50 mL) and extracted with EA (2 X 40 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to give **43-4** (1.10 g, crude) as a yellow solid. MS: m/z 236.9 [M+H]⁺.

[0301] Compound **43** (46 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **43-4**. MS: m/z 575.3 [M+H]⁺, 598.1 [M+Na]⁺.

EXAMPLE 32
Preparation of Compound 44



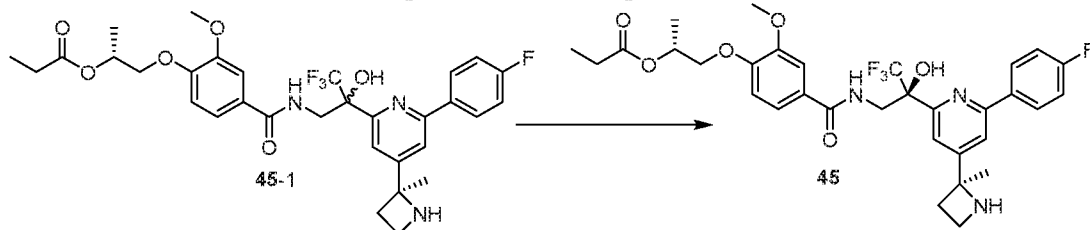
[0302] A solution of **44-1** (800 mg, 1.41 mmol), TEA (281 mg, 2.77 mmol) and Boc_2O (309 mg, 1.41 mmol) in toluene (2 mL) stirred at 110 °C for 2 h. The solution was concentrated, and the residue was purified by column chromatography using 25% EA in PE to give **44-2** (582 mg, 62%) as a white solid. MS: m/z 665.9 $[\text{M}+\text{H}]^+$.

[0303] To a solution of **44-2** (580 mg, 0.87 mmol) and imidazole (118 mg, 1.74 mmol) in DCM (20 mL) was added TBSCl (159 mg, 1.05 mmol, 1.21 eq.). The mixture was stirred at 20 °C for 1 h, washed with water (20 mL) and concentrated. The residue was purified by column chromatography using 10% of EA in PE to give **44-3** (562 mg, 82.7%) as a colorless oil. MS: m/z 780.1 $[\text{M}+\text{H}]^+$.

[0304] A mixture of **44-3** (560 mg, 0.72 mmol) and Lawesson reagent (290 mg, 0.72 mmol) in toluene (3 mL) was heated to 110 °C and stirred for 1 h. The solution was quenched with H_2O (5 mL) and extracted with EA (2 X 10 mL). The organic phase was concentrated and purified by column chromatography using 15% EA in PE to give **44-4** (121 mg, 21.1%) as a yellow solid. MS: m/z 796.2 $[\text{M}+\text{H}]^+$.

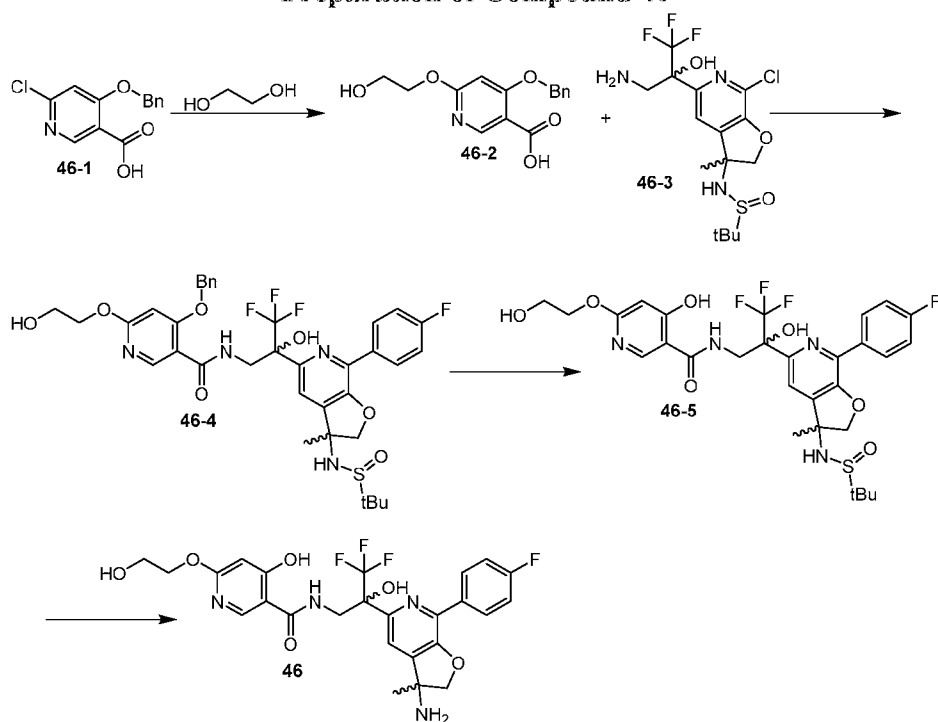
[0305] A mixture of **44-4** (110 mg, 138 μ mol) in HCl/MeOH (4 M, 5 mL) was stirred at 20 °C for 20 mins, concentrated and purified by prep-HPLC (HCl) to give **44** (16 mg, 19.9%) as a yellow solid. MS: m/z 582.0 $[M+H]^+$, 604.0 $[M+Na]^+$.

EXAMPLE 33
Preparation of Compound 45



[0306] Compound **45-1** (226 mg) was purified by SFC (Column: Chiralpak AD-3 150×4.6mm I.D., 3 μ m Mobile phase: A: CO₂ B:iso-propanol (0.05% DEA) Gradient: from 5% to 40% of B in 5.5min and hold 40% for 2 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35 °C Wavelength: 220nm" "Column: Chiralcel OJ-3 150×4.6mm I.D., 3 μ m Mobile phase: A: CO₂ B:methanol (0.05% DEA) Gradient: from 5% to 40% of B in 5.5min and hold 40% for 2 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35 °C Wavelength: 220nm) to get **45** (180 mg, 79.6%) as a white solid. MS: m/z 634.1 $[M+H]^+$.

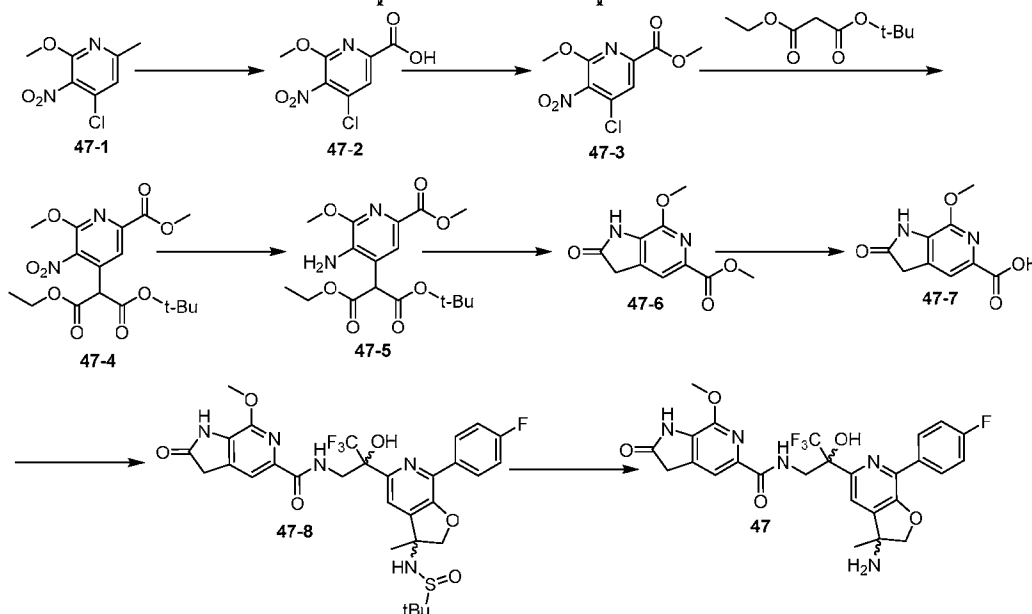
EXAMPLE 34
Preparation of Compound 46



[0307] Compound **46-1** was prepared according to a similar procedure as provided in Sakairi et al., *Journal of Arzneimittel-Forschung/Drug Research* (2012) 62(11):537-544, and compound **46-3** was prepared according to procedures as provided in WO 2015/26792 A1.

[0308] To a solution of **46-1** (1.0 g, 3.8 mmol) in ethylene glycol (20 mL) was added *t*-BuOK (1.3 g, 11.4 mmol). The mixture was stirred at 130 °C for 1 h under microwave irradiation. The mixture was poured into water (50 mL) and extracted with EA (3 X 20 mL). The organic phase was dried over Na₂SO₄ and concentrated to give **46-2** (820 mg, crude) as a white solid. MS: *m/z* 290.1 [M+H]⁺.

[0309] Compound **46** (7.1 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **46-2** and **46-3**. MS: *m/z* 575.1 [M+Na]⁺.

EXAMPLE 35**Preparation of Compound 47**

[0310] Compound **47-1** was prepared according to a similar procedure as provided in Urban et al., *Journal of Helvetica Chimica Acta* (1964) 47:363-379.

[0311] To a solution of **47-1** (10.0 g, 49.4 mmol) in H_2SO_4 (80 mL) was added CrO_3 (14.8 g, 148.1 mmol) in small portions and kept at an internal temperature below 70 °C. After addition, the mixture was stirred at 60 °C for 2 h. The reaction was poured into ice/water (200 mL). The slurry was filtered, washed with water (3 X 20 mL), and dried over Na_2SO_4 to give **47-2** (8.20 g, crude) as a white solid. MS: m/z 233.1 $[\text{M}+\text{H}]^+$.

[0312] To a solution of **47-2** (8.1 g, 34.8 mmol) in MeOH (90 mL) was added SOCl_2 (16.6 g, 139.3 mmol) slowly. The mixture was stirred at 50 °C for 2 h. The mixture was then diluted with water (100 mL), neutralized to pH 7~8 using aq. NaHCO_3 and extracted with EA (2 X 50 mL). The organic layers were washed with brine (2 X 10 mL), dried over Na_2SO_4 , filtered and concentrated to give **47-3** (6.80 g, crude) as a yellow solid. MS: m/z 247.1 $[\text{M}+\text{H}]^+$.

[0313] A mixture of **47-3** (1.0 g, 4.1 mmol), Cs_2CO_3 (4.0 g, 12.2 mmol) and maleic acid ester (2.29g, 12.2 mmol) in 2-methyltetrahydrofuran (10 mL) was stirred at 80 °C for 2 h. The mixture was diluted with EA (20 mL) and water (30 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated. The residue

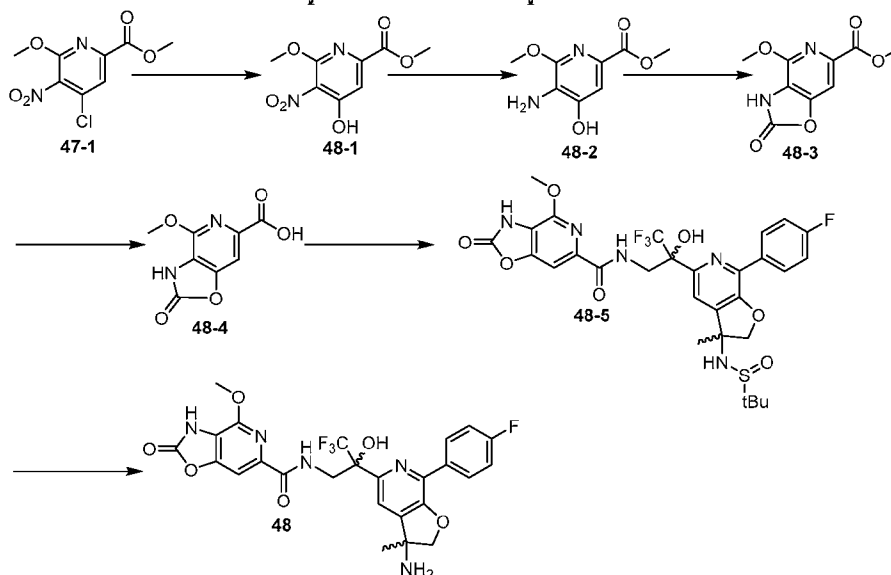
was purified by column chromatography using 3~15% EA in PE to give **47-4** (1.2 g, 74.2 %) as a white solid. MS: m/z 399.1 $[M+H]^+$.

[0314] A mixture of **47-4** (0.95 mg, 2.4 mmol) and Pd/C (20.0 mg) in MeOH (10 mL) was stirred under H_2 (15 PSI) at 20 °C for 17 h. The mixture was filtered, and the filtrate was concentrated to give **47-5** (0.87 g, crude) as a white solid. MS: m/z 369.0 $[M+H]^+$.

[0315] To a solution of **47-5** (0.8 g, 2.2 mmol) in MeOH (2 mL) was added conc. HCl (12 M, 0.78 mL). The mixture was stirred at 70 °C for 1 h. The reaction was concentrated, and the residue was purified by column chromatography using 30~100% EA in PE to give **47-6** (172 mg, 33.8%) as a light yellow solid. MS: m/z 222.9 $[M+H]^+$.

[0316] Compound **47** (7.1 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **47-6**. MS: m/z 561.9 $[M+H]^+$.

EXAMPLE 36
Preparation of Compound 48



[0317] A mixture of **47-1** (1.05 g, 4.26 mmol), CH_3COOK (2.09 g, 21.29 mmol) and H_2O (154 mg, 8.52 mmol) in DMSO (10 mL) was heated to 90 °C and stirred for 1 h. TLC (PE:EA = 5:1) showed the reaction was complete. The reaction was diluted with water (30 mL), and extracted with EA (2 X 30 mL). The organic phase was concentrated, and the

residue was purified by column chromatography on silica gel using 6~20% EA in PE to give **48-1** (0.91 g, 93.6%) as a light yellow solid. MS: m/z 229.0 $[M+H]^+$.

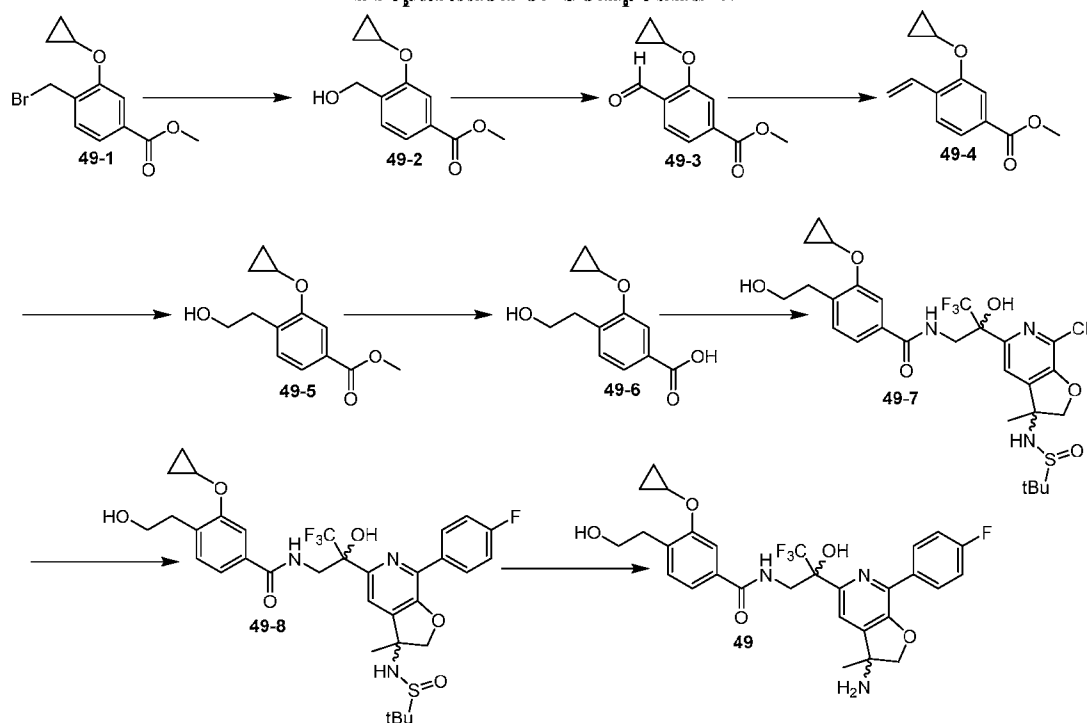
[0318] A mixture of **48-1** (0.91 g, 4.0 mmol) and Pd/C (300 mg) in CH₃OH (40 mL) was stirred at 25 °C for 12 h under H₂ (50 Psi). The mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography using 10~30% EA in PE to give **48-2** (0.52 g, 65.7%) as a light yellow solid. MS: m/z 198.9 $[M+H]^+$.

[0319] A solution of **48-2** (0.5 g, 2.52 mmol) and CDI (0.49 g, 3.02 mmol) in THF (15 mL) was stirred at 25 °C for 2 h. TLC (DCM:MeOH = 20:1) showed the reaction was completed. The mixture was concentrated to give crude **48-3** (720 mg) as a light yellow solid. MS: m/z 224.8 $[M+H]^+$.

[0320] Compound **48** (35 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **48-3**. MS: m/z 564.0 $[M+H]^+$.

EXAMPLE 37

Preparation of Compound 49



[0321] A mixture of **49-1** (1.0 g, 3.5 mmol), CaCO₃ (1.05 g, 10.5 mmol) in dioxane (10 mL) and H₂O (10 mL) was heated at 140 °C under microwave for 30 mins. The mixture was cooled to RT, and extracted with EA (2 X 20 mL). The organic phase was

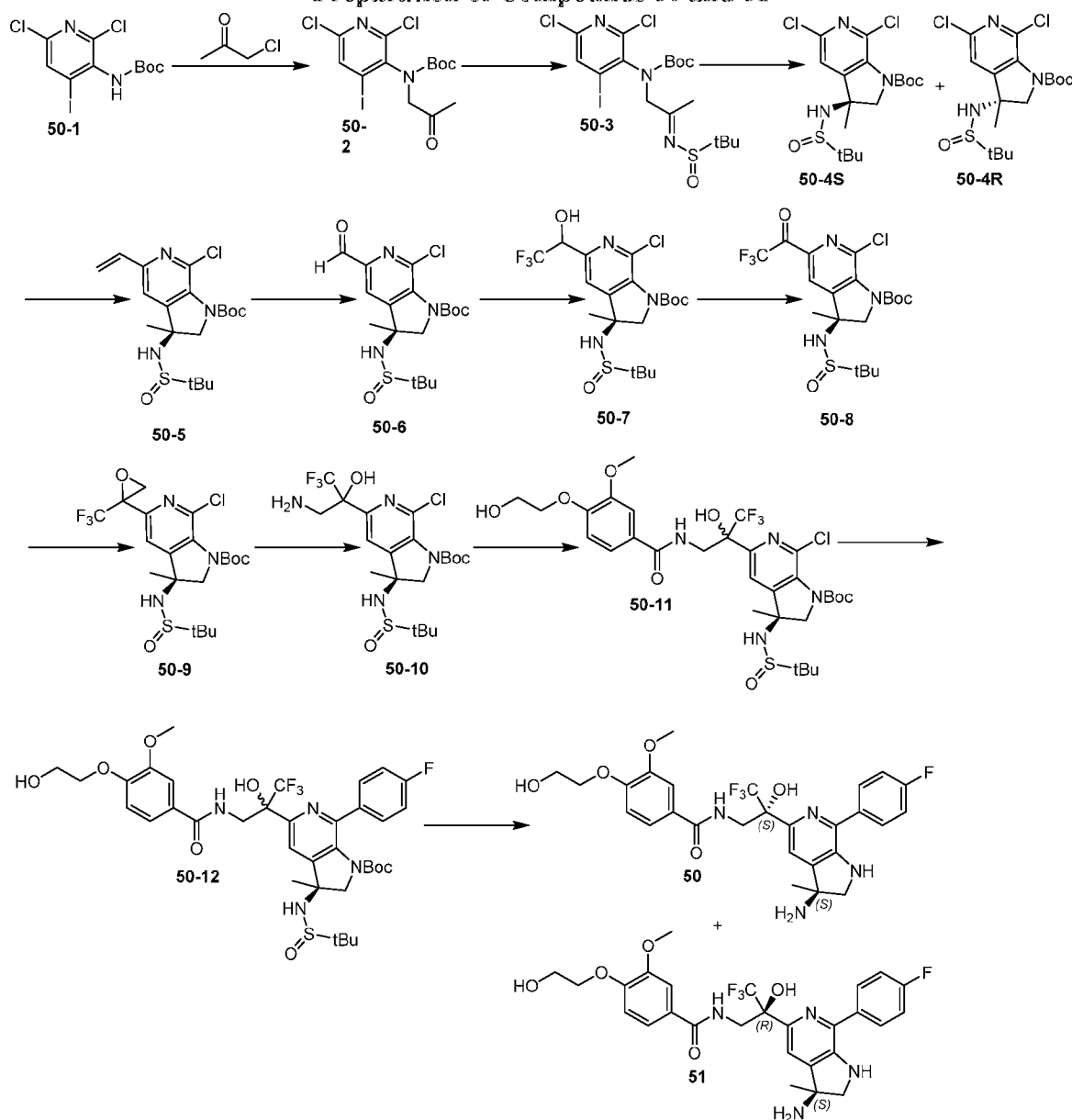
washed with brine, dried over Na₂SO₄, concentrated and purified by column chromatography using 10% EA in PE to give **49-2** (0.65 g, 83.5%).

[0322] To a solution of **49-2** (650 mg, 2.9 mmol) in DCM (10 mL) was added Dess-Martin (1.36 g, 3.2 mmol). The mixture was stirred at 20 °C for 1 h, and the reaction was quenched with aq. Na₂S₂O₃, and extracted with EA (2 X 20 mL). The organic phase was washed with brine, dried over Na₂SO₄, concentrated and purified by column chromatography using 3~10% EA in PE to give **49-3** (612 mg, 98.3%) as a white solid. MS: m/z 221.0 [M+H]⁺.

[0323] To a solution of **49-3** (330 mg, 1.50 mmol) in THF (15 mL) was added MeMgBr (3 M, 0.55 mL) dropwise at -78 °C. The mixture was stirred at -78 °C for 20 mins. The reaction was quenched with sat. NH₄Cl and extracted with EA (2 X 20 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue and 4-methylbenzenesulfonic acid (109 mg, 0.63 mmol) were dissolved in toluene (20 mL) and heated to 110 °C for 1 h with stirring. The mixture was concentrated and purified by column chromatography using 2~10% EA in PE to give **49-4** (231 mg, 83%) as a colorless oil. MS: m/z 219.1 [M+H]⁺.

[0324] To a solution of **49-4** (150 mg, 0.69 mmol) in THF (5 mL) was added BH₃-THF (1 M, 6.9 mL). The mixture was stirred at 0 °C for 3 h, followed by addition of NaOH (1 M, 6.89 mL) and H₂O₂ (0.67 mL). The mixture was stirred for 1 h and then diluted with EA (20 mL) and water (10 mL). The organic phase was washed with brine, dried over Na₂SO₄, concentrated and purified by column chromatography using 10~20% EA in PE to give **49-5** (52 mg, 31%) as a white solid. MS: m/z 237.1 [M+H]⁺.

[0325] Compound **49** (65 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **49-5**. MS: m/z 575.9 [M+H]⁺.

EXAMPLE 38**Preparation of Compounds 50 and 51**

[0326] Compound 50-1 was prepared according to a similar procedure as provided in WO 2015/26792 A1.

[0327] To a solution of 50-1 (7.50 g, 19.28 mmol) in DMF (100 mL) was added NaH (848, mg, 21.21 mmol, 60% purity) and 1-chloropropan-2-one (1.96 g, 21.2 mmol) at RT with stirring. The mixture was stirred at 30 °C for 1 h and diluted with water (500 mL). A white precipitate was formed, filtered and washed with water (200 mL) and PE

(100 mL). The solid was dried under vacuum to give **50-2** (7.5 g, 87.4%). MS: m/z 445.1 $[M+H]^+$.

[0328] A mixture of **50-2** (7.50 g, 16.85 mmol), R-2-methylpropane-2-sulfonamide (3.27 g, 26.96 mmol) and $Ti(OEt)_4$ (11.53 g, 50.55 mmol) in THF (60 mL) was stirred at 70 °C for 1 h under N_2 . The mixture was concentrated, and the residue was dissolved in EA (100 mL). The solution was poured into sat. aq. $NaHCO_3$ (50 mL) and stirred for 2 mins. The mixture was filtered through a celite pad, and the cake was washed with EA (2 X 50 mL). The combined organic phase was concentrated and purified by column chromatography using PE:EA = 10:1~1:1 to give **50-3** (7.3 g, 79%) as a brown oil. MS: m/z 548.0 $[M+H]^+$.

[0329] To a solution of $EtMgBr$ (3 M, 4.6 mL) in dry THF (50 mL) was added $n-BuLi$ (2.5 M, 11 mL) at -78 °C with stirring. After 10 mins, a solution of **50-3** (7.5 g, 13.68 mmol) in dry THF (20 mL) was added dropwise, and the reaction was stirred at -78 °C for 30 mins. The reaction was quenched by the addition of H_2O (10 mL) at -78 °C. The mixture was warmed to RT and extracted with EA (2 X 40 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 5~10% EA in PE to give **50-4R** (1.6 g, 27.7%) and **50-4S** (1.4 g, 24.4%) as pale yellow solids. MS: m/z 422.1 $[M+H]^+$.

[0330] A mixture of **50-4S** (1.4 g, 3.3 mmol), potassium trifluoro(vinyl)boranuide (581 mg, 4.34 mmol), Na_2CO_3 (923 mg, 8.71 mmol) and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) in EtOH (100 mL) was stirred at 80 °C for 1 h under N_2 . The mixture was concentrated, and the residue was purified by column chromatography using 10~20% EA in PE to give **50-5** (1.3 g, 82.8%) as a white solid. MS: m/z 414.0 $[M+H]^+$.

[0331] To a solution of **50-5** (1.2 g, 2.9 mmol) in DCM (80 mL) was bubbled ozone at -78 °C for 30 mins. After the excess ozone was purged by N_2 , Me_2S (720 mg, 11.6 mmol) was added. The mixture was stirred at -78 °C for 30 mins. The mixture was concentrated and purified by column chromatography using 10~20% EA in PE to give **50-6** (1.01 g, 87.3%) as a yellow solid. MS: m/z 416.1 $[M+H]^+$.

[0332] To a mixture of **50-6** (1.0 g, 2.4 mmol) and $TMSCF_3$ (1.02 g, 7.2 mmol) in DMF (10 mL) was added TBAF (1 M, 2.4 mL) dropwise at -10 °C. The mixture was stirred for 1 h, partitioned between EA (60 mL) and water (60 mL). The aqueous was

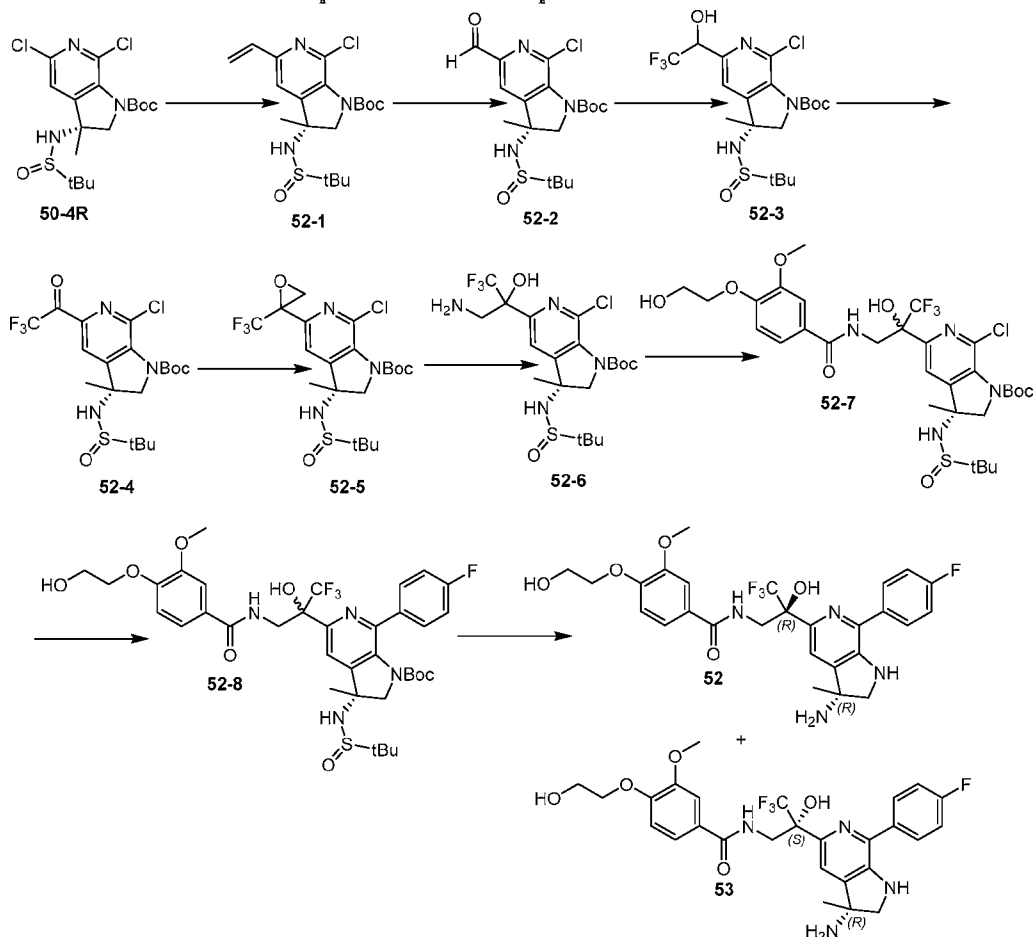
extracted with EA (2 X 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 2% MeOH in DMC to give **50-7** (790 mg, 67.7%) as a white solid. MS: m/z 486.1 $[\text{M}+\text{H}]^+$.

[0333] To a solution of **50-7** (790 mg, 1.63 mmol) in DCM (6 mL) was added DMP (793 mg, 1.87 mmol). The mixture was stirred at RT for 1 h. The reaction quenched with sat. aq. Na_2SO_3 , and extracted with EA (2 X 30 mL). The organic phase was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 5~20% EA in PE to give **50-8** (750 mg, 95.3%) as a white solid. MS: m/z 502.1 $[\text{M}+\text{H}_3\text{O}]^+$.

[0334] To a solution of $t\text{-BuOK}$ (217 mg, 1.94 mmol) in CH_3CN (30 mL) was added Me_3SOI (375 mg, 1.71 mmol) in one portion. After stirring at RT for 5 mins, the mixture was left standing for a while. The clean liquid containing the ylide was poured into a solution of **50-8** (750 mg, 1.55 mmol) in CH_3CN (10 mL) which had been previously degassed. The mixture was stirred at RT for 10 mins, and then concentrated to give a residue. The residue was further purified by column chromatography using 0~20% EA in DCM to give **50-9** (310 mg, 40.2%) as a pale yellow oil. MS: m/z 498.1 $[\text{M}+\text{H}]^+$.

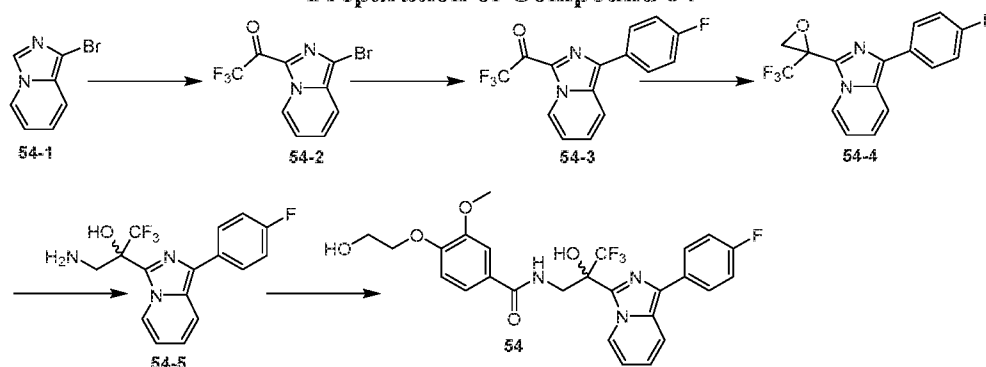
[0335] A mixture of **50-9** (310 mg, 0.62 mmol) in NH_3/MeOH (7 M, 30 mL) was stirred at 25 °C for 1 h. The reaction was concentrated to give crude **50-10** (322 mg, crude) as a yellow solid. MS: m/z 515.1 $[\text{M}+\text{H}]^+$.

[0336] Compounds **50** (55 mg, a white solid) and **51** (60 mg, a yellow solid) were prepared using methods similar to those for preparing **21** from **50-10**, and by prep-HPLC (basic condition) for separation. Compounds **50** and **51** are shown above with relative stereochemistry arbitrarily assigned. **50**: MS: m/z 565.1 $[\text{M}+\text{H}]^+$; **51**: MS: m/z 565.1 $[\text{M}+\text{H}]^+$.

EXAMPLE 39**Preparation of Compounds 52 and 53**

[0337] Compounds **52** (31 mg, a white solid) and **53** (33 mg, a yellow solid) were prepared using methods similar to those for preparing **50** from **50-4R**, and by prep-HPLC (basic condition) for separation. Compounds **52** and **53** are shown above with relative stereochemistry arbitrarily assigned. **52**: MS: m/z 565.1 $[M+H]^+$; **53**: MS: m/z 565.1 $[M+H]^+$.

EXAMPLE 40
Preparation of Compound 54



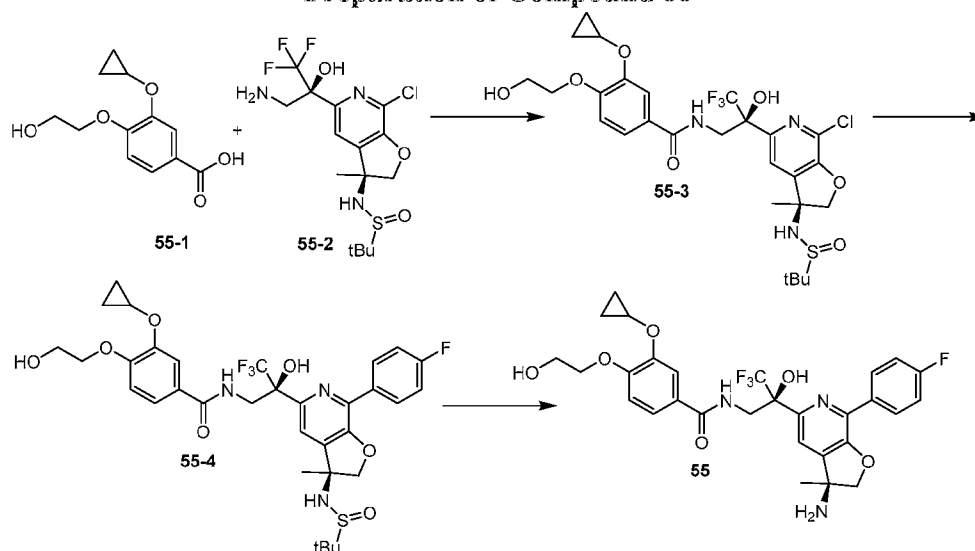
[0338] Compound **54-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1.

[0339] To a solution of **54-1** (900 mg, 4.6 mmol) in DMF (8 mL) was added TFAA (1.06 g, 5.0 mmol) at 0 °C. The solution was slowly warmed to 25 °C and stirred for 2 h. The mixture was poured into water (30 mL), and the precipitate was collected. The precipitate was dried to afford **54-2** (1.1 g, 82.1%) as a yellow solid. MS: m/z 293,295 $[M+H]^+$.

[0340] A mixture of **54-2** (1.0 g, 3.4 mmol), 4-F-Phenylboronic acid (954 mg, 6.8 mmol), Cs_2CO_3 (1.67 g, 5.1 mmol) and $Pd(dppf)Cl_2$ (250 mg, 0.34 mmol) in dioxane (10 mL) and H_2O (2 mL) was heated to 130 °C under microwave with stirring for 0.5 h. The mixture was cooled to RT, diluted with water (50 mL) and EA (50 mL). The organic phase was washed with brine, concentrated and purified by column chromatography using 10% EA in PE to give **54-3** (721 mg, 68.6%) as a yellow solid. MS: m/z 308.8 $[M+H]^+$.

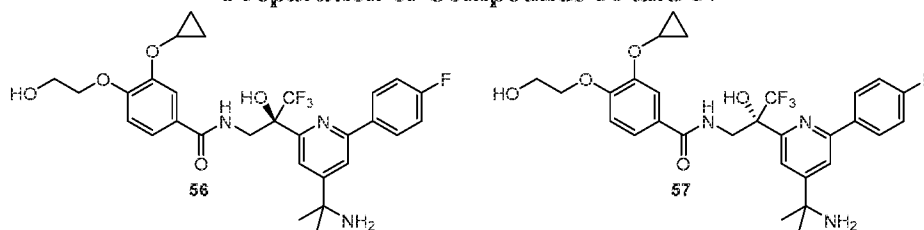
[0341] Compound **54** (66 mg, a pale yellow solid) was prepared using methods similar to those for preparing **50** from **54-3**. MS: m/z 533.9 $[M+H]^+$.

EXAMPLE 41
Preparation of Compound 55

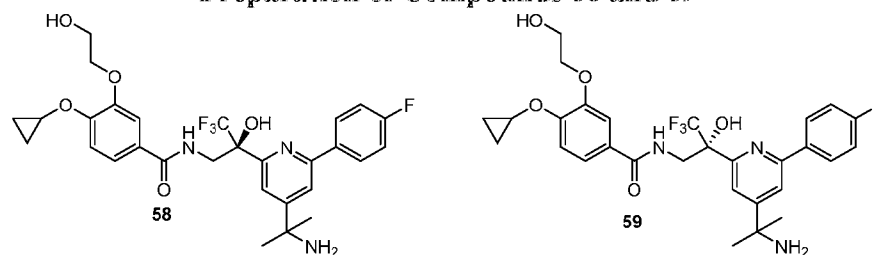


[0342] Compound **55-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound **55** (46 mg, a pale yellow solid) was prepared using methods similar to those for preparing **21** from **55-1** and **55-2**. MS: m/z 592.0 $[M+H]^+$.

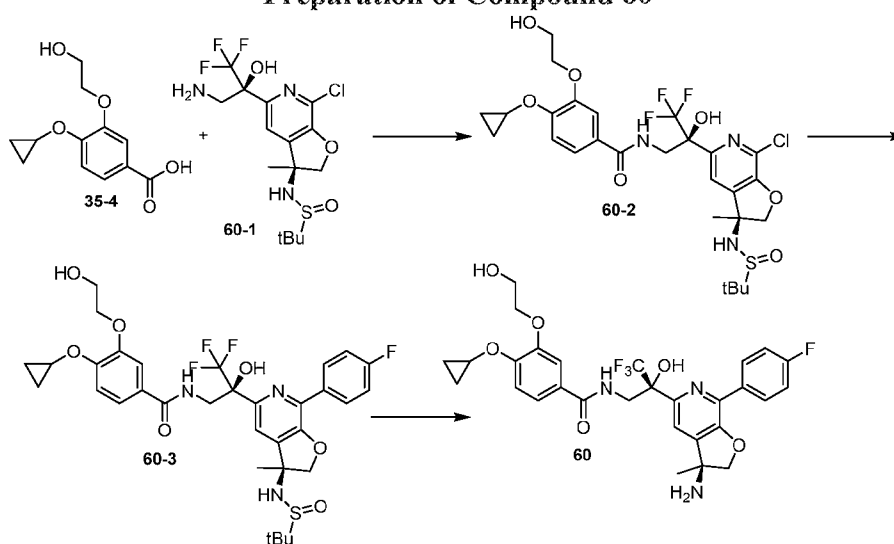
EXAMPLE 42
Preparation of Compounds 56 and 57



[0343] Compound **34** (37 mg) was separated by SFC (Column: Lux Cellulose-2 150×4.6mm I.D., 3 μ m; Mobile phase: A: CO₂ B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5.5min and hold 40% for 3 mins, then 5% of B for 1.5 min; Flow rate: 2.5mL/min Column temperature: 40 °C) and HPLC to give **56** (13.1 mg) and **57** (13.2 mg). **56**: MS: m/z 578.0 $[M+H]^+$; **57**: MS: m/z 578.0 $[M+H]^+$.

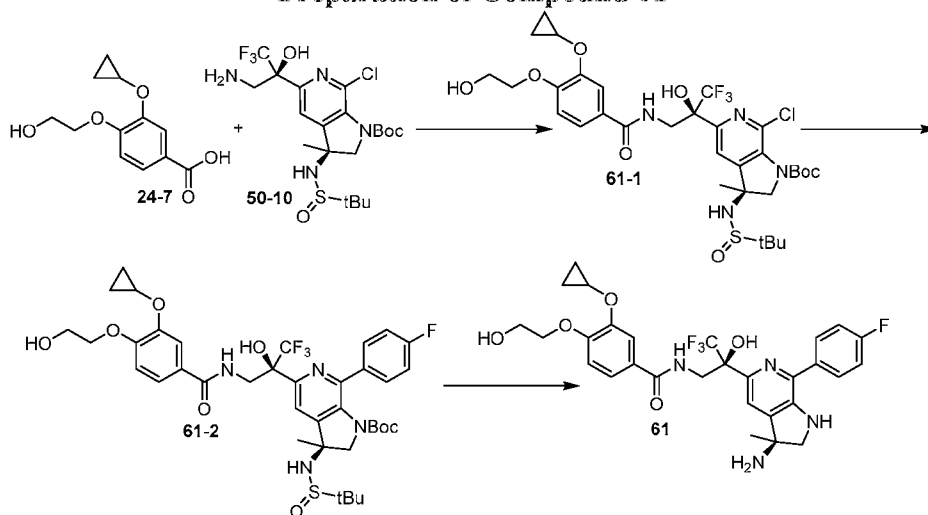
EXAMPLE 43**Preparation of Compounds 58 and 59**

[0344] Compound **36** (73 mg) was separated by SFC (Column: Lux Cellulose-2 150×4.6mm I.D., 3 μ m; Mobile phase: A: CO₂ B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5.5min and hold 40% for 3 mins, then 5% of B for 1.5 mins; Flow rate: 2.5mL/min Column temperature: 40 °C) and HPLC to give **58** (17.1 mg) and **59** (17.3 mg). **58**: MS: m/z 578.1 [M+H]⁺; **59**: m/z 578.1 [M+H]⁺.

EXAMPLE 44**Preparation of Compound 60**

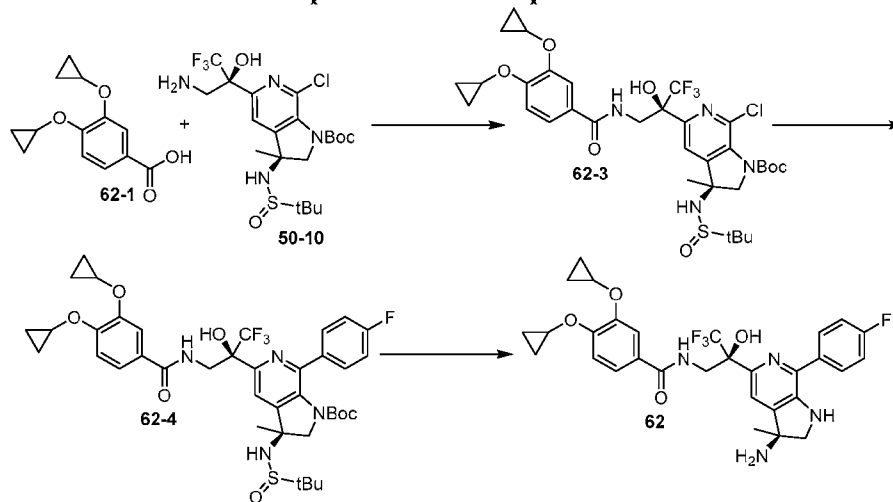
[0345] Compound **60-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound **60** (35.2 mg, a pale yellow solid) was prepared using methods similar to those for preparing **21** from **35-4** and **60-1**. MS: m/z 592.1 [M+H]⁺.

EXAMPLE 45
Preparation of Compound 61

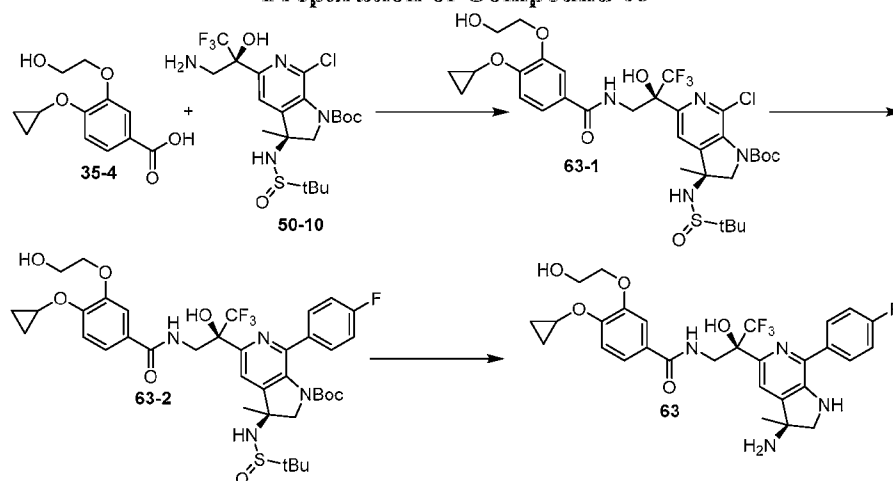


[0346] Compound **61** (35.2 mg, a pale yellow solid) was prepared using methods similar to those for preparing **21** from **27-47** and **50-10**. MS: m/z 591.1 $[M+H]^+$.

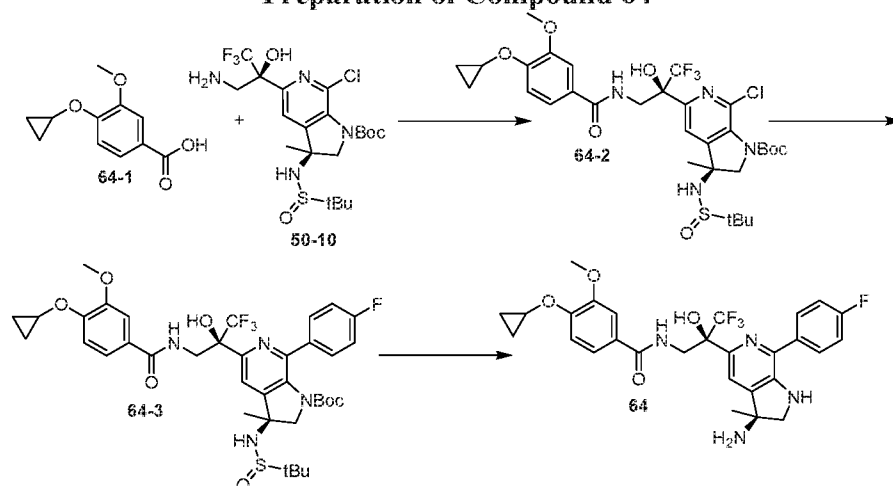
EXAMPLE 46
Preparation of Compound 62



[0347] Compound **62** (11 mg, a pale yellow solid) was prepared using methods similar to those for preparing **21** from **62-1** and **50-10**. MS: m/z 609.1 $[M+Na]^+$.

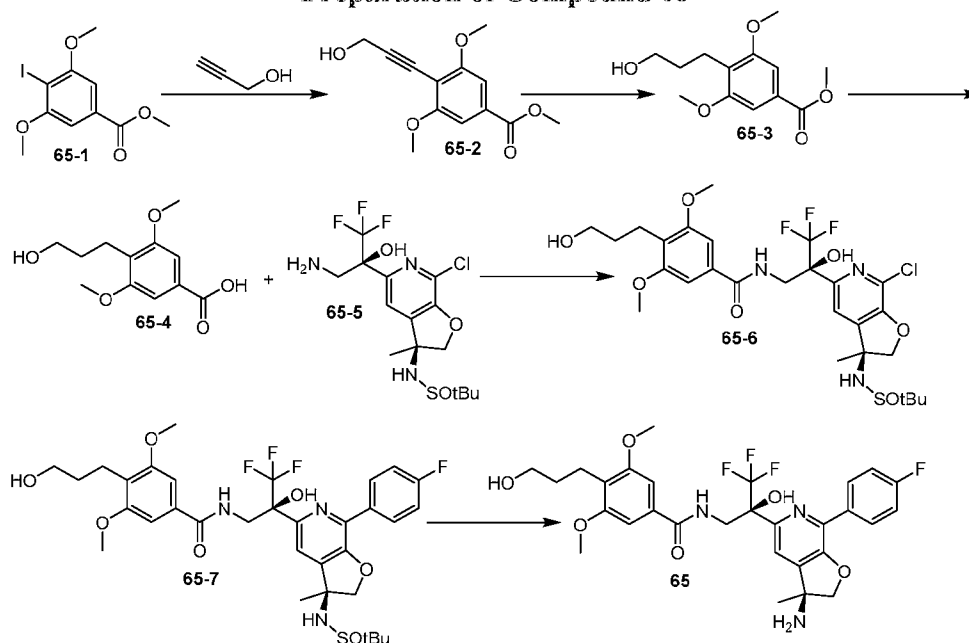
EXAMPLE 47**Preparation of Compound 63**

[0348] Compound **63** (15 mg, a pale yellow solid) was prepared using methods similar to those for preparing **21** from **35-4** and **50-10**. MS: m/z 613.2 $[M+Na]^+$.

EXAMPLE 48**Preparation of Compound 64**

[0349] Compound **64-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound **63** (46 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **64-1** and **50-10**. MS: m/z 561.1 $[M+H]^+$.

EXAMPLE 49
Preparation of Compound 65



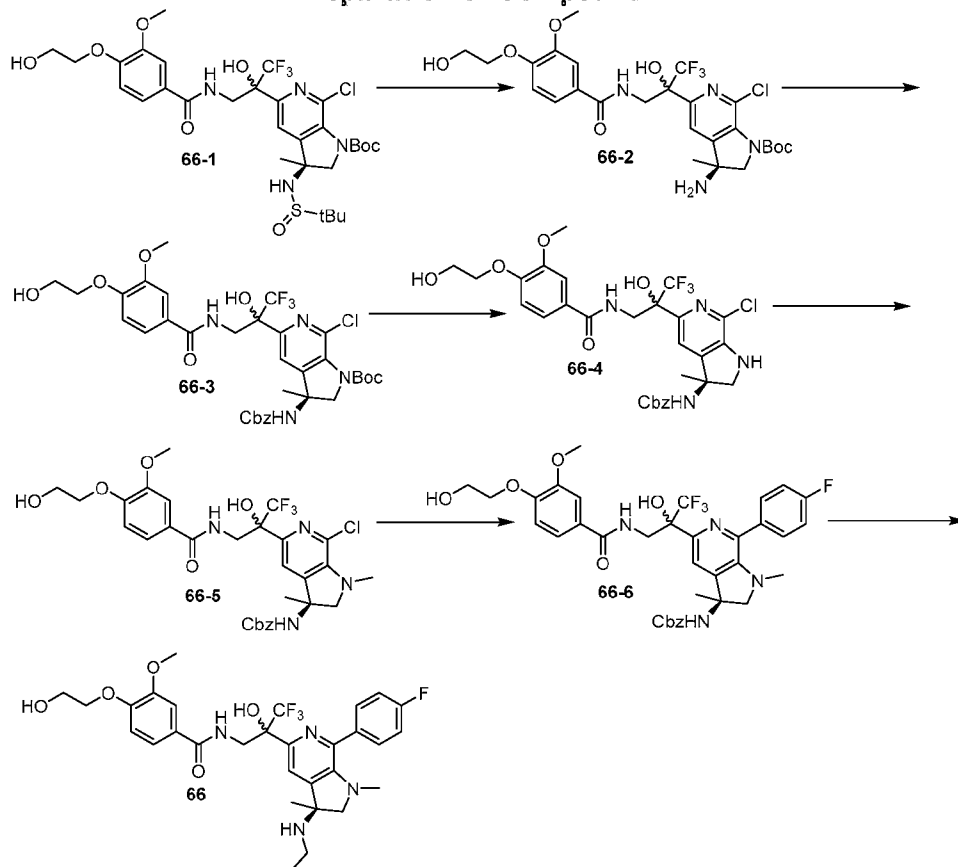
[0350] Compound **65-1** was prepared according to a similar procedure as provided in Chiummiento et al., *European Journal of Organic Chemistry* (2012) 2012(1):188-192, and compound **65-5** was prepared according to a similar procedure as provided in WO 2015/26792 A1.

[0351] A mixture of **65-1** (3.22 g, 10 mmol), prop-2-yn-1-ol (1.12 g, 20 mmol), Pd(PPh₃)₂Cl₂ (351 mg, 0.5 mmol), CuI (190 mg, 1 mmol), PPh₃ (262 mg, 1 mmol) and TEA (50 mL) in DMF (100 mL) was heated to 60 °C for 12 h under N₂ with stirring. The reaction was cooled to RT, poured into water (200 mL), and extracted with EA (2 X 50 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography using 20~50% EA in PE to give **2** (1.9 g, 76%) as a pale yellow solid. MS: m/z 250.9 [M+H]⁺.

[0352] A mixture of **65-2** (1.9 g, 7.6 mmol) and Pd/C (10%, 200 mg) in MeOH (100 mL) was stirred at RT under hydrogen (45 PSI) for 12 h. The mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography using 20% EA in PE to give **65-3** (1.3 g, 67.4%) as a white solid. MS: m/z 254.9 [M+H]⁺.

[0353] Compound **65** (52.6 mg, a white solid) was prepared using methods similar to those for preparing **21** from **65-3** and **65-5**. MS: m/z 616.1 [M+Na]⁺.

EXAMPLE 50
Preparation of Compound 66



[0354] To a solution of **66-1** (150 mg, 0.21 mmol) in MeOH (3 mL) was added HCl/MeOH (4 M, 105 μ L) at 25 $^{\circ}$ C. The mixture was stirred at 25 $^{\circ}$ C for 1 h. The reaction was quenched by the addition of a sat. NaHCO₃ solution and extracted with EA (2 X 10 mL). The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated to give **66-2** (130 mg, crude) as a white solid. MS: m/z 627.2 [M+Na]⁺.

[0355] A mixture of **66-2** (130 mg, crude), CbzCl (73 mg, 0.43 mmol), NaHCO₃ (72 mg, 0.86 mmol) in DCM (10 mL) and H₂O (5 mL) was stirred at 25 $^{\circ}$ C for 1 h. The mixture was diluted with EA (30 mL) and water (30 mL). The organic phase was separated, washed with brine, dried over Na₂SO₄, filtered and concentrated to give **66-3** (160 mg, crude) as a colorless oil. MS: m/z 739.1 [M+H]⁺.

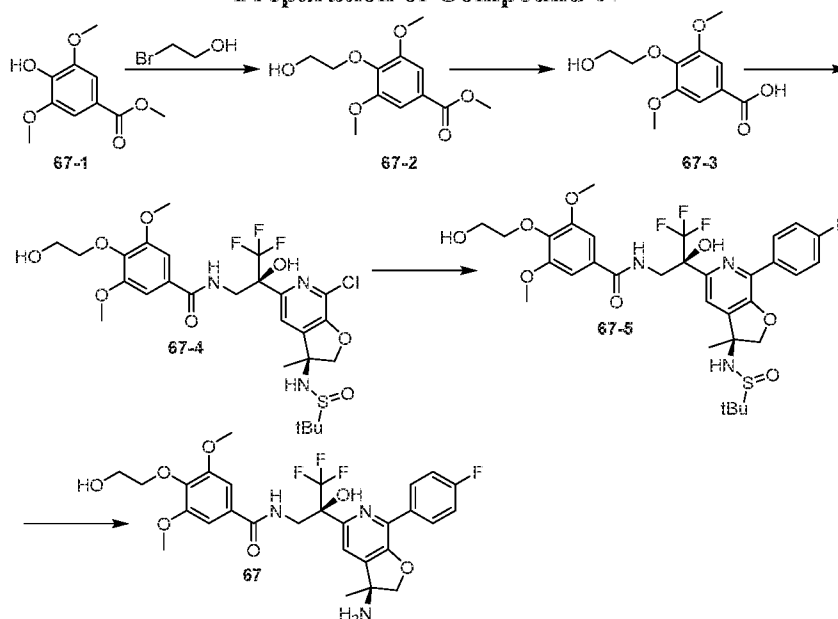
[0356] A mixture of **66-3** (160 mg, crude) in HCl/MeOH (4 M, 5 mL) was stirred at 25 °C for 1 h. The mixture was concentrated to give **66-4** (120 mg, crude) as a yellow oil. MS: m/z 639.1 $[M+H]^+$.

[0357] To a stirring solution of **66-4** (100 mg, crude), aq. HCHO (0.11 mL, 38%) and AcOH (0.1 mL) in MeOH (10 mL) was added NaBH₃CN (30 mg, 0.47 mmol) at RT. The mixture was stirred for 16 h, diluted with water (30 mL) and extracted with EA (2 X 20 mL). The organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 50~100% EA in PE to give **66-5** (81 mg) as a colorless oil. MS: m/z 653.1 $[M+H]^+$.

[0358] A mixture of **66-5** (81 mg, 0.12 mmol), 4-F-phenyl boronic acid (34 mg, 0.24 mmol), Pd(PPh₃)₄ (7.1 mg, 0.006 mmol) and K₂CO₃ (17 mg, 0.12 mmol) in dioxane (3 mL) and H₂O (0.5 mL) was heated to 110 °C by microwave and stirred for 30 mins. The reaction was cooled to RT, diluted with EA (10 mL) and water (10 mL). The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated to give **66-6** (71 mg, crude) as a yellow solid. MS: m/z 713.1 $[M+H]^+$.

[0359] A mixture of **66-6** (71 mg, crude) and Pd/C (10%, 20 mg) in EtOH (10 mL) was stirred under H₂ (15 Psi) at RT for 16 h. The mixture was concentrated, and the residue was purified by prep-HPLC (basic condition) to give **66** (11 mg) as a white solid. MS: m/z 629.1 $[M+Na]^+$.

EXAMPLE 51
Preparation of Compound 67

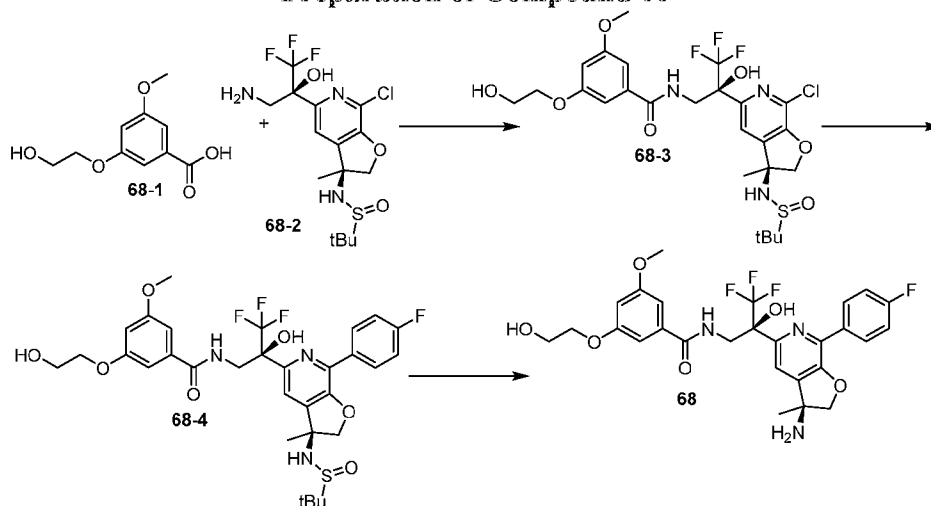


[0360] Compound 67-1 was prepared according to a similar procedure as provided in EP2786986 A2.

[0361] To a solution of 67-1 (2.1 g, 10 mmol) in DMF (20 mL) was added NaH (60%, 400 mg, 10 mmol) at 0 °C. The mixture was stirred for 30 mins, followed by addition of bromoethanol (3.12 g, 25 mmol). The reaction was stirred at 80 °C for 2 h, and cooled to RT. The reaction was quenched with H₂O, and extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrate. The residue was purified by column chromatography using 10~20% EA in PE to give 67-2 (1.9 g, 74%) as a white solid. MS: m/z 256.9 [M+H]⁺.

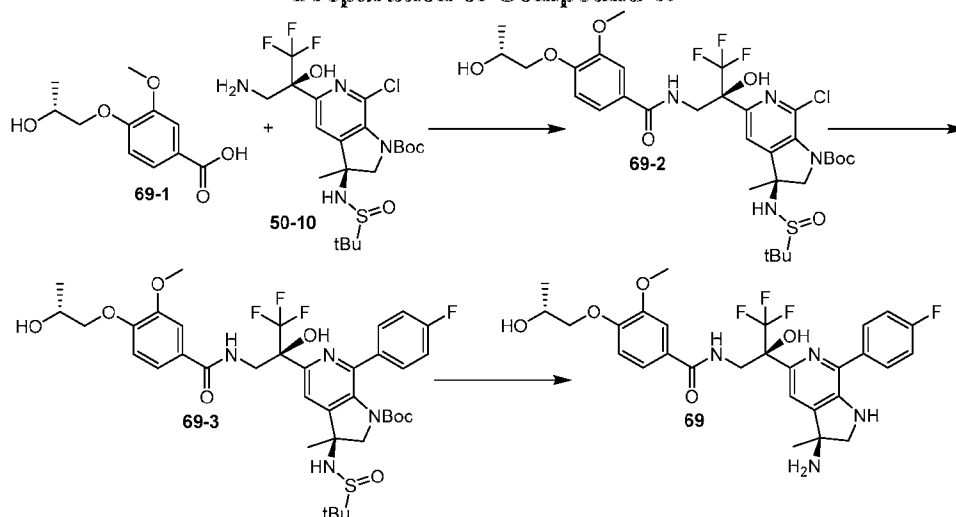
[0362] Compound 67 (57 mg, a white solid) was prepared using methods similar to those for preparing 21 from 67-1 and phenyl boronic acid. MS: m/z 596.1 [M+H]⁺.

EXAMPLE 52
Preparation of Compound 68



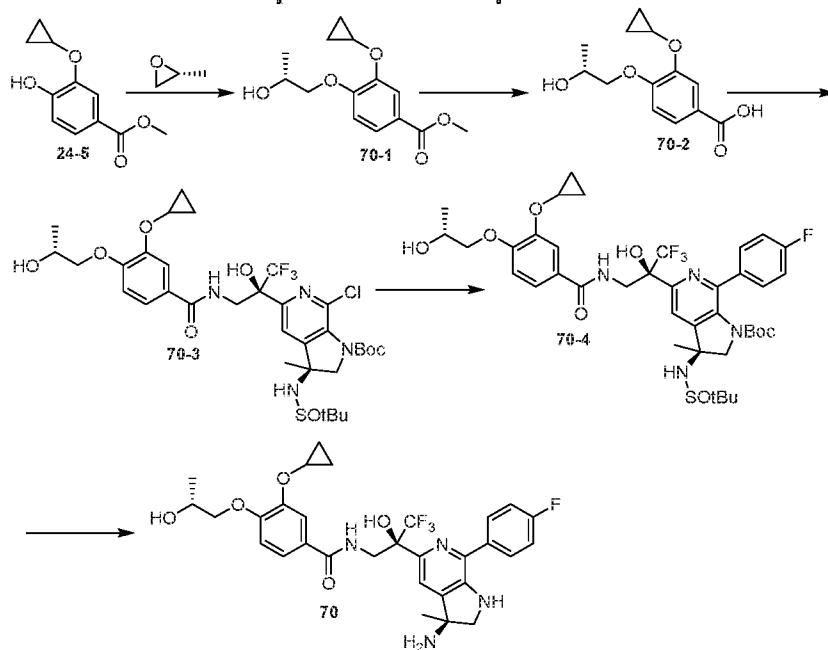
[0363] Compound **68-1** was prepared according to a similar procedure as provided in WO 2013/41457 A1, and compound **68-2** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound **68** (22 mg, a pale yellow solid) was prepared using methods similar to those for preparing **21** from **68-1** and **68-2**. MS: m/z 566.1 $[M+H]^+$.

EXAMPLE 53
Preparation of Compound 69



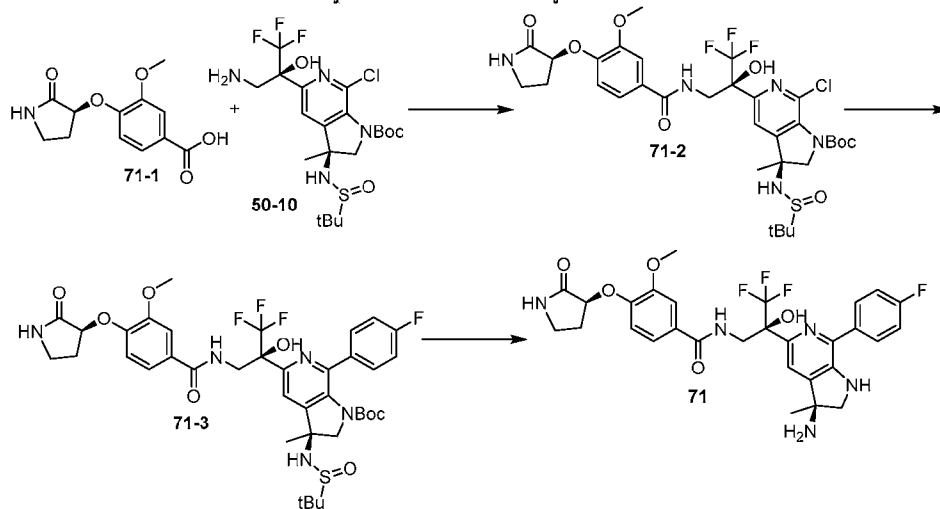
[0364] Compound **69-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound **69** (17 mg, a white solid) was prepared using methods similar to those for preparing **21** from **69-1** and **50-10**. MS: m/z 579.1 $[M+H]^+$.

Preparation of Compound 70



[0365] Compound **70** (21 mg, a white solid) was prepared using methods similar to those for preparing **21** and **38** from **24-5**. MS: m/z 605.1 [M+H]⁺.

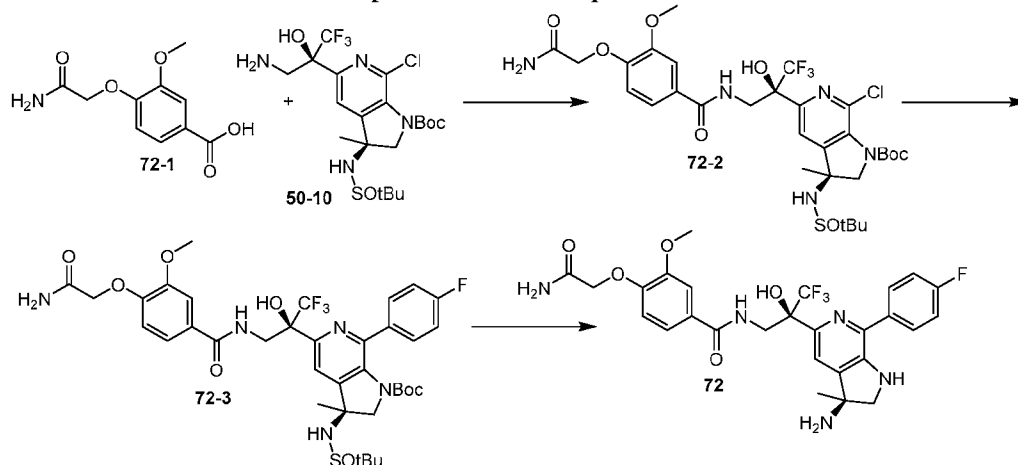
Preparation of Compound 71



[0366] Compound **71-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound **71** (2.1 mg, a white solid) was prepared using methods similar to those for preparing **50** from **71-1** and **50-10**. MS: m/z 626.3 $[M+Na]^+$.

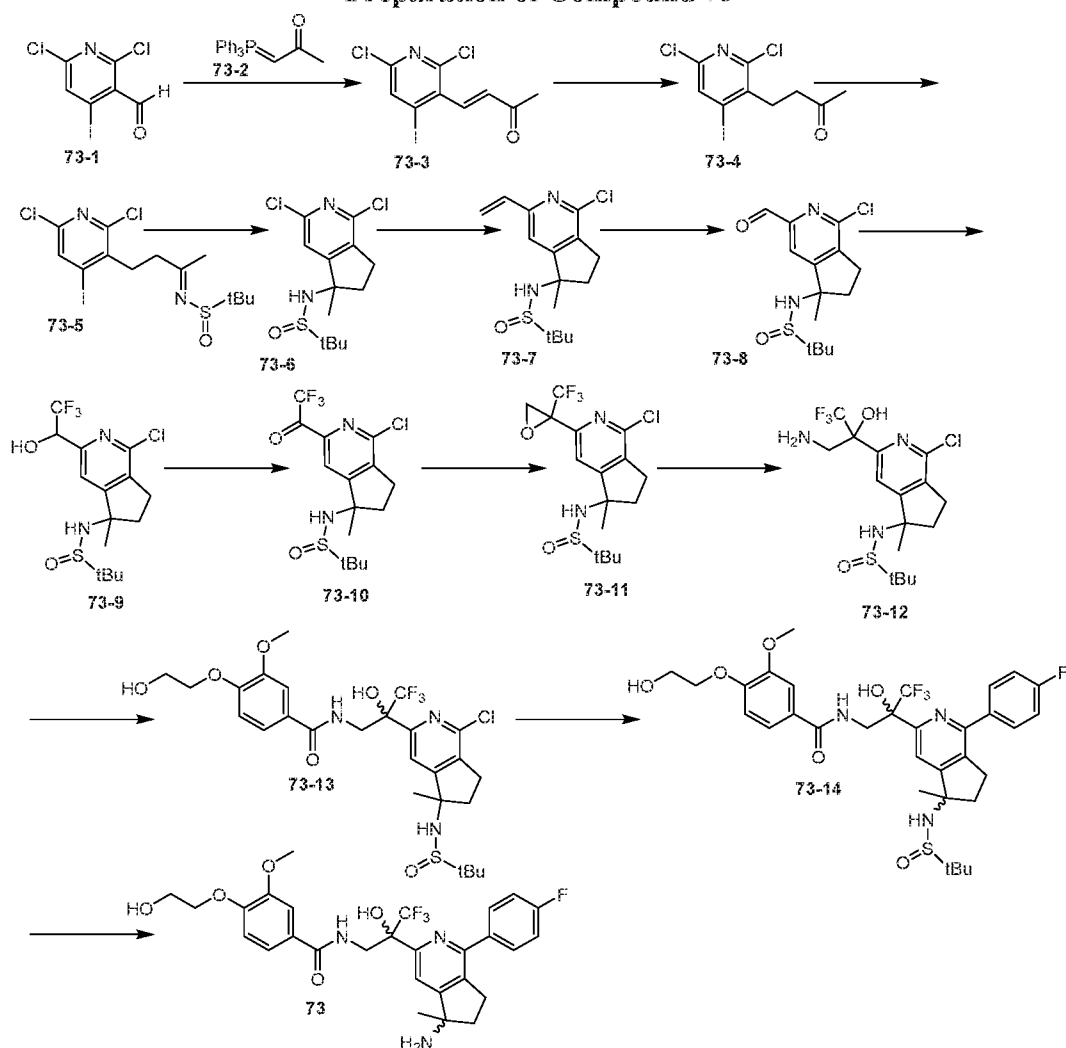
EXAMPLE 56

Preparation of Compound 72



[0367] Compound **72-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound **72** (20 mg, a white solid) was prepared using methods similar to those for preparing **50** from **72-1** and **50-10**. MS: m/z 578.2 $[M+H]^+$.

EXAMPLE 57
Preparation of Compound 73



[0368] Compound 73-1 was prepared according to a similar procedure as provided in Panda et al., Synlett (2011) 11(5):689-693, and Compound 73-1 was prepared according to a similar procedure as provided in Maeno et al., Chemistry Letters (2012) 41(8):801-803.

[0369] A mixture of 73-1 (4.5 g, 14.9 mmol) and 73-2 (4.75 g, 14.9 mmol) in THF (100 mL) was stirred at 25 °C for 2 h. The mixture was then concentrated and purified by column chromatography using 5~10% EA in PE to give 73-33 (4.7 g, 92.2%) as a bright yellow solid. MS: m/z 341.9 [M+H]⁺.

[0370] A mixture of 73-3 (2.3 g, 6.73 mmol) and Rh(PPh₃)₃Cl (933 mg, 1.01 mmol) in EtOH (20 mL) was stirred under H₂ (50 Psi) at 25 °C for 48 h. The mixture was

concentrated and purified by column chromatography using 5~10% EA in PE to give **73-4** (1.5 g, 65%). MS: m/z 343.9 $[M+H]^+$.

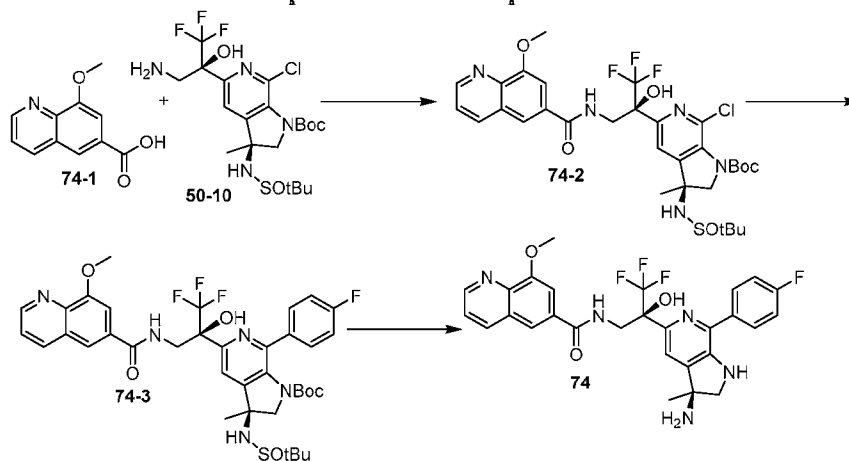
[0371] A mixture of **73-4** (1.0 g, 2.91 mmol), 2-methylpropane-2-sulfinamide (423 mg, 3.49 mmol) and $Ti(OEt)_4$ (1.39 g, 6.11 mmol) in THF (30 mL) was stirred at 80 °C for 2 h. The mixture was concentrated. The residue was dissolved in EA (20 mL) and poured into aq. $NaHCO_3$ (20 mL) with stirring for 2 mins. The mixture was filtered through a celite pad. The filtered cake was washed with EA (2 X 50 mL). The combined organic phase was concentrated and purified by flash column using 5~20% EA in PE to give **73-5** (1.0 g, 77%). MS: m/z 446.9 $[M+H]^+$.

[0372] $n-BuLi$ (2.5 M, 2.69 mL) was added to a solution of $EtMgBr$ (3 M, 1.12 mL) in dry THF (30 mL) dropwise at 0 °C. After stirring for 10 mins, the mixture was cooled to -78 °C. A solution of **73-5** (1.0 g, 2.24 mmol) in dry THF (5 mL) was added to the above solution dropwise. After addition, the reaction was stirred at -78 °C for 30 mins, quenched with water (10 mL) and extracted with EA (2 X 50 mL). The organic phase was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 5~10% EA in PE to give **73-6** (450 mg, 62.5%) as a yellow oil. MS: m/z 321.0 $[M+H]^+$.

[0373] Compound **73** (3.2 mg, a yellow solid) was prepared using methods similar to those for preparing **50** from **73-6**. MS: m/z 564.1 $[M+H]^+$.

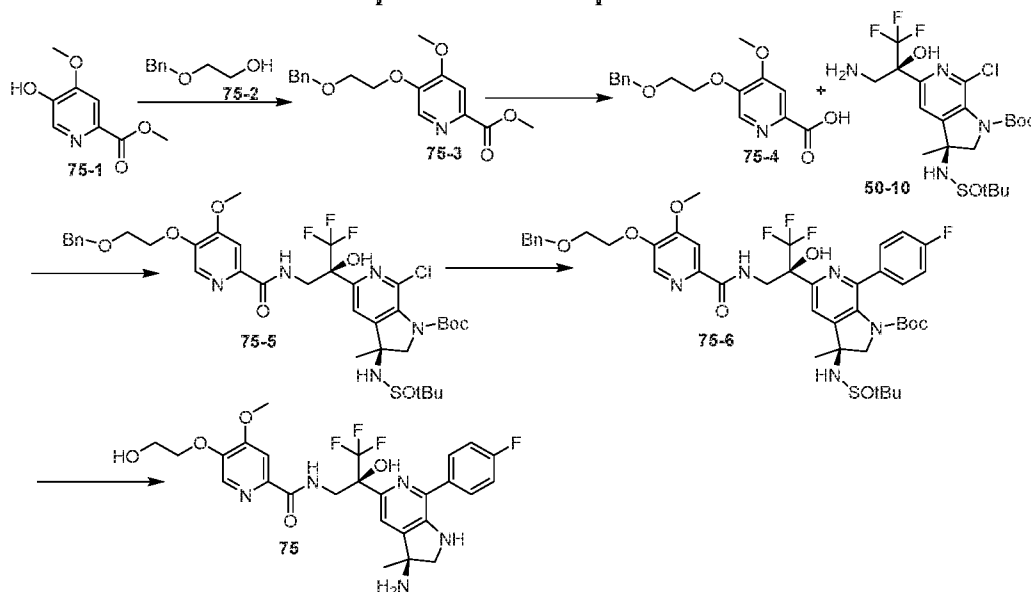
EXAMPLE 58

Preparation of Compound 74

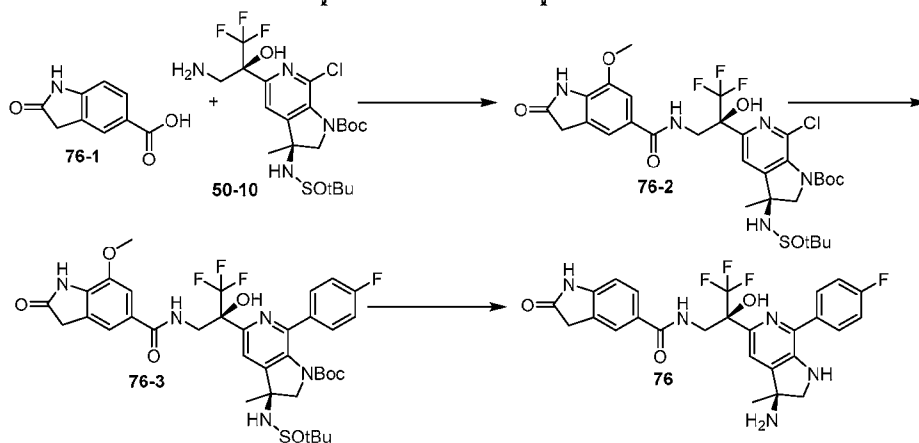


[0374] Compound **74-1** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compound **74** (8 mg, a white solid) was prepared using methods similar to those for preparing **50** from **74-1** and **50-10**. MS: m/z 556.2 $[M+H]^+$.

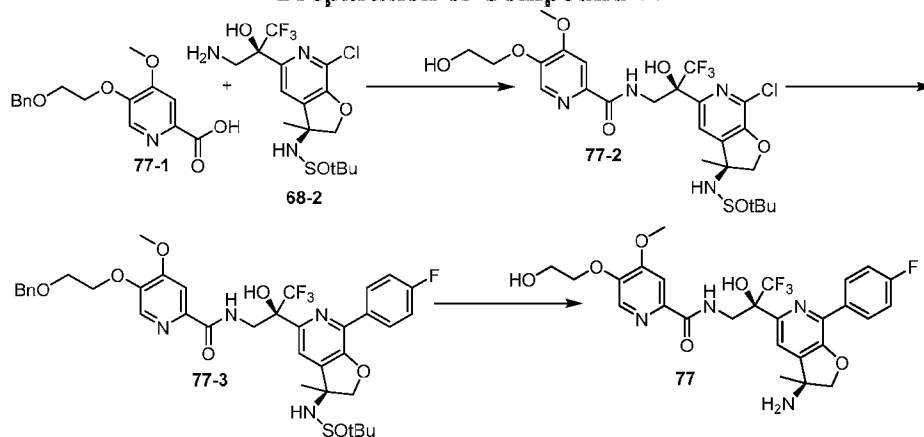
EXAMPLE 59 Preparation of Compound **75**



[0375] Compound **75-1** was prepared according to a similar procedure as provided in Patt et al., Tetrahedron Letters (1997) 38(8):1297-1300. Compound **75** (12 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **75-1** and **50-10**. MS: m/z 566.1 $[M+H]^+$.

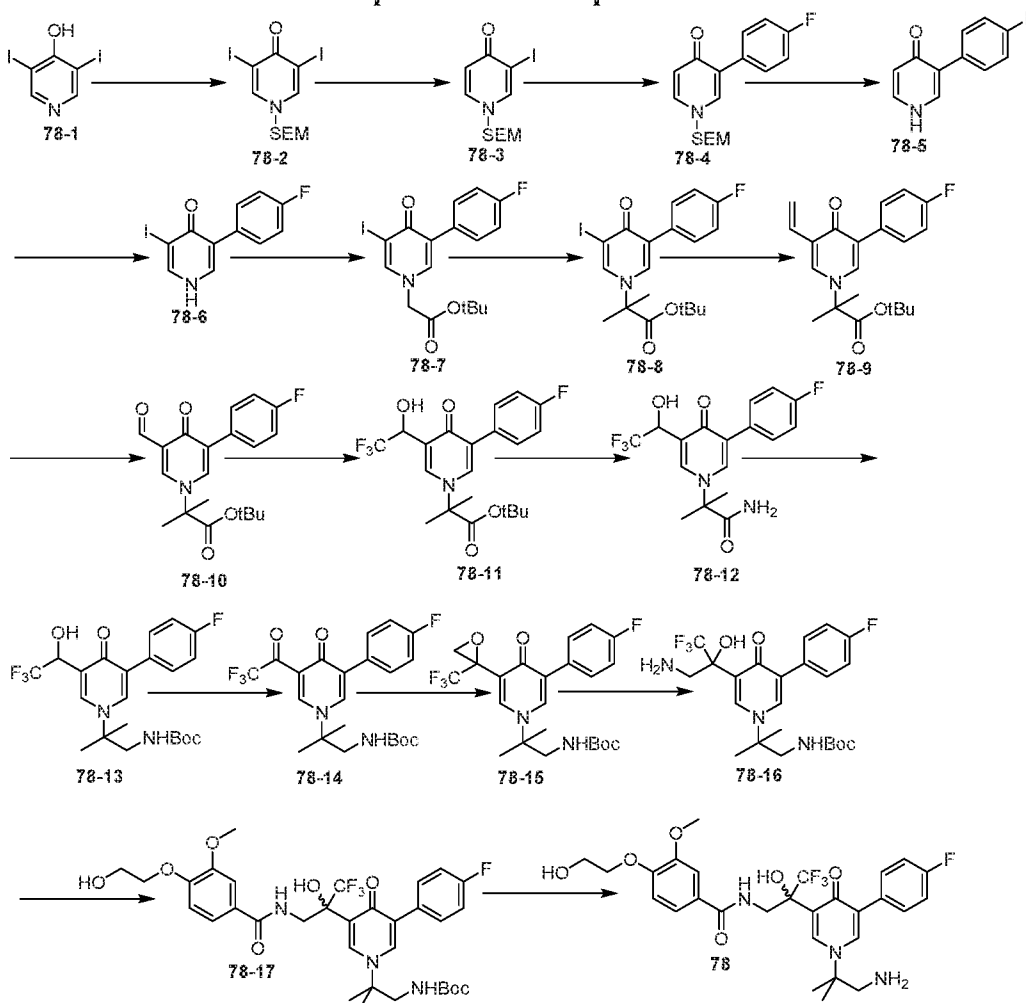
EXAMPLE 60**Preparation of Compound 76**

[0376] Compound **76** (8 mg, a white solid) was prepared using methods similar to those for preparing **21** from **76-1** and **50-10**. MS: m/z 531.2 $[M+H]^+$.

EXAMPLE 61**Preparation of Compound 77**

[0377] Compound **77** (9.7 mg, a white solid) was prepared using methods similar to those for preparing **21** from **77-1** and **68-2**. MS: m/z 567.1 $[M+H]^+$.

EXAMPLE 62
Preparation of Compound 78



[0378] Compound **78-1** was prepared according to a similar procedure as provided in Rousseau et al., *Tetrahedron Letters* (1997) 38(14):2467-2470.

[0379] To a stirring solution of **78-1** (67 g, 193 mmol) in DMF (50 mL) was added NaH (60%, 11.6 g, 290 mmol) in portion at 0 °C. After 30 mins, SEM-Cl (38.6 g, 231.77 mmol) was added dropwise and stirred for 1 h at 25 °C. The reaction was quenched with aq. NH₄Cl, and extracted with EA (3 X 200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 10% EA in DCM to give **78-2** (84 g, 91.2%) as a white solid. MS: m/z 477.9 [M+H]⁺.

[0380] To a stirring solution of **78-2** (84 g, 176 mmol) in THF (500 mL) was added i-PrMgCl (2 M, 132 mL) dropwise at -78 °C for 1 h. The reaction was quenched aq. NH₄Cl, and extracted with EA (3 X 300 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give crude **78-3** (51 g, crude) as a red oil. MS: m/z 351.9 [M+H]⁺.

[0381] A mixture of **78-3** (50 g, crude), 4-F-phenyl boronic acid (23.9 g, 170.8 mmol), Pd(dppf)Cl₂ (5.2 g, 7.1 mmol) and Cs₂CO₃ (92.8 g, 285 mmol) in dioxane (500 mL) and H₂O (50 mL) was stirred at 80 °C for 12 h under N₂. The reaction was cooled to RT, and extracted with EA (3 X 500 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 50% EA in DCM to give **78-4** (40.7 g, 90.4%) as a yellow oil. MS: m/z 319.9 [M+H]⁺.

[0382] To a solution of **78-4** (40.7 g, 125 mmol) in THF (300 mL) was slowly added HCl (12 M, 120 mL). The mixture was stirred at 25 °C for 1 h, neutralized by NaHCO₃, and extracted with EA (3 X 200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give **78-5** (28.3 g, crude) as a red oil. MS: m/z 190.0 [M+H]⁺.

[0383] A mixture of **78-5** (28 g, crude) and NIS (40 g, 177.6 mmol) in CH₃CN (400 mL) was stirred at 80 °C for 12 h. The mixture was cooled to RT, and the reaction was quenched with aqueous Na₂SO₃. A brown precipitate was formed and collected by filtration. The precipitate was dried to give **78-6** (35 g, 75.1%) as a brown solid. MS: m/z 315.9 [M+H]⁺.

[0384] To a solution of **78-6** (32 g, 101.6 mmol) in THF (400 mL) was added NaH (60%, 6.5 g, 163 mmol) in portions at 0 °C. The mixture was stirred at 0 °C for 30 mins, followed by addition of tert-butyl 2-bromoacetate (25.8 g, 132 mmol) dropwise. The reaction was stirred at 25 °C for 1.5 h, quenched with aq. NH₄Cl, and extracted with EA (3 X 300 mL). The Combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 10% EA in DCM to give **78-7** (35 g, 80.3%) as a yellow solid. MS: m/z 429.9 [M+H]⁺.

[0385] To a solution of **78-7** (35 g, 81.5 mmol) in THF (400 mL) was added NaHMDS (1 M, 489 mL) at -78 °C. After 30 mins, MeI (116 g, 815 mmol) was

added, and the mixture was stirred at -78 °C for 2 h. The reaction was quenched by aq. NH_4Cl , and extracted with EA (3 X 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 10% EA in DCM to give **78-8** (28 g, 75.1%) as a red oil. MS: m/z 458.1 $[\text{M}+\text{H}]^+$.

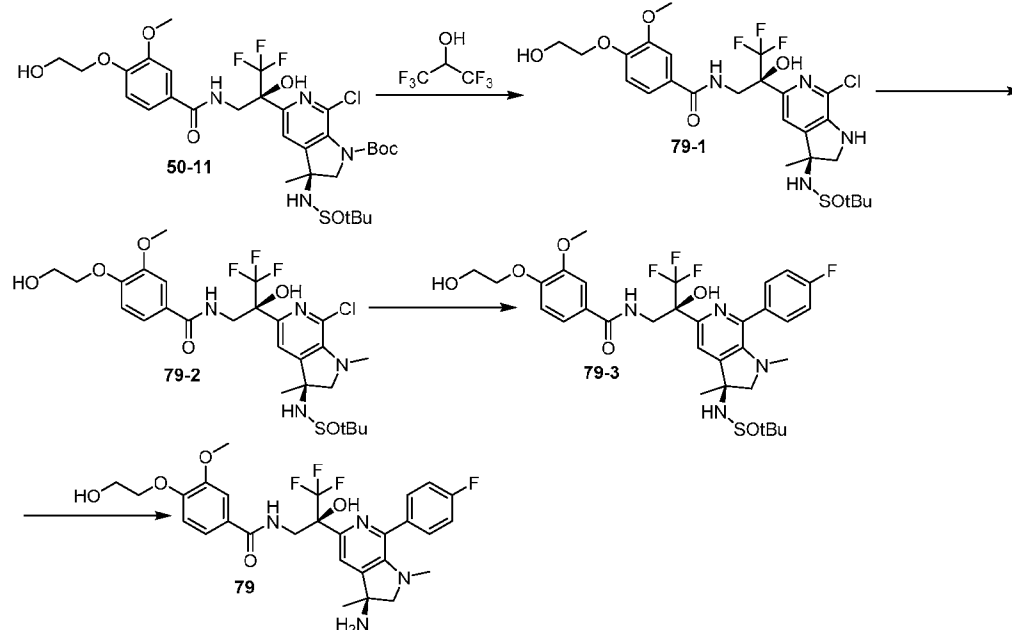
[0386] Compound **78-11** was prepared using methods similar to those for preparing **51** from **78-8**.

[0387] A solution of **78-11** (8.1 g, 18.9 mmol) in HCl/MeOH (4 M, 41 mL) was stirred at 70 °C for 2 h and concentrated. The residue was neutralized by aq. NaHCO_3 , and extracted with EA (2 X 50 mL). The organic phase was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 20% EA in DCM to give the methyl ester (6.0 g, 81.8%) as a yellow oil. A mixture of the methyl ester (6.0 g, 15.5 mmol) in NH_3/MeOH (7 M, 50 mL) was stirred at 60 °C in a sealed vial for 18 h. The reaction was concentrated, and the residue was purified by column chromatography using 25% EA in DCM to give **78-12** (4.5 g, 78%) as a yellow oil. MS: m/z 372.9 $[\text{M}+\text{H}]^+$.

[0388] A mixture of **78-12** (1.5 g, 4 mmol) in $\text{BH}_3\text{-THF}$ (1 M, 20 mL) was stirred at 80 °C for 1 h. The reaction was quenched by MeOH (50 mL), and the mixture was concentrated. The residue was purified by prep-HPLC to give the amine (50 mg) as a yellow solid. To a solution of the amine in DCM (5 mL) were added TEA (0.1 mL) and $(\text{Boc})_2\text{O}$ (46 mg, 0.21 mmol). The mixture was stirred at 25 °C for 3 h and then concentrated. The residue was purified by prep-TLC (EA:PE=1:1) to give **78-13** (61 mg) as a yellow solid. MS: m/z 458.9 $[\text{M}+\text{H}]^+$.

[0389] Compound **78** (3.5 mg, a white solid) was prepared using methods similar to those for preparing **51** from **78-13**. MS: m/z 582.2 $[\text{M}+\text{H}]^+$.

EXAMPLE 63
Preparation of Compound 79

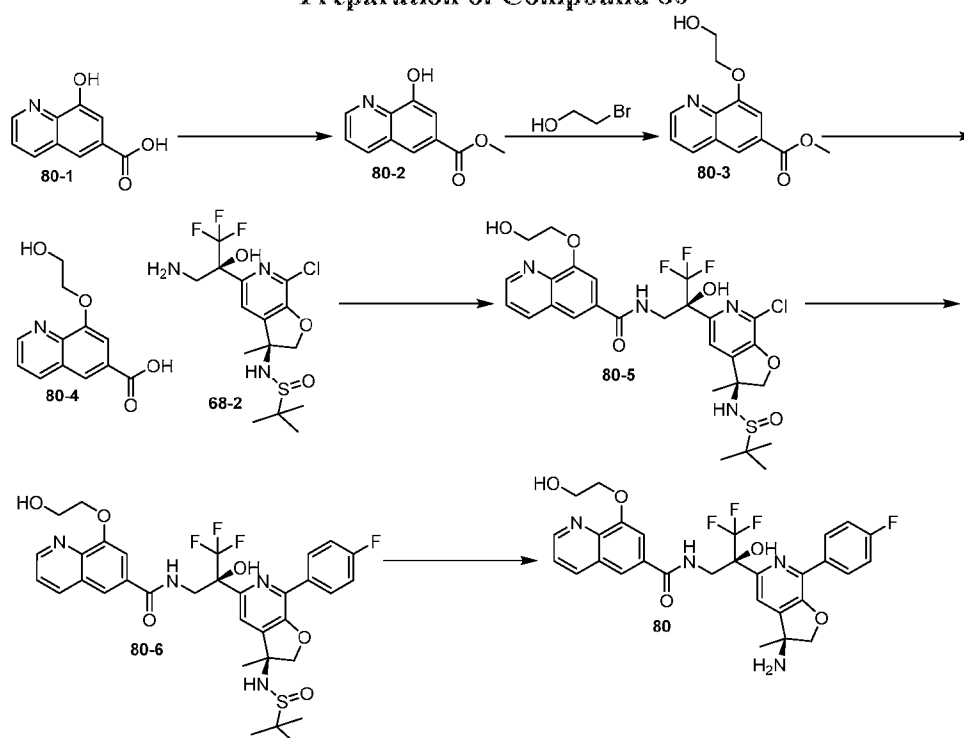


[0390] A mixture of **50-11** (100 mg, 0.14 mmol) in HFIP (1,1,1,3,3,3-Hexafluoro-2-propanol, 1.00 mL) was heated at 90 °C for 20 mins under microwave. The mixture was concentrated and purified by prep-TLC (EA) to give **79-1** (21 mg, 24.5 %) as a colorless oil. MS: m/z 609.1 $[M+H]^+$.

[0391] A mixture of **79-1** (21 mg, 0.033 mmol), aq. HCHO (0.8 mL, 35%) and NaBH_3CN (90 mg, 1.43 mmol) in MeOH (5 mL) was stirred at 25 °C for 24 h. The mixture was concentrated and purified by prep-TLC (DCM: MeOH = 20:1) to give **79-2** (18 mg, 88%) as a white solid. MS: m/z 623.1 $[M+H]^+$.

[0392] Compound **79** (8.5 mg, a white solid) was prepared using methods similar to those for preparing **51** from **79-2**. MS: m/z 579.1 $[M+H]^+$.

EXAMPLE 64
Preparation of Compound 80



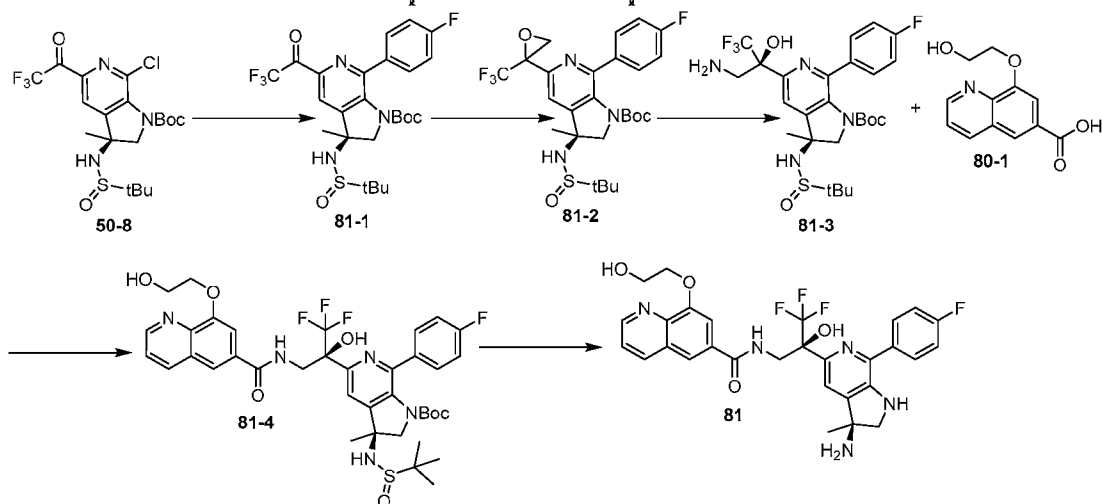
[0393] Compound **80-1** was prepared according to a similar procedure as provided in Sosič et al., *Journal of Medicinal Chemistry* (2013) 56(2):521-533.

[0394] To a solution of **80-1** (2 g, 10.6 mmol) in MeOH (60 mL) was added SOCl_2 (10 mL) slowly. The mixture was heated to 70 °C for 12 h and concentrated to give crude **80-2** (1.08 g, crude) as a white solid. MS: m/z 204.1 $[\text{M}+\text{H}]^+$.

[0395] A mixture of **80-2** (1.08 g, crude), K_2CO_3 (1.4 g, 10.1 mmol) and 2-bromoethanol (4.2 g, 34.2 mmol) in MeCN (10 mL) was stirred at 90 °C for 10 h. The reaction was cooled to RT, filtered, and the filtrate was concentrated. The residue was purified by prep-HPLC (FA condition) to give **80-3** (350 mg) as a white solid. MS: m/z 248.1 $[\text{M}+\text{H}]^+$.

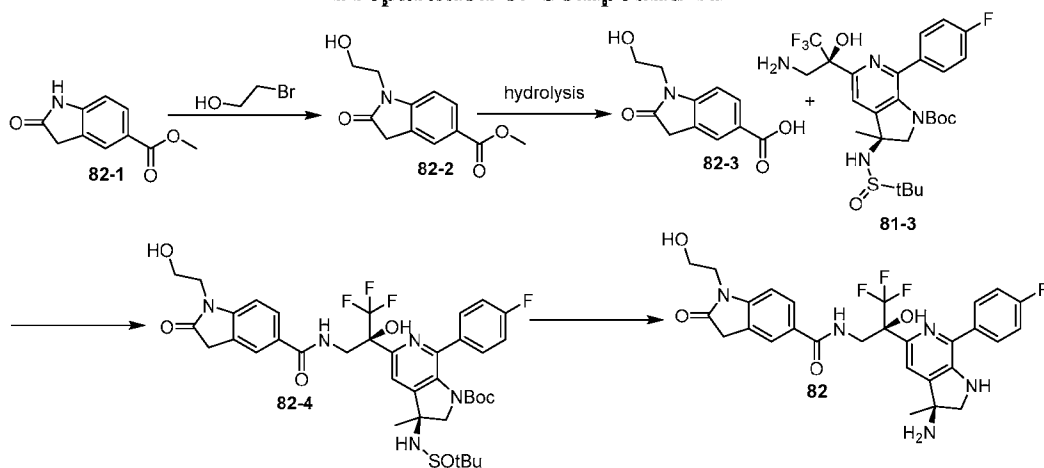
[0396] Compound **80** (26 mg, a white solid) was prepared using methods similar to those for preparing **21** from **80-3** and **68-2**. MS: m/z 587.1 $[\text{M}+\text{H}]^+$.

EXAMPLE 65
Preparation of Compound 81



[0397] Compound **81-3** was prepared using methods similar to those for preparing **51**, and **81-3** was separated by prep-HPLC from the racemic material. Compound **81** (22.5 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **81-3** and **68-2**. MS: m/z 608.1 $[M+Na]^+$.

EXAMPLE 66
Preparation of Compound 82

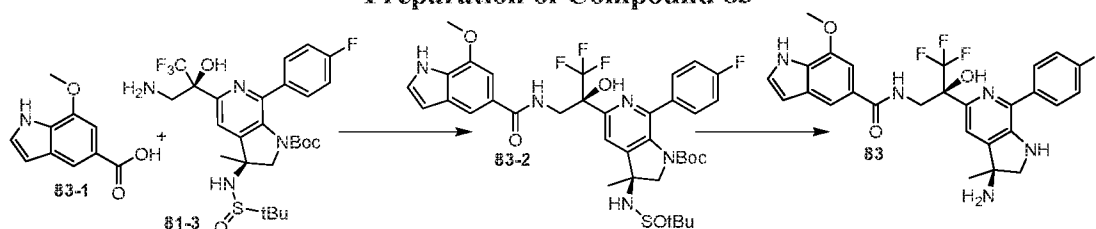


[0398] A mixture of **82-1** (200 mg, 1.05 mmol), K_2CO_3 (435 mg, 3.15 mmol) and bromo-ethanol (260 mg, 2.1 mmol) in DMF (2 mL) was stirred at 80 °C for 4 h. The mixture was cooled to RT, and then diluted with EA (20 mL) and water (30 mL). The organic phase was washed with brine and dried over Na_2SO_4 . The solution was concentrated, and the

residue was purified by prep-TLC (EA:PE = 1:1) to give **82-2** (93 mg, 37.6%) as a white solid. MS: m/z 236.1 $[M+Na]^+$.

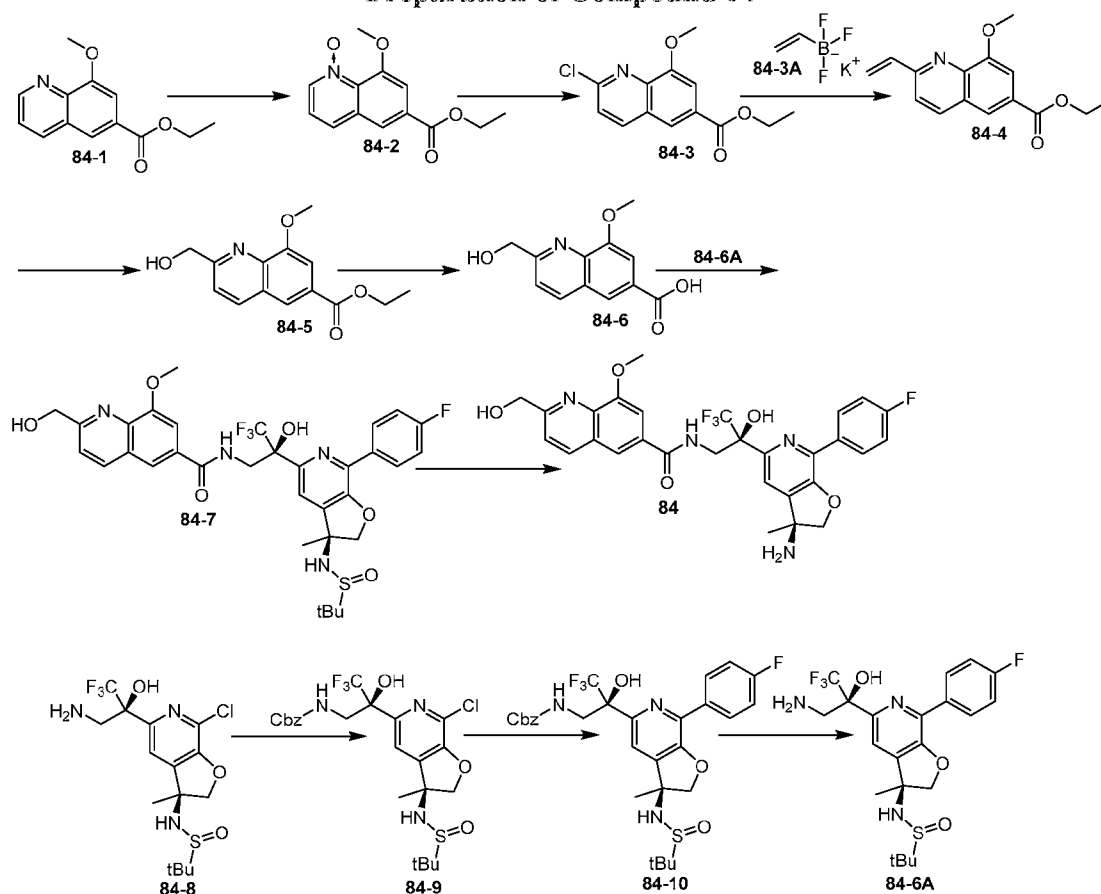
[0399] Compound **82** (14 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **82-2** and **81-3**. MS: m/z 574.1 $[M+H]^+$.

EXAMPLE 67
Preparation of Compound 83



[0400] Compound **83-1** was prepared according to a similar procedure as provided in Ezquerra et al., Journal of Organic Chemistry (1996) 61(17):5804-5812. Compound **83** (32 mg, a yellow solid) was prepared using methods similar to those for preparing **21** from **83-1** and **81-3**. MS: m/z 566.1 $[M+Na]^+$.

EXAMPLE 68
Preparation of Compound 84



[0401] Compound **84-1** was prepared according to a similar procedure as provided in WO 2010/132615 A1, and compound **84-8** was prepared according to a similar procedure as provided in WO 2015/26792 A1.

[0402] To a mixture of **84-1** (2.0 g, 8.65 mmol) in CHCl_3 (10 mL) was added m-CPBA (4.97 g, 21.62 mmol, 75% purity). The mixture was stirred at 60 °C for 3 h and concentrated to give crude **84-2** (1.81 g, crude) as a yellow solid, which was used for next step without purification. MS: m/z 247.9 $[\text{M}+\text{H}]^+$.

[0403] A mixture of **84-2** (1.8 g, crude) in POCl_3 (17.8 mL) was stirred at 90 °C for 3 h. The reaction was quenched with H_2O (350 mL). The mixture was neutralized slowly with aq. NaOH to pH 7~8 and extracted with EA (550 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 0~20% EA in PE as eluent to give **84-3** (805 mg, crude) as a white solid, which was used for next step without purification. MS: m/z 266.1 $[\text{M}+\text{H}]^+$.

[0404] To a mixture of **84-3** (805 mg, crude) and **84-3A** (812 mg, 6.06 mmol) in EtOH (40 mL) was added Pd(dppf)Cl₂ (222 mg, 0.303 μmol) and Na₂CO₃ (642 mg, 6.06 mmol). The mixture was stirred at 70 °C for 3 h. The mixture was concentrated, and the residue was purified by column chromatography using 5~20% EA in PE as eluent to give **84-4** (692 mg, 88.7%) as a white solid. MS: m/z 258.1 [M+H]⁺.

[0405] To a mixture of **84-4** (500 mg, 1.94 mmol) in dioxane (6 mL), H₂O (6 mL) and t-BuOH (3 mL) were added OsO₄ (147 mg, 0.58 mmol) and NMO (273 mg, 2.33 mmol). The mixture was stirred at 25 °C for 20 mins. NaIO₄ (2.07 g, 9.70 mmol) was added with stirring at 25 °C for 10 mins. The mixture was quenched with H₂O (20 mL) and extracted with EA (100 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was dissolved in MeOH (8 mL) and NaBH₄ (145 mg, 3.88 mmol) was added. The mixture was stirred at 25 °C for 20 mins. The reaction was quenched with H₂O (100 mL) and extracted with EA (100 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography using 20~100% EA in PE as eluent to give **84-5** (346 mg, 68.3%) as a white solid. MS: m/z 261.9 [M+H]⁺.

[0406] To a mixture of **84-5** (300 mg, 1.15 mmol) in EtOH (5 mL) was added a solution of NaOH (138 mg, 3.45 mmol) in H₂O (5 mL). The mixture was stirred at 70 °C for 1 h with monitoring by LCMS. The mixture was cooled to RT, acidified with 1N HCl to pH=3 and concentrated. The residue was triturated into MeOH (30 mL). The solid was removed, and the filtrate was concentrated to give **84-6** (254 mg, crude) as a brown solid. MS: m/z 234.2 [M+H]⁺.

[0407] To a mixture of **84-8** (2.5 g, 6.01 mmol) in DCM (10 mL) were added TEA (1.8 g, 18.03 mmol) and CbzCl (2.1 g, 12.02 mmol). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated, and the residue was purified by column chromatography using 10~100% EA in PE as eluent to give **84-9** (2.9 g, 66.8%) as a colorless oil. MS: m/z 550.1 [M+H]⁺.

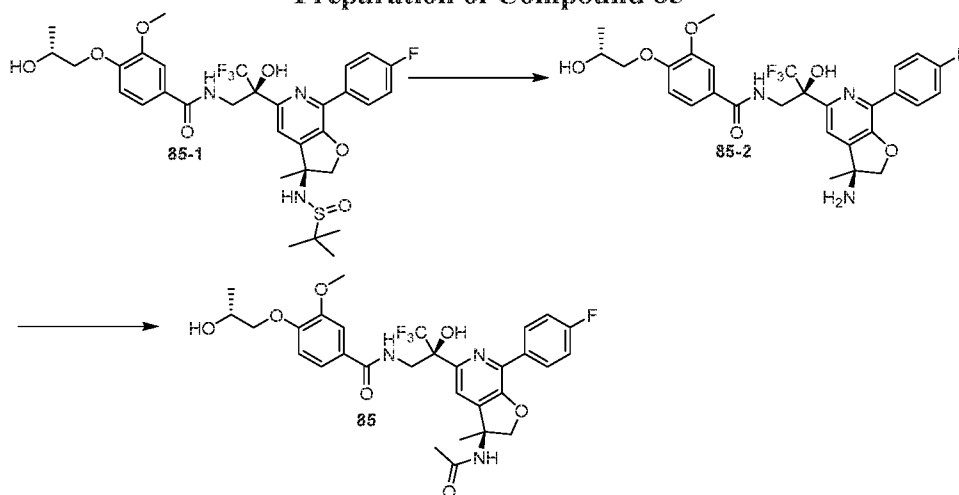
[0408] A mixture of **84-9** (1.5 g, 2.73 mmol), (4-fluorophenyl)boronic acid (1.2 g, 8.19 mmol), K₂CO₃ (754 mg, 5.46 mmol) and Pd(PPh₃)₄ (315 mg, 273 μmol) in dioxane (20 mL) and H₂O (4 mL) was heated to 100 °C for 12 h under N₂. The mixture was concentrated, and the residue was purified by column chromatography using 10~80% EA in PE as eluent to give **84-10** (1.15 g, 69.1%) as a white solid. MS: m/z 610.1 [M+H]⁺.

[0409] A mixture of **84-10** (1.0 g, 1.64 mmol) and Pd/C (10% purity, 500 mg) in MeOH (15 mL) was stirred under H₂ (45 psi) at 25 °C for 12 h. The mixture was filtered, and the filtrate was concentrated to give crude **84-6A** (732 mg, crude) as a colorless oil. MS: m/z 476.1 [M+H]⁺.

[0410] A mixture of **84-6** (98 mg, 420 μmol), HATU (40 mg, 105 μmol) and DIPEA (41 mg, 315 μmol) in DMF (2.00 mL) was stirred at 25 °C for 30 mins. Compound **84-6A** (50 mg, 105 μmol) was added, and the reaction was stirred at 25 °C for 30 mins with monitored by LCMS. The reaction was quenched with H₂O (100 mL) and extracted with EA (100 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-TLC using DCM:MeOH = 10:1 as eluent to give **84-7** (41 mg, 38.6%) as a colorless oil. MS: m/z 691.3 [M+H]⁺.

[0411] To a mixture of **84-7** (41 mg, 58 μmol) in MeOH (3 mL) was added HCl/MeOH (4.0 M, 3 mL). The mixture was stirred at 25 °C for 15 mins with monitored by LCMS. The mixture was concentrated, and the residue was purified by prep-HPLC (HCl condition) to give **84** (15 mg, 45%) as a yellow solid. MS: m/z 587.3 [M+H]⁺.

EXAMPLE 69 Preparation of Compound 85



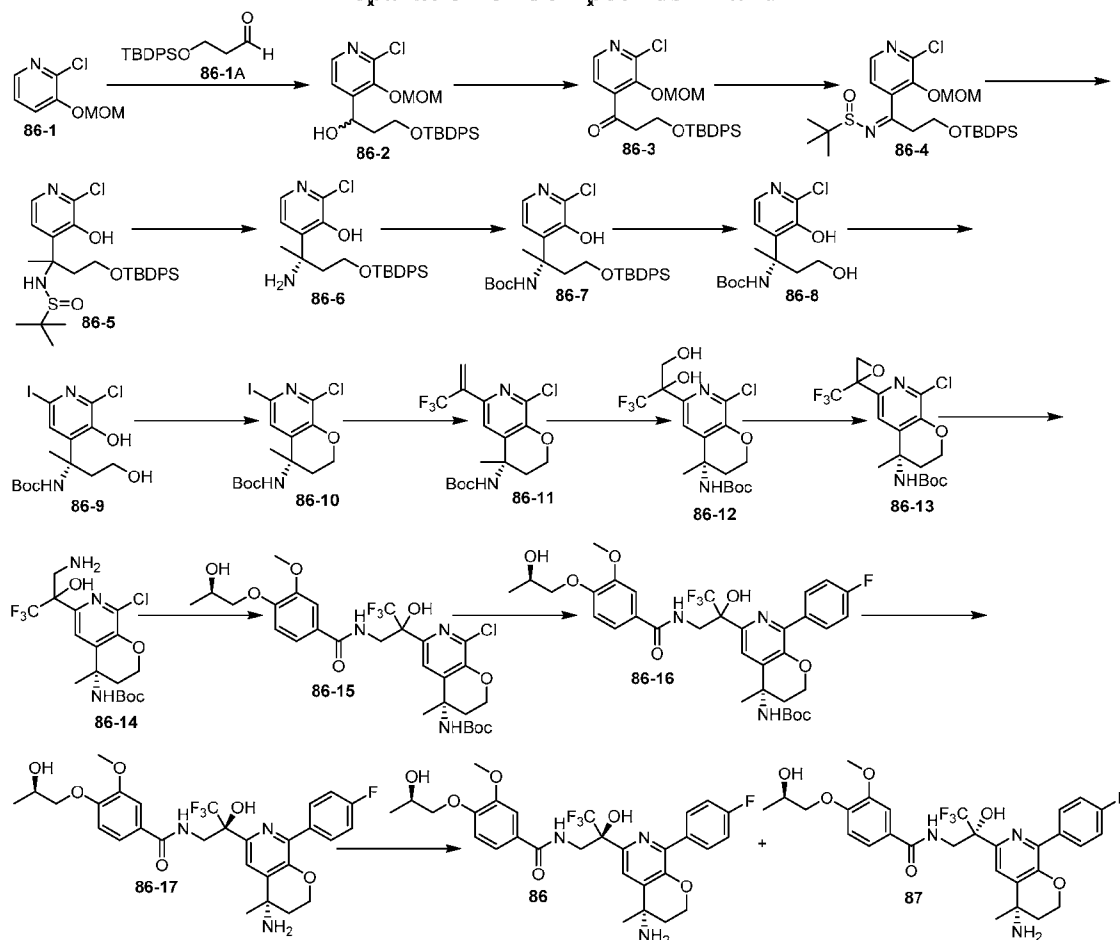
[0412] Compounds **85-1** and **85-2** were prepared according to a similar procedure as provided in WO 2015/26792 A1.

[0413] To a mixture of **85-2** (100 mg, 173 μmol) in EtOH (4 mL) was added ethyl ethanimidate hydrochloride (43 mg, 345 μmol). The mixture was stirred at 70 °C for

12 h with monitored by LCMS. The mixture was concentrated, and the residue was purified by prep-HPLC (HCl condition) to give **85** (75 mg, 70.1%) as a white solid. MS: m/z 622.3 $[M+H]^+$.

EXAMPLE 70

Preparation of Compounds 86 and 87



[0414] Compound **86-1** was prepared according to a similar procedure as provided in US 2007/155744 A1, and compound **86-1A** was prepared according to a similar procedure as provided in Barry et al., Organic Letters (2005) 7(13):2683-2686.

[0415] *n*-BuLi (2.5 M, 110.6 mL) was added to the solution of **86-1** (32.0 g, 184.33 mmol) in THF (100 mL) at -78 °C with stirring for 20 mins. Compound **86-1A** (90.3 g, 276.50 mmol) was added and stirred at -78 °C for 1 h with monitored by LCMS. The reaction was quenched with aq. NH_4Cl (100 mL) and extracted with EA (2 X 500 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and

concentrated. The residue was purified by column chromatography using 10~20% EA in PE as eluent to give **86-2** (52.1 g, 58.1%) a yellow oil. MS: m/z 486.0 $[M+H]^+$.

[0416] To a solution of **86-2** (52.0 g, 106.98 mmol) in DCM (200 mL) was added DMP (113.4 g, 267.45 mmol). The mixture was stirred at 25 °C for 1 h with monitoring by TLC. The reaction was quenched with aq. Na_2SO_3 (100 mL), aq. $NaHCO_3$ (300 mL) and extracted with EA (2 X 300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 5~15% EA in PE as eluent to give **86-3** (42.1 g, 81.3%) as a yellow oil.

[0417] A mixture of **86-3** (42.0 g, 86.77 mmol), 2-methylpropane-2-sulfinamide (15.8 g, 130.16 mmol) and $Ti(OEt)_4$ (49.5 g, 216.93 mmol) in toluene (200 mL) was stirred at 90 °C for 2 h. The solution was concentrated, and the residue was dissolved in EA (200 mL). The solution was poured into aq. $NaHCO_3$ (200 mL) and stirred for 2 mins. The mixture was filtered through a celite pad, and the filter cake was washed with EA (200 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 5~20% EA in PE as eluent to give **86-4** (28.3 g, 55.6%) as a yellow oil.

[0418] To a solution of **86-4** (28.3 g, 47.8 mmol) in DCM (200 mL) was added $MeMgBr$ (3 M, 95.7 mL) at -45 °C with stirring. The mixture was stirred at -45 °C for 2 h and at 25 °C for 0.5 h. The reaction was quenched with aq. NH_4Cl (200 mL) and extracted with EA (2 X 500 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 10~25% EA in PE as eluent to give **86-5** (26.4 g, 99.0%) as a yellow solid.

[0419] To a solution of **86-5** (26.4 g, 47.21 mmol) in MeOH (100 mL) was added $HCl/MeOH$ (0.2 M, 236 mL). The mixture was stirred at 25 °C for 5 mins with monitoring by LCMS. The reaction was quenched with aq. $NaHCO_3$ (100 mL) and extracted with EA (500 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 10~50% EA in PE as eluent to give **86-6** (9.2 g, 42.8%) as a yellow oil. MS: m/z 455.1 $[M+H]^+$.

[0420] A solution of **86-6** (9.2 g, 20.2 mmol) and Boc_2O (17.6 g, 80.9 mmol) in toluene (30 mL) was stirred at 110 °C for 4 h with monitoring by TLC. The

mixture was concentrated and purified by column chromatography using 5~30% EA in PE as eluent to give **86-7** (8.8 g, 78.2%) as a yellow oil.

[0421] To a solution of **86-7** (8.7 g, 15.7 mmol) in THF (150 mL) was added 3HF.TEA (20.2 g, 125.4 mmol). The mixture was stirred at 25 °C for 3 h with monitoring by TLC. The reaction was quenched with H₂O (100 mL) and extracted with EA (300 mL). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography using 20~60% EA in PE as eluent to give **86-8** (4.5 g, 89.6%) as a yellow solid. MS: m/z 361.9 [M+H]⁺.

[0422] A mixture of solution of **86-8** (4.5 g, 14 mmol) in DMF (40 mL) was added NIS (4.74 g, 21 mmol). The mixture was stirred at 25 °C for 0.5 h with monitoring by TLC. The reaction was quenched with aq. Na₂SO₃ (200 mL) and extracted with EA (300 mL). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography using 5~40% EA in PE as eluent to give **86-9** (5.3 g, 85.2%) as a yellow solid. MS: m/z 443.0 [M+H]⁺.

[0423] To a solution of **86-9** (5.0 g, 11.3 mmol) and PPh₃ (3.6 g, 13.55 mmol) in THF (60 mL) was added DIAD (2.74 g, 13.55 mmol) dropwise at 20 °C. The mixture was stirred at 20 °C for 1 h, concentrated. The residue was purified by column chromatography using 1~10% EA in PE as eluent to give **86-10** (2.7 g, 81.3%) as a white solid. MS: m/z 424.9 [M+H]⁺.

[0424] A mixture of **86-10** (500 mg, 1.18 mmol), **86-10A** (339 mg, 1.53 mmol), Pd(dppf)Cl₂ (86 mg, 118 μmol) and Cs₂CO₃ (767 mg, 2.35 mmol) in DME (8 mL) and H₂O (2 mL) was heated at 95 °C for 40 mins under microwave. The mixture was concentrated, and the residue was purified by column chromatography using 5~30% EA in PE as eluent to give **86-11** (1.3 g, 70.1%, 4 batches) as a white solid. MS: m/z 392.9 [M+H]⁺.

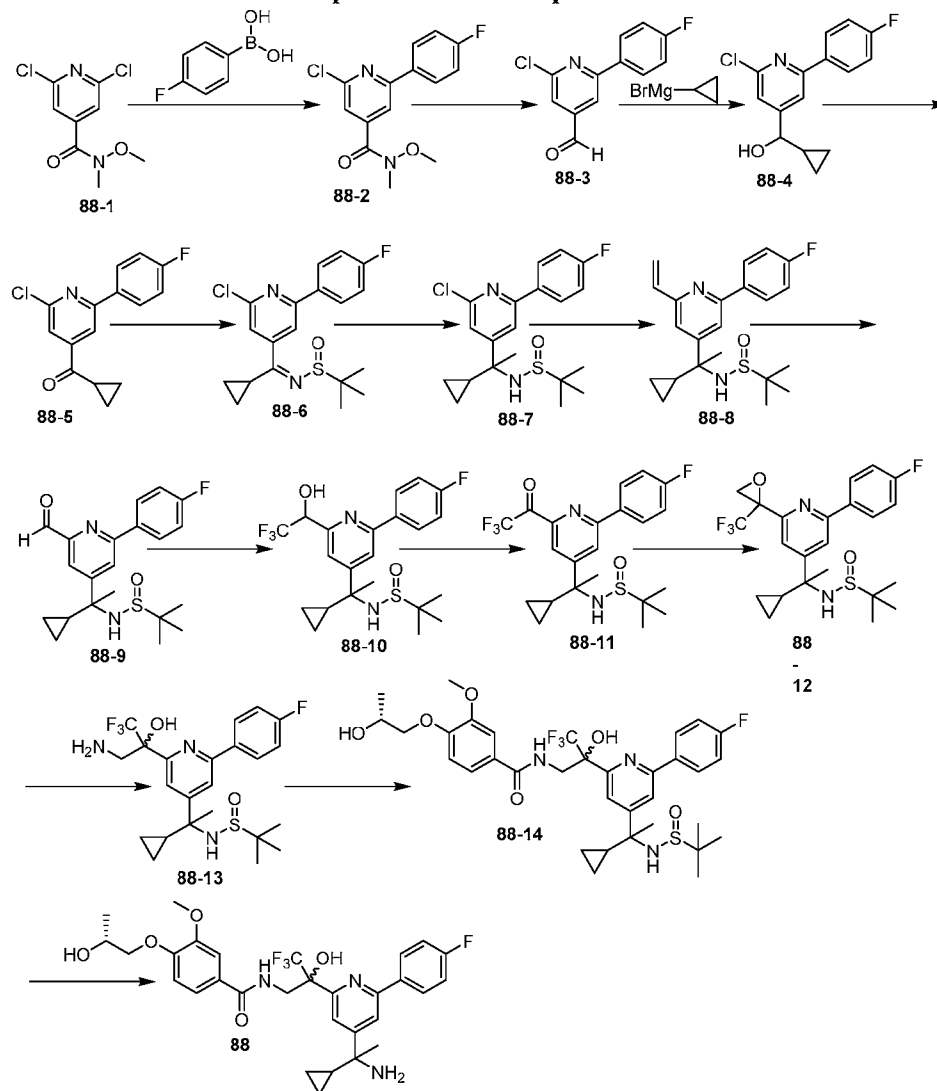
[0425] A mixture of **86-11** (1.3 g, 3.31 mmol), (DHQD)₂PHAL (516 mg, 662 μmol), K₂OsO₄·2H₂O (244 mg, 662 μmol) and NMO (582 mg, 4.97 mmol) in t-BuOH (20 mL) and H₂O (6 mL) was stirred at 20 °C for 16 h under N₂. The reaction was quenched with aq. Na₂S₂O₃ (20 mL) and extracted with EA (200 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash silica gel chromatography using 0~2% MeOH in DCM as eluent to give **86-12** (1.3 g, 92.2%) as a colorless oil. MS: m/z 426.9 [M+H]⁺.

[0426] To a stirring mixture of **86-12** (268 mg, 628 μmol) in THF (30 mL) at 0 °C was added NaH (63 mg, 1.57 mmol, 60% purity) with stirring for 30 mins. TsCl (144 mg, 754 μmol) was added, and the mixture was stirred at 0 °C for 30 mins with monitoring by LCMS. The reaction was quenched with H₂O (20 mL) and extracted with EA (4 X 30 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give **86-13** (256 mg, crude) as a white solid, which was used into the next step without further purification. MS: m/z 408.9 [M+H]⁺.

[0427] A mixture of **86-13** (250 mg, crude) in NH₃/MeOH (7M, 20 mL) was stirred at 15 °C for 10 h with monitoring by LCMS. The mixture was concentrated to give **86-14** (262 mg, crude) as a white solid. MS: m/z 426.0 [M+H]⁺.

[0428] Compounds **86-14A** was prepared according to a similar procedure as provided in WO 2015/26792 A1. Compounds **86** (95 mg, a white solid) and **87** (86 mg, a white solid) were prepared using methods similar to those for preparing **21** from **86-14A** and **86-14**. **86**: MS: m/z 616.1 [M+Na]⁺, and **87**: MS: m/z 616.1 [M+Na]⁺. Compounds **86** and **87** are shown above with relative stereochemistry arbitrarily assigned.

EXAMPLE 71
Preparation of Compound 88



[0429] Compound **88-1** was prepared according to a similar procedure as provided in WO 2009/114552 A1.

[0430] A mixture of **88-1** (20.0 g, 85.1 mmol), boronic acid (13.1 g, 93.6 mmol), Pd(dppf)Cl₂ (3.1 g, 4.25 mmol) and TBAF (1 M, 127.6 mL) in DCM (400 mL) was stirred at 25 °C for 12 h under N₂. The solution was concentrated, and the residue was diluted with H₂O (1 L) and extracted with EA (800 mL). The organic phase was washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 5~20% EA in PE as eluent to give **88-2** (17.2 g, 68.6%) as a yellow oil. MS: m/z 295.7 [M+H]⁺.

[0431] To a solution of **88-2** (8.0 g, 27.2 mmol) in THF (100 mL) was added DIBAL-H (1 M, 54.3 mL) dropwise at -30 °C. The mixture was stirred at 25 °C for 1 h with monitoring by TLC. The reaction was quenched with a saturated NH₄Cl (50 mL) and extracted with EA (2 X 250 mL). The organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 1~20% EA in PE as eluent to give **88-3** (4.1 g, 63.3%) as a white solid. MS: m/z 237.7 [M+H]⁺.

[0432] To a solution of **88-3** (9.0g, 38.2 mmol) in THF (100 mL) was added Grignard reagent (0.5 M, 305 mL) at 25 °C under N₂. After addition, the mixture was stirred at 25 °C for 1 h. The solution was poured into aq. NH₄Cl (200 mL) and stirred and extracted with EA (2 X 250 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 1~20% EA in PE as eluent to give **88-4** (6.30 g, 59.4%) as a yellow oil. MS: m/z 277.9 [M+H]⁺.

[0433] To a solution of **88-4** (6.3 g, 22.7 mmol) in DCM (150 mL) was added DMP (19.2 g, 45.4 mmol) at 25 °C. The mixture stirred at 25 °C for 2 h. The reaction was quenched by saturated Na₂SO₃ (300 mL) and extracted with DCM (2 X 250 mL). The organic phase was washed with aq. NaHCO₃ (200 mL) and brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 1~20% EA in PE as eluent to give **88-5** (4.4 g, 70.4%) as a white solid. MS: m/z 276.8 [M+H]⁺.

[0434] A mixture of **88-5** (3.6 g, 13.06 mmol), NH₂SOtBu (4.7 g, 39.18 mmol) and Ti(OEt)₄ (8.9 g, 39.18 mmol) in THF (100 mL) was stirred at 70 °C for 2 h. The reaction was quenched by aq. NaHCO₃ (10 mL) with stirring until white titanium salts precipitate was formed. The solid was filtered through a celite pad. The filtrate was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography using 5~30% EA in PE as eluent to give **88-6** (4.2 g, 85.1%) as a yellow oil. MS: m/z 379.8 [M+H]⁺.

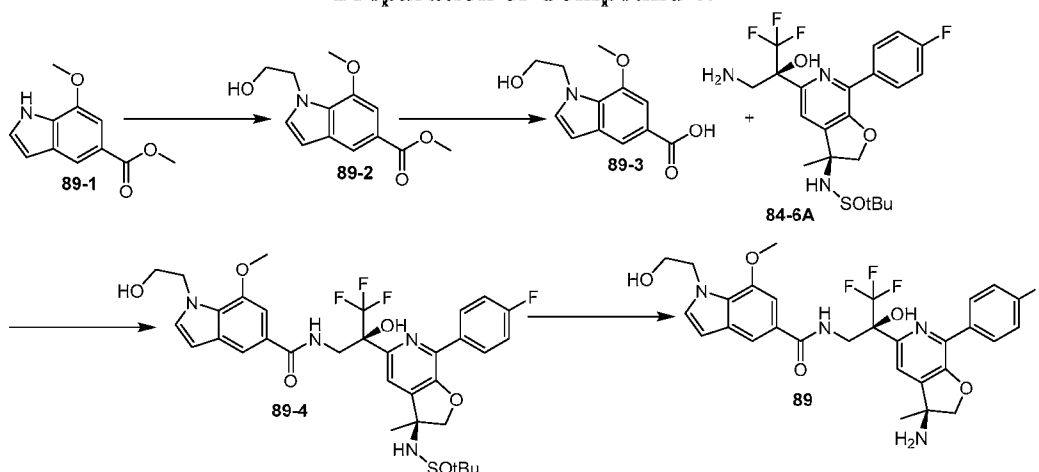
[0435] To a solution of **88-6** (4.0 g, 10.6 mmol) in THF (50 mL) was added MeMgBr (3 M, 10.5 mL) dropwise at 25 °C under N₂. The mixture was stirred at 25 °C for 1 h. The reaction was quenched with aq. NH₄Cl (100 mL) and extracted with EA (250 mL).

The organic phase was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 5~50% EA in PE as eluent to give **88-7** (4.1 g, 96.5%) as a yellow oil. MS: m/z 394.9 $[\text{M}+\text{H}]^+$.

[0436] Compound **88-7** was synthesized using method similar to those for preparing **86-5**. Compound **88-8** and **88-9** were synthesized using methods similar to those preparing **50-5** and **50-6**.

[0437] Compound **88** (32 mg, a white solid) was prepared using methods similar to those for preparing **51** from **88-9**. MS: m/z 592.1 $[\text{M}+\text{H}]^+$.

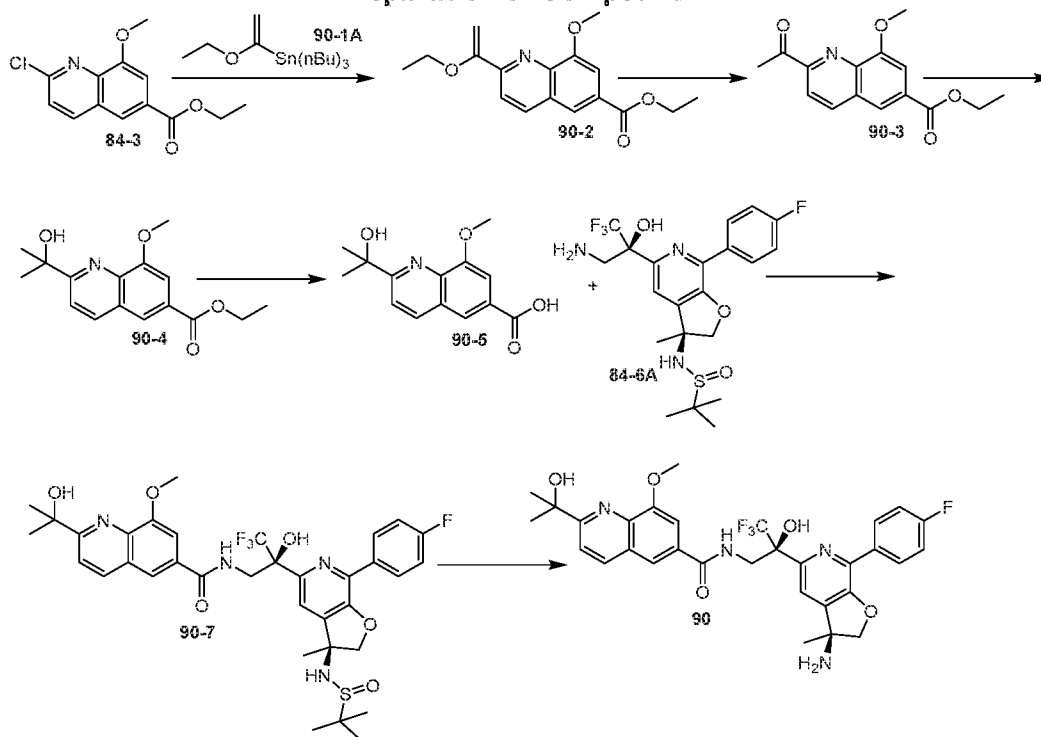
EXAMPLE 72 Preparation of Compound 89



[0438] Compound **89-1** was prepared according to a similar procedure as provided in Ezquerro et al., Journal of Organic Chemistry (1996) 61(17):5804-5812.

[0439] To a solution of **89-1** (400 mg, 1.95 mmol) in DMF (5 mL) was added NaH (60%, 234 mg, 5.85 mmol) in one portion at 0 °C. The mixture was stirred for 30 mins. 2-bromoethanol (730 mg, 5.85 mmol) was added, and the mixture was stirred at 60 °C for 5 h. The reaction was quenched with H_2O (100 mL) and extracted with EA (50 mL). The organic layer was washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 1~20% EA in PE as eluent to give **89-2** (57 mg, 11.5%) as a colorless oil. MS: m/z 250.1 $[\text{M}+\text{H}]^+$.

[0440] Compound **89** (1.86 mg, a white solid) was prepared using methods similar to those for preparing **21** from **89-2** and **84-6A**. MS: m/z 589.0 $[\text{M}+\text{H}]^+$.

EXAMPLE 73**Preparation of Compound 90**

[0441] A mixture of **84-3** (1.5 g, 5.65 mmol), K_2CO_3 (1.4 g, 10.17 mmol), **90-1A** (4.1 g, 11.30 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (413 mg, 0.56 mmol) in DMF (15 mL) was stirred at 90 °C for 12 h under N_2 . The reaction was quenched with H_2O (200 mL) and extracted with EA (300 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated to give **90-2** (810 mg, crude) as a brown solid. MS: m/z 301.9 $[\text{M}+\text{H}]^+$.

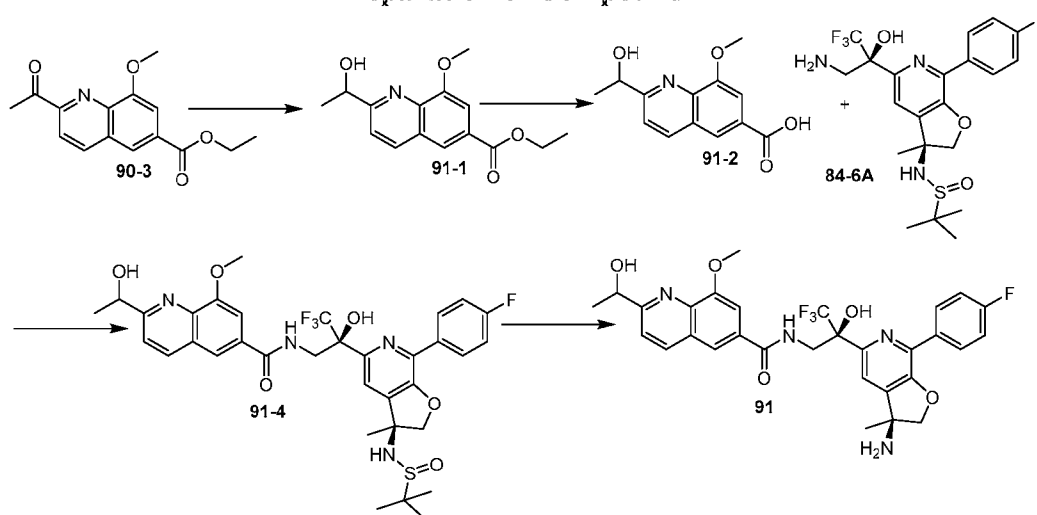
[0442] To a solution of **90-2** (0.8 g, crude) in THF (8 mL) was added HCl (3 M, 2 mL). The mixture was stirred at 25 °C for 10 mins. The reaction was quenched with aq. NaHCO_3 (60 mL) and extracted with EA (2 X 50 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 5~50% EA in PE as eluent to give **90-3** (561 mg, 77.3 %) as a yellow oil. MS: m/z 290.1 $[\text{M}+\text{H}]^+$.

[0443] To a mixture of **90-3** (400 mg, 1.46 mmol) in THF (5 mL) was added MeMgBr (3.0 M, 0.6 mL) at -40 °C under N_2 . The mixture was stirred at -40 °C for 30 mins. The reaction was quenched with aq. NH_4Cl (30 mL) and extracted with EA (2 X 50 mL).

The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 10~50% EA in PE as eluent to give **90-4** (232 mg, 54.9%) as a red oil. MS: m/z 273.9 $[\text{M}+\text{H}]^+$.

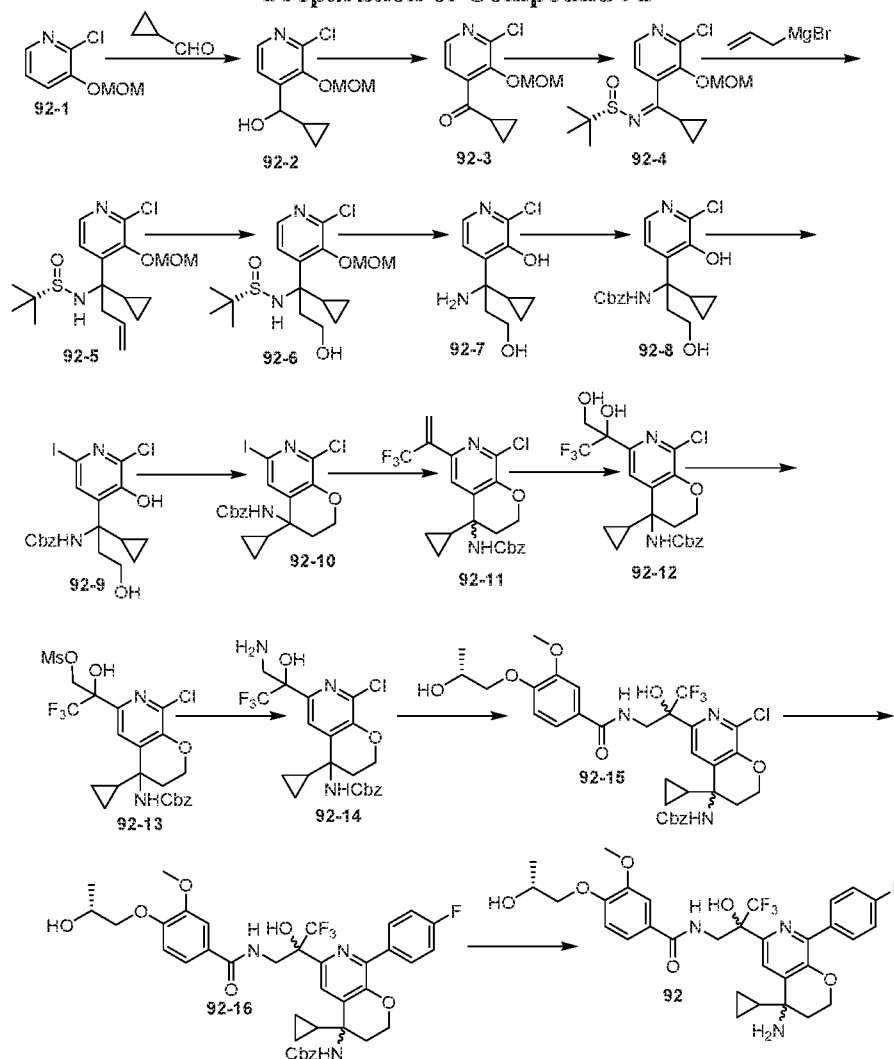
[0444] Compound **90** (23 mg, a white solid) was prepared using methods similar to those for preparing **21** from **89-4** and **84-6A**. MS: m/z 615.1 $[\text{M}+\text{H}]^+$.

EXAMPLE 74 Preparation of Compound 91



[0445] To a solution of **90-3** (200 mg, 0.73 mmol) in MeOH (5 mL) was added NaBH_4 (56 mg, 1.46 mmol) at 25 °C. The mixture was stirred at 25 °C for 10 mins, and the reaction was quenched with H_2O (30 mL) and extracted with EA (50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 20~60% EA in PE as eluent to give **91-1** (153 mg, 75.9%) as a colorless oil. MS: m/z 276.2 $[\text{M}+\text{H}]^+$.

[0446] Compound **91** (10 mg, a white solid) was prepared using methods similar to those for preparing **21** from **91-1** and **84-6A**. MS: m/z 601.1 $[\text{M}+\text{H}]^+$.

EXAMPLE 75**Preparation of Compound 92**

[0447] Compound **92-1** was prepared according to a similar procedure as provided in US 2007/155744 A1.

[0448] To a solution of **92-1** (22.0 g, 126.7 mmol) in THF (220 mL) was added n-BuLi (2.5 M, 76 mL) in dropwise at -78 °C under N₂. After addition, the mixture was stirred at -78 °C for 30 mins and followed by addition of aldehyde (13.3 g, 190.1 mmol). The reaction was stirred for 1.5 h at -78 °C. The reaction was quenched with aq. NH₄Cl (300 mL) and extracted with EA (2 X 500 mL). The combined organic phases were washed with brine (300 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 10~20% EA in PE as eluent to give **92-2** (30.2 g, 97.2%) as a yellow oil. MS: m/z 243.8 [M+H]⁺.

[0449] To a solution of **92-2** (28.0 g, 114.9 mmol) in MeCN (250 mL) was added IBX (48.3 g, 172.3 mmol) in portions. The mixture was stirred at 85 °C for 3 h. The mixture was cooled to 20 °C, and the solid was removed by filtration. The filtrate was concentrated, and the residue was purified by column chromatography using 10~20% EA in PE as eluent to give **92-3** (24.7 g, 86.5%) as a yellow oil. MS: m/z 241.8 [M+H]⁺.

[0450] A mixture of **92-3** (13.0 g, 53.79 mmol), NH₂SOtBu (7.8 g, 64.55 mmol) and Ti(OEt)₄ (27.0 g, 118.34 mmol) in toluene (120 mL) was stirred at 90 °C for 5 h. The mixture was cooled to 20 °C and poured into aq. NaHCO₃ (150 mL). The solid was filtered through a short pad of celite, and the filtrate was extracted with EA (3 X 200 mL). The combined organic phase was washed with brine (150 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 10~20% EA in PE as eluent to give **92-4** (5.5 g, 27.8%) as a yellow oil. MS: m/z 344.9 [M+H]⁺.

[0451] To a solution of **92-4** (5.5 g, 15.9 mmol) in THF (55 mL) was added Grignard reagent (1 M, 64 mL) dropwise at -78 °C under N₂. The mixture was stirred at -78 °C for 1 h. The reaction was quenched with NH₄Cl (100 mL) and extracted with DCM (3 X 150 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 10~50% EA in PE as eluent to give **92-5** (2.3 g, 37.3%) as colorless oil. MS: m/z 387.0 [M+H]⁺.

[0452] Ozone was bubbled into a solution of **92-5** (5.0 g, 12.9 mmol) in MeOH (30 mL) and DCM (30 mL) at -78 °C for 30 mins. After excess O₃ was purged by nitrogen, NaBH₄ (2.4 g, 63.9 mmol) was added to the solution at 0 °C. The mixture was stirred for 1 h. The reaction was quenched with H₂O (100 mL) and extracted with DCM (3 X 120 mL). The combined organic phase was washed with brine (100 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 50~80% EA in PE as eluent to give **92-6** (2.8 g, 55.4%) as a colorless oil. MS: m/z 391.8 [M+H]⁺.

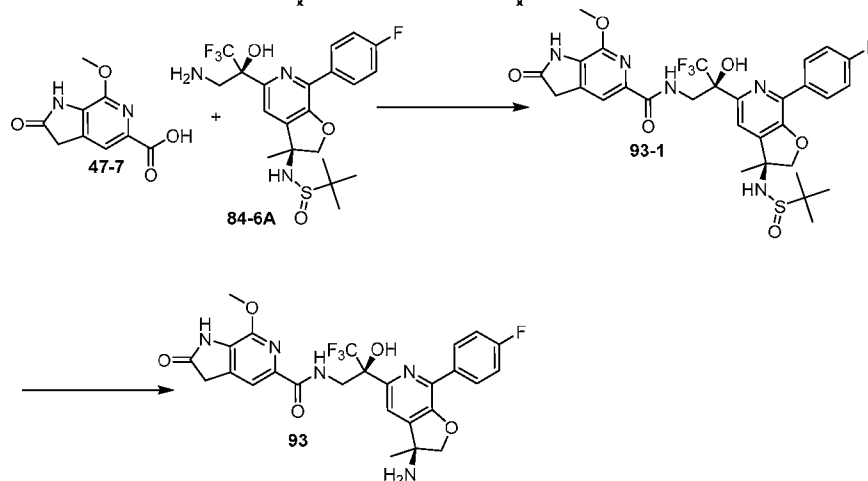
[0453] To a solution of **92-6** (2.7 g, 7.03 mmol) in MeOH (25 mL) was added HCl/MeOH (4 M, 25 mL). The solution was stirred at 20 °C for 4 h, neutralized with aq. NaHCO₃ and extracted with DCM (3 X 150 mL × 3). The combined organic phase was

washed with brine (50 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 5~15% MeOH in DCM as eluent to give **92-7** (1.4 g, 80.3%) as a yellow solid. MS: m/z 242.9 $[\text{M}+\text{H}]^+$.

[0454] To a solution of **92-7** (1.4 g, 5.6 mmol) in pyridine (14 mL) was added TMSCl (3.1 g, 27.9 mmol) under N_2 . The mixture was stirred at 20 °C for 5 h, followed by the addition of CbzCl (1.9 g, 11.2 mmol). The mixture was stirred for 11 h at 20 °C. The solution was concentrated, and the residue was purified by column chromatography using 1~10% MeOH in DCM as eluent to give **92-8** (821 mg, 39.1%) as a white solid. MS: m/z 377.0 $[\text{M}+\text{H}]^+$.

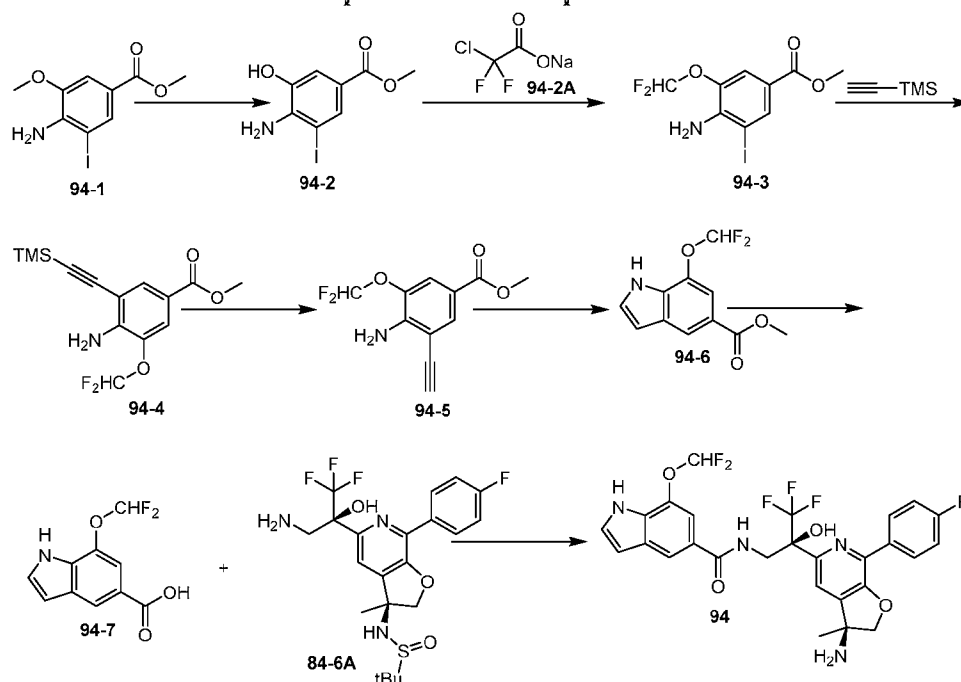
[0455] Compound **92** (10 mg, a white solid) was prepared using methods similar to those for preparing **87** from **92-8**. MS: m/z 620.1 $[\text{M}+\text{H}]^+$.

EXAMPLE 76 Preparation of Compound 93



[0456] Compound **93** (35 mg, a white solid) was prepared using methods similar to those for preparing **21** from **47-7** and **84-6A**. MS: m/z 562.0 $[\text{M}+\text{H}]^+$.

EXAMPLE 77
Preparation of Compound 94



[0457] To a solution of **94-1** (7.1 g, 23 mmol) in DCM (10 mL) was added BBr_3 (3 mL) at 0 °C. The mixture was stirred at 0 °C for 30 mins, and the reaction was quenched with aq. NaHCO_3 (150 mL) and extracted with EA (300 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 30~80% EA in PE as eluent to give **94-2** (4.8 g, 71.3%) as a yellow oil. MS: m/z 293.8 $[\text{M}+\text{H}]^+$.

[0458] To a solution of **94-2** (4.8 g, 16.4 mmol) in DMF (10 mL) was added Cs_2CO_3 (16.1 g, 49.1 mmol) and **94-2A** (3.8 g, 24.6 mmol). The mixture was stirred at 80 °C for 1 h. The mixture was cooled to RT, diluted with H_2O (50 mL) and extracted with EA (2 X 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 5~40% EA in PE as eluent to give **94-3** (3.9 g, 69.4%) as a white solid. MS: m/z 343.9 $[\text{M}+\text{H}]^+$.

[0459] A mixture of **94-3** (3.9 g, 11.4 mmol), **94-3A** (2.2 g, 22.7 mmol), Et_3N (5.8 g, 57 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (399 mg, 0.57 mmol) and CuI (433 mg, 2.27 mmol) in toluene (20 mL) was stirred at 25 °C for 12 h under N_2 . The mixture was diluted

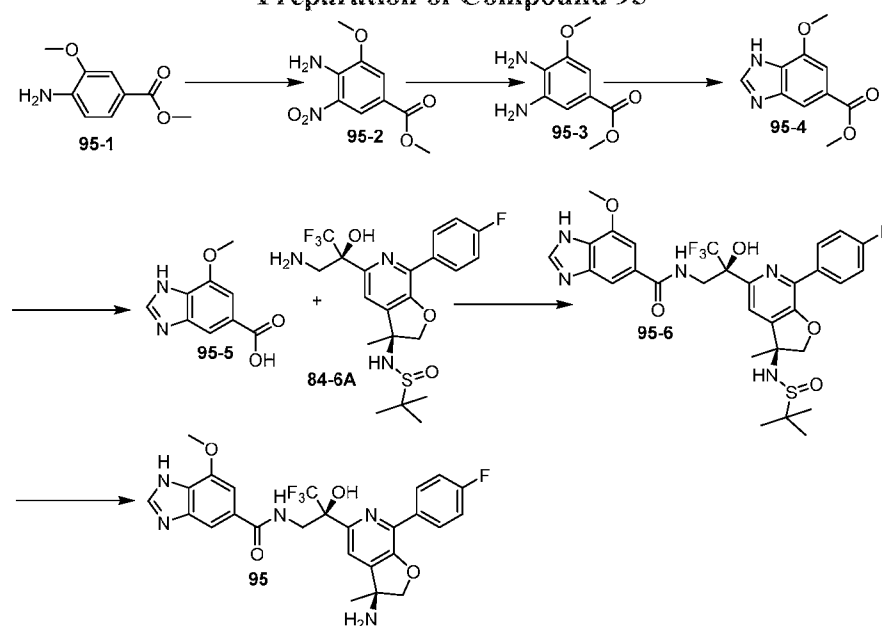
with H₂O (50 mL) and extracted with EA (150 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 10~40% EA in PE as eluent to give **94-4** (2.8 g, 78.6%) as a yellow oil. MS: m/z 313.9 [M+H]⁺.

[0460] To a solution of **94-4** (1.2 g, 3.8 mmol) in THF (5 mL) was added TBAF (3.0 g, 11.49 mmol). The mixture was stirred at 25 °C for 10 mins, concentrated and purified by column chromatography using 10~40% EA in PE as eluent to give **94-5** (650 mg, 69.2%) as a yellow oil. MS: m/z 241.8 [M+H]⁺.

[0461] A mixture of **94-5** (390 mg, 1.6 mmol) CuI (772 mg, 4.0 mmol) and TBAF (636 mg, 2.4 mmol) in DMF (5 mL) stirred at 120 °C for 30 mins. The reaction was cooled to RT, diluted with H₂O (50 mL) and extracted with EA (2 X 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 10~50% EA in PE as eluent to give **94-6** (250 mg, 64.2%) as a white solid. MS: m/z 241.8 [M+H]⁺.

[0462] Compound **94** (41 mg, a white solid) was prepared using methods similar to those for preparing **21** from **94-6** and **84-6A**. MS: m/z 581.0 [M+H]⁺.

EXAMPLE 78 Preparation of Compound 95



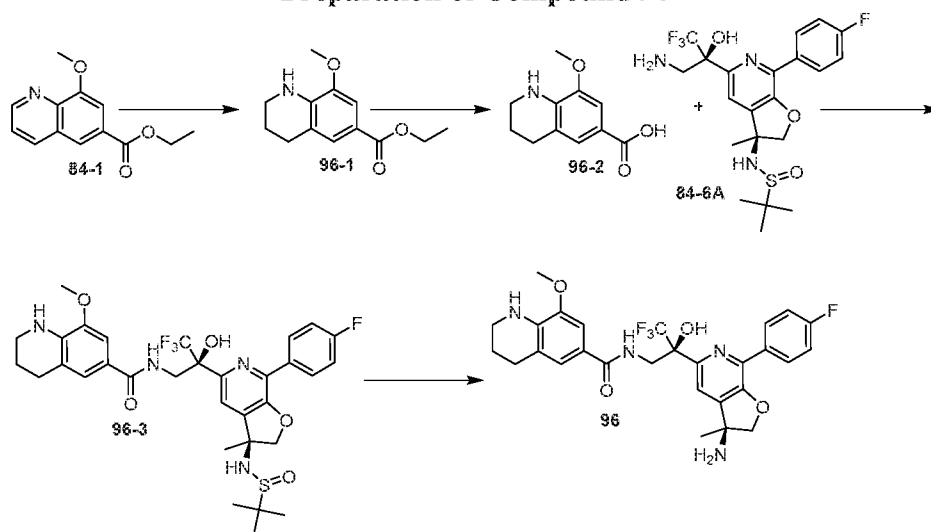
[0463] To a mixture of **95-1** (1.5 g, 8.3 mmol) in TFA (10 mL) was added KNO_3 (1.3 g, 12.4 mmol) in portions. The mixture was stirred at 0 °C for 3 h. The reaction was quenched with H_2O (80 mL) and extracted with EA (3 X 50 mL). The organic layer was washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography using 10~60% EA in PE as eluent to give **95-2** (1.5 g, 80.0%) as a yellow solid. MS: m/z 226.9 $[\text{M}+\text{H}]^+$.

[0464] A mixture of **95-2** (1.5 g, 6.6 mmol) and Pd/C (500 mg, 10% purity) in MeOH (15 mL) was stirred under H_2 (45 PSI) at 25 °C for 12 h. The mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography using 50~100% EA in PE as eluent to give **95-3** (900 mg, 69.2%) as a yellow solid. MS: m/z 197.0 $[\text{M}+\text{H}]^+$.

[0465] A mixture of **95-3** (500 mg, 2.55 mmol) in HCOOH (6 mL) was stirred at 100 °C for 12 h. The mixture was concentrated and purified by column chromatography using 2~10% MeOH in DCM as eluent to give **95-4** (120 mg, 22.8%) as a white solid. MS: m/z 207.1 $[\text{M}+\text{H}]^+$.

[0466] Compound **95** (23 mg, a white solid) was prepared using methods similar to those for preparing **21** from **95-4** and **84-6A**. MS: m/z 545.9 $[\text{M}+\text{H}]^+$.

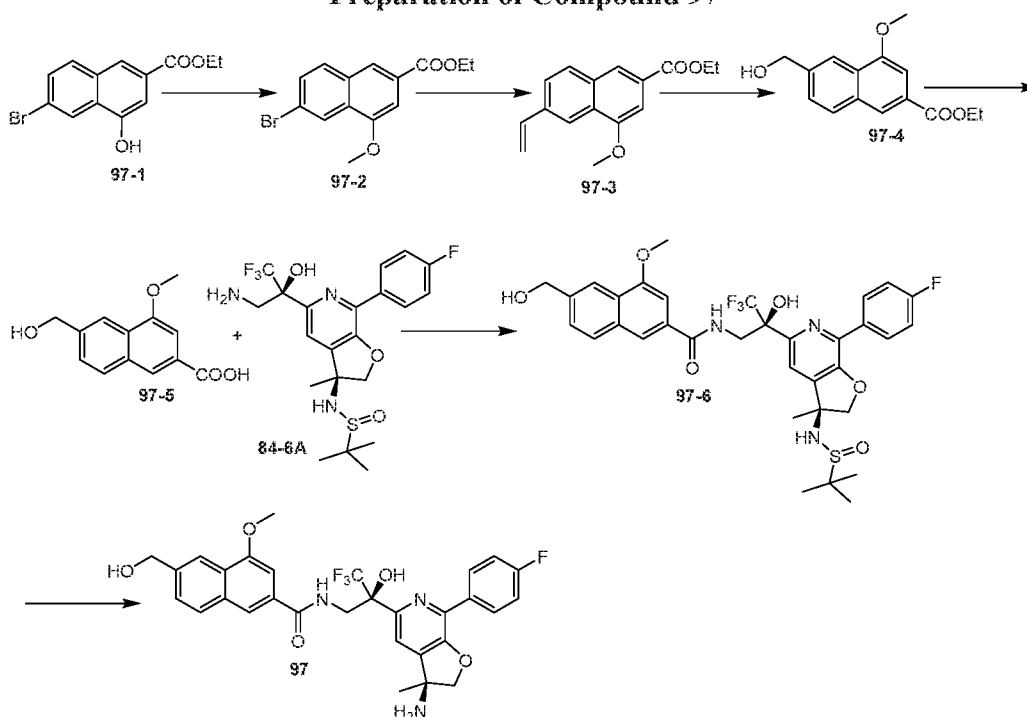
EXAMPLE 79 Preparation of Compound 96



[0467] A mixture of **84-1** (1.5 g, 5.60 mmol) and Pd/C (500 mg, 10% purity) in MeOH (15 mL) and HCl (1 mL) was stirred under H₂ (45 psi) at 25 °C for 12 h. The mixture was filtered, and the filtrate was concentrated. The residue was neutralized by aq. Na₂CO₃ and extracted with EA (200 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography using 10~50% EA in PE as eluent to give **96-1** (1.2 g, 91.0%) as a yellow solid. MS: m/z 236.2 [M+H]⁺.

[0468] Compound **95** (38 mg, a light yellow solid) was prepared using methods similar to those for preparing **21** from **96-1** and **84-6A**. MS: m/z 561.1 [M+H]⁺.

EXAMPLE 80 Preparation of Compound 97



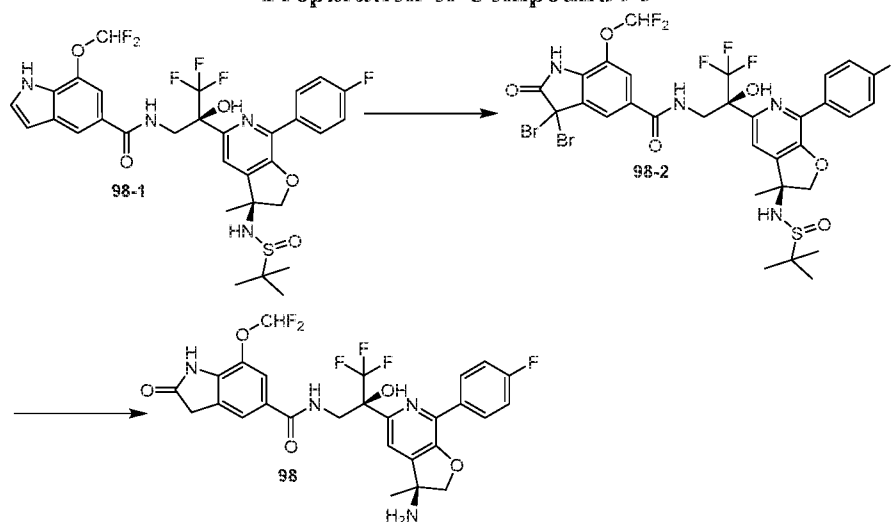
[0469] Compound **97-1** was prepared using methods similar to those described in US 2003/176506 A1.

[0470] To a mixture of **97-1** (2.6 g, 8.8 mmol) in DMF (10 mL) was added NaH (60%, 353 mg, 8.8 mmol) in portions. After stirring for 5 mins, MeI (4.1 g, 28.4 mmol) was added. The mixture was stirred at 50 °C for 1 h and then cooled to RT. The reaction was quenched with H₂O (150 mL) and extracted with EA (150 mL). The organic layer was dried

over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 10~15% EA in PE as eluent to give **97-2** (2.2 g, 78.9%) as a white solid.

[0471] Compound **97** (39 mg, a light yellow solid) was prepared using methods similar to those for preparing **84** from **97-2** and **84-6A**. MS: m/z 601.1 $[\text{M}+\text{H}]^+$.

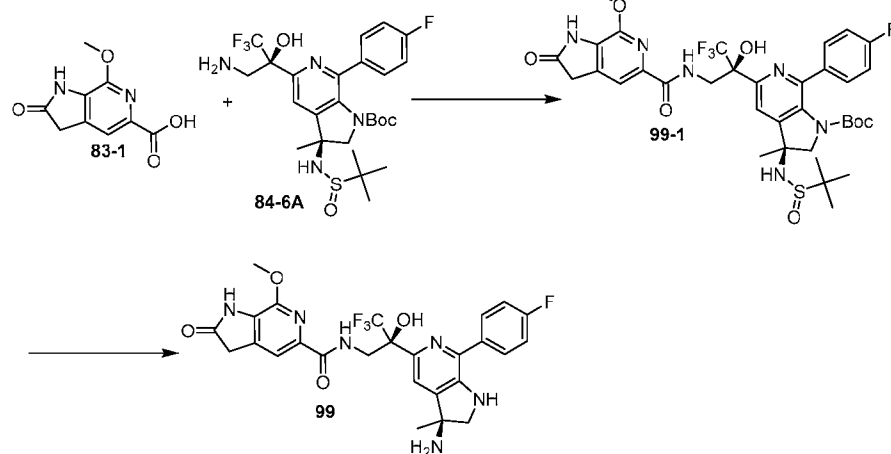
EXAMPLE 81 Preparation of Compound 98



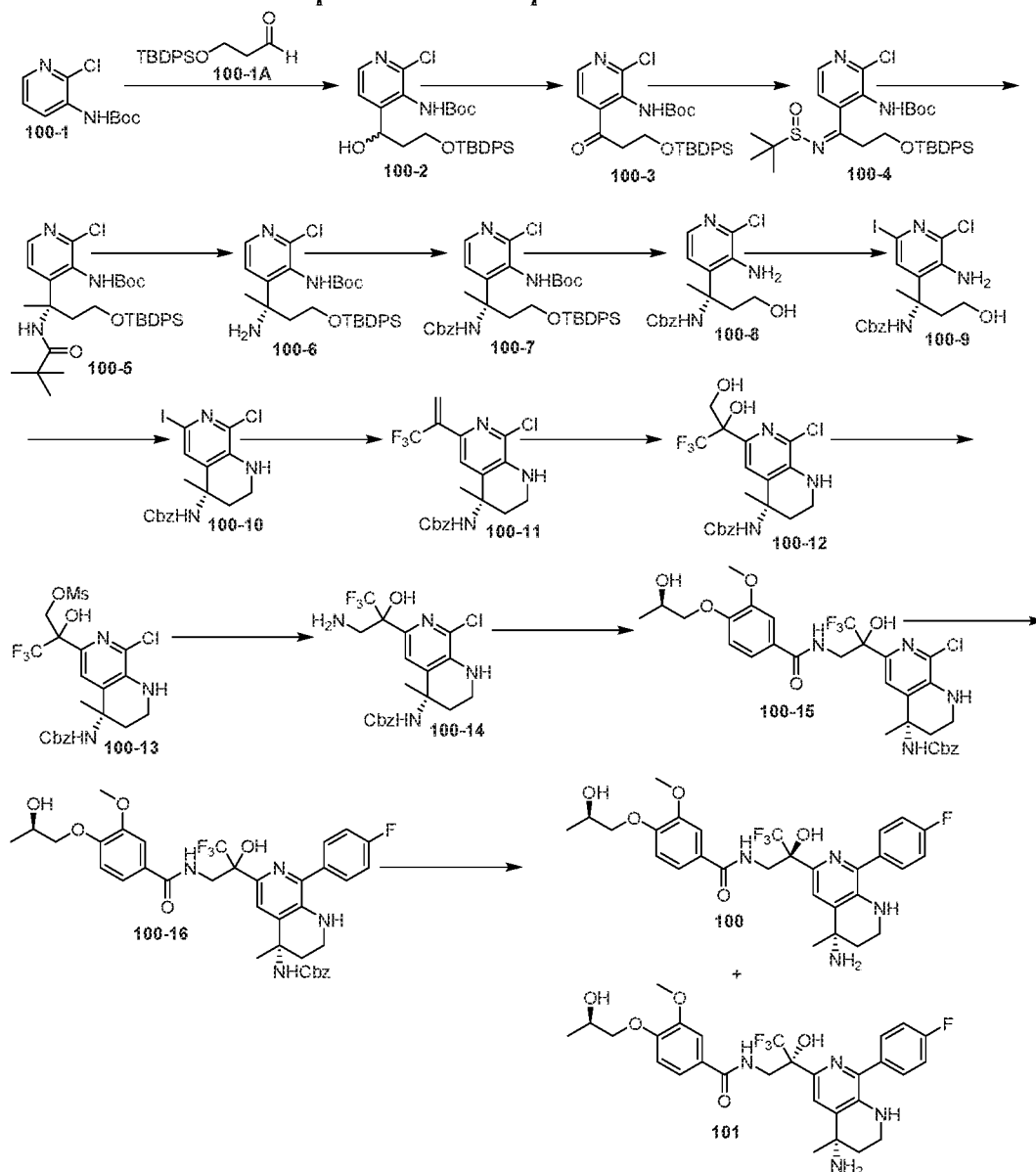
[0472] To a mixture of **98-1** (85 mg, 124 μmol) in *i*-PrOH (1 mL) and H_2O (100 μL) was added NBS (110 mg, 620 μmol). The mixture was stirred at 25 $^\circ\text{C}$ for 1 h. The reaction was diluted with aqueous NaHCO_3 (30 mL) and extracted with EA (50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated to give **98-2** (92 mg, crude) as a white solid. MS: m/z 587.1 $[\text{M}+\text{H}]^+$.

[0473] To a solution of **98-2** (91 mg, crude) in AcOH (1 mL) was added zinc powder (70 mg, 1.06 mmol). The mixture was stirred at 70 $^\circ\text{C}$ for 1 h. The mixture was cooled to RT, neutralized by aqueous NaHCO_3 and extracted with EA (50 mL). The organic layers was washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC (HCl condition) to give **98** (21 mg, 31.6%) as a white solid. MS: m/z 597.0 $[\text{M}+\text{H}]^+$.

EXAMPLE 82
Preparation of Compound 99

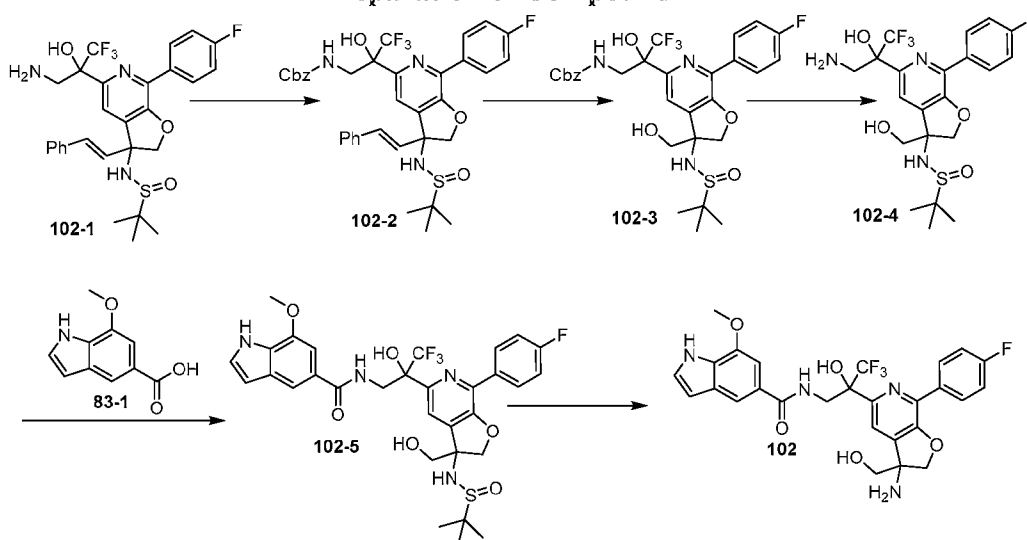


[0474] Compound **99** (1.5 mg, a white solid) was prepared using methods similar to those for preparing **21** from **83-1** and **84-6A**. MS: m/z 561.0 $[M+H]^+$.

EXAMPLE 83**Preparation of Compounds 100 and 101**

[0475] Compound **100-1** was prepared using methods similar to those described in Demont et al., *Journal of Medicinal Chemistry* (2015) 58(14):5649-5673; and compound **100-1A** was prepared using methods similar to those described in Barry et al., *Organic Letters* (2005) 7(13):2683-2686.

[0476] Compounds **100** (4.6 mg, a light yellow solid) and **101** (6.5 mg, a light yellow solid) were prepared using methods similar to those for preparing **87** from **100-1** and **100-1A**. **100**: MS: m/z 593.1 $[M+H]^+$; and **101**: MS: m/z 593.1 $[M+H]^+$.

EXAMPLE 84**Preparation of Compound 102**

[0477] Compound **102-1** was prepared using methods similar to those described in WO 2015/26792 A1.

[0478] To a mixture of **102-1** (1.8 g, crude) and TEA (646 mg, 6.38 mmol) in DCM (20 mL) was added CbzCl (817 mg, 4.79 mmol) with stirring. The mixture was stirred 25 °C for 1 h. The mixture was then concentrated and purified by column chromatography using 10~100% EA in PE as eluent to give **102-2** (0.95 g) as a white solid. MS: m/z 698.1 $[M+H]^+$.

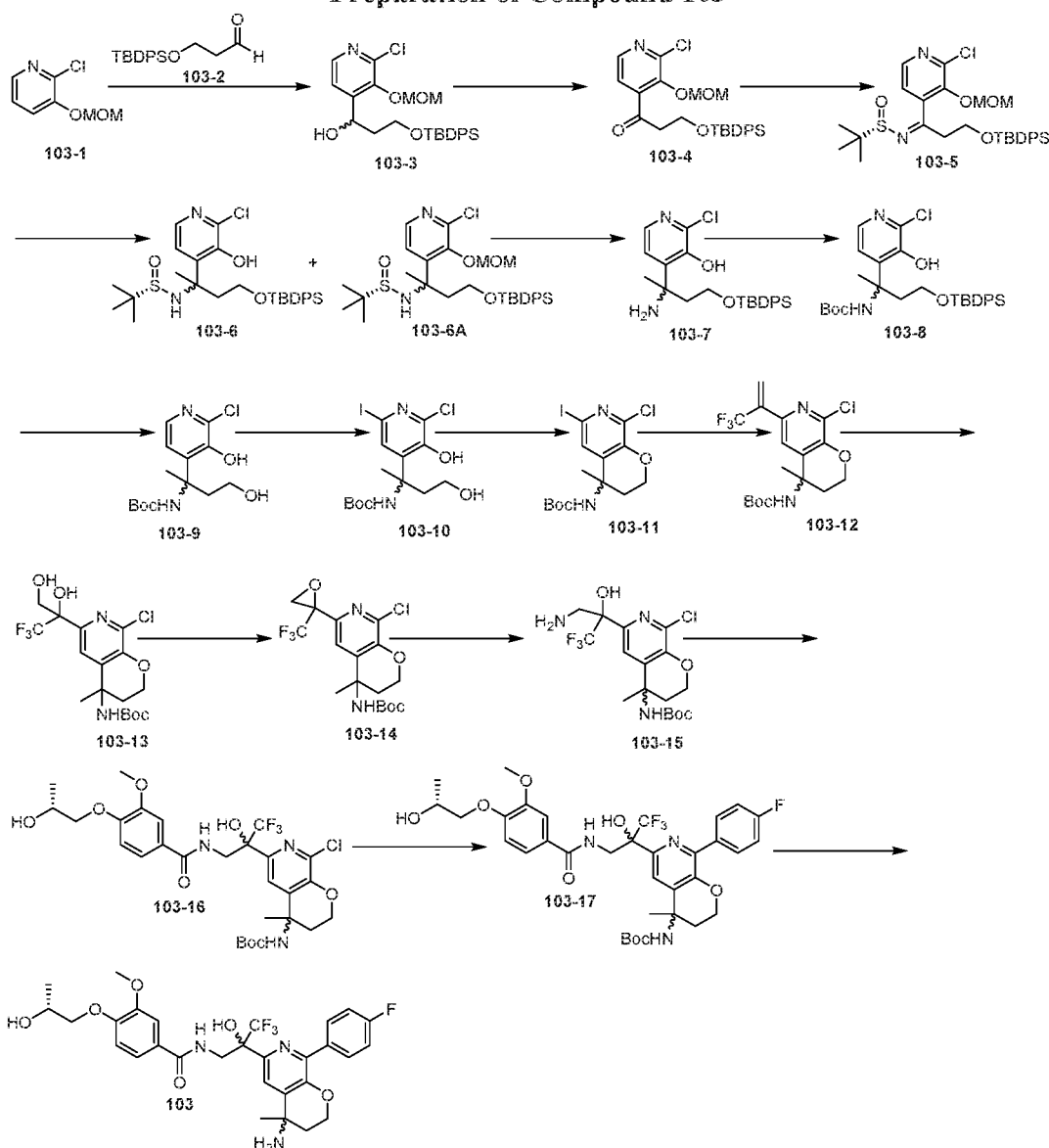
[0479] Ozone was bubbled into a solution of **102-2** (0.95 g) in MeOH (15 mL) at -78 °C for 5 mins. After excess O₃ was purged by N₂, NaBH₄ (163 mg, 4.3 mmol) was added in portions. The mixture was stirred at 25 °C for 10 mins. The reaction was quenched with H₂O (100 mL) and extracted with EA (150 mL). The organic layer was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 1~10% MeOH in DCM as eluent to give **102-3** (683 mg, crude) as a colorless oil. MS: m/z 626.0 $[M+H]^+$.

[0480] A mixture of **102-3** (680 mg, crude) and Pd/C (300 mg, 10% purity) in MeOH (15 mL) was stirred under H₂ (45 PSI) at 50 °C for 12 h. The mixture was filtered, and the filtrate was concentrated to give **102-4** (496 mg, crude) as a colorless oil. MS: m/z 492.0 $[M+H]^+$.

[0481] Compound **102** (32 mg, a white solid) was prepared using methods similar to those for preparing **21** from **83-1** and **102-1**. MS: m/z 582.9 [M+H]⁺.

EXAMPLE 85

Preparation of Compound 103



[0482] To a stirring mixture of **103-1** (1.7 g, 1.0 eq.) and TMEDA (1.61 mL, 1.05 eq.) in THF (0.5 M) at -78 °C was added dropwise a solution of n-BuLi in hexane (4.3 mL, 1.05 eq., 2.5 M in hexane). The mixture was stirred at -78 °C for 1 h before a solution of aldehyde **103-2** (4.2 g, 1.4 eq.) in THF (1.0 M) was added. The mixture was stirred for 1 h at

-78 °C before the reaction was quenched with a sat. NH_4Cl solution. The mixture was diluted with EtOAc. A normal work-up with EtOAc was followed. The crude product was purified via a silica gel column to afford the desired product was a colorless oil (4.1 g, 86%). LC/MS 486.15 m/z $[\text{M}+\text{H}]^+$.

[0483] To a stirring mixture of **103-3** (4.1 g, 1.0 eq.) in DCM (28 mL) at RT was added DMP reagent (5.4 g, 1.8 eq.). The mixture was stirred at RT until all of **103-3** was consumed. The reaction was quenched with a sat. NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ solution. A normal work-up with EtOAc was followed. The crude product was purified via a silica gel column to afford **103-4** (3.34 g). LC/MS 484.2 m/z $[\text{M}+\text{H}]^+$.

[0484] To a stirring mixture of **103-4** (3.34 g, 1.0 eq.) in toluene (0.3 M, deoxygenated prior to use) were added S-sulfonamide (990 mg, 1.2 eq.) and $\text{Ti}(\text{OEt})_4$ (3.2 mL, 2.3 eq.). The mixture was stirred at 95 °C for several hours. The mixture was cooled to RT and diluted with toluene. The reaction was quenched with a saturated NaHCO_3 solution, and celite was added. The mixture was stirred at RT for 20 mins before it was filtered through a plug of celite. The crude product mixture was purified via a silica gel column to afford **103-5** as a colorless oil. LC/MS 587.2 m/z $[\text{M}+\text{H}]^+$.

[0485] To a stirring mixture of **103-5** (2.6 g, 1.0 eq.) in DCM (17 mL) at -45 °C was added dropwise a solution of MeMgBr in Et_2O (7.4 mL, 3.0 M). The mixture was stirred at -45 °C for several hours before the cold bath was removed. The mixture was stirred at RT for 10 mins, and the reaction was slowly quenched with a saturated NH_4Cl solution. The mixture was diluted with EtOAc. A normal work-up with EtOAc was followed. The crude product was purified via a silica gel column to afford **103-6** as a reddish oil as the major product, and a small amount of **103-6A**. LC/MS 559.2 and 603.2 m/z $[\text{M}+\text{H}]^+$.

[0486] To a stirring mixture of **103-6** and **103-6A** (950 mg, 1.0 eq.) in MeOH (10 mL) at RT was added a solution of HCl in dioxane (2 mL, 1.2 eq.). The mixture was stirred for 10 mins before it was concentrated under reduced pressure to afford the crude **103-7**. Crude **103-7** was purified via a silica gel column to afford **103-7**. LC/MS 455.1 m/z $[\text{M}+\text{H}]^+$.

[0487] To a stirring mixture of **103-7** (470 mg, 1.0 eq.) in DCM (4.1 mL) at 0 °C was added TEA (975 μL) and $(\text{Boc})_2\text{O}$ (675 mg). The mixture was stirred at 0 °C for 20 mins and warmed to RT. The mixture was stirred at RT for 3 h before it was quenched with

a saturated NaHCO_3 solution. A normal work-up with EtOAc was followed. The crude product was purified via a silica gel column to afford **103-8** as a colorless oil. LC/MS 555.2 m/z $[\text{M}+\text{H}]^+$.

[0488] To a stirring mixture of **103-8** (280 mg) in THF (2.0 mL) at 0 °C (plastic vial) was added 3HF.TEA (1.3 eq.). The mixture was stirred at RT for 20 mins. The mixture was poured into a cold beaker that contained a saturated NaHCO_3 solution. The mixture was diluted with EtOAc and a normal aqueous work with EtOAc was followed. The crude mixture was purified via a silica gel to afford **103-9**. LC/MS 317.2 m/z $[\text{M}+\text{H}]^+$.

[0489] To a stirring mixture of **103-9** (88 mg) in DMF (1.0 mL) at RT was added NIS (81 mg). The mixture was stirred at RT for 1 h before it was quenched with a 20% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. A normal aqueous work up with EtOAc was followed. The crude mixture was purified via a silica gel to afford **103-10**. LC/MS 443.0 m/z $[\text{M}+\text{H}]^+$.

[0490] To a stirring mixture of **103-10** (96 mg) in THF (1.0 mL) at RT were added PPh_3 (109 mg) and DIAD (110 μL). The mixture was reacted at RT for 1 h before it was concentrated under reduced pressure to afford **103-11**. LC/MS 425 m/z $[\text{M}+\text{H}]^+$.

[0491] To a stirring mixture of **103-11** (63 mg) in DME/water (0.15 M, 10:1 deoxygenated prior to use) were added boronic ester (34 mg), Cs_2CO_3 (110 mg) and $\text{PdCl}_2(\text{dppf})$ (23 mg). The mixture was carried out under microwave irradiation reaction at 110 °C for 45 mins. The mixture was diluted with water and EtOAc. A normal aqueous work up with EtOAc was followed. The crude mixture was purified via a silica gel to afford **103-12**. LC/MS 393.2 m/z $[\text{M}+\text{H}]^+$.

[0492] To a stirring mixture of **103-12** (43 mg) in t-BuOH/water (0.5 mL each) were added NMO (65 mg) and $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (12 mg). The mixture was stirred at RT overnight. The reaction was quenched with a saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution and diluted with EtOAc. A normal aqueous work up with EtOAc was followed. The crude mixture was purified via a silica gel to afford **103-13**. LC/MS 427.1 m/z $[\text{M}+\text{H}]^+$.

[0493] To a stirring mixture of **103-13** (36 mg) in THF (1.0 mL) at 0 °C was added NaH (8.5 mg, 60% by weight). The mixture was stirred at 0 °C for 30 mins before TsCl (19.3 mg) was added. The mixture was stirred for 30 mins and quickly warmed to RT for 5 mins. The reaction was quenched with water and diluted with EtOAc. A normal

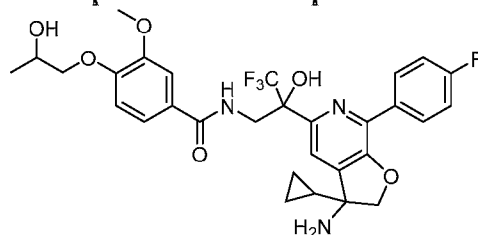
aqueous work up with EtOAc was followed. The crude mixture was purified via a silica gel to afford **103-14**. LC/MS 409.1 m/z [M+H]⁺.

[0494] To a stirring mixture of **103-14** (26 mg) in DMF (0.96 mL) at RT was added NH₄OH (20 µL). The mixture was stirred at RT until all the starting material was consumed. The reaction was quenched with water and diluted with EtOAc. A normal aqueous work up with EtOAc was followed. The crude mixture (containing **103-15**) was taken directly to the next reaction without further purification. LC/MS 426.1 m/z [M+H]⁺.

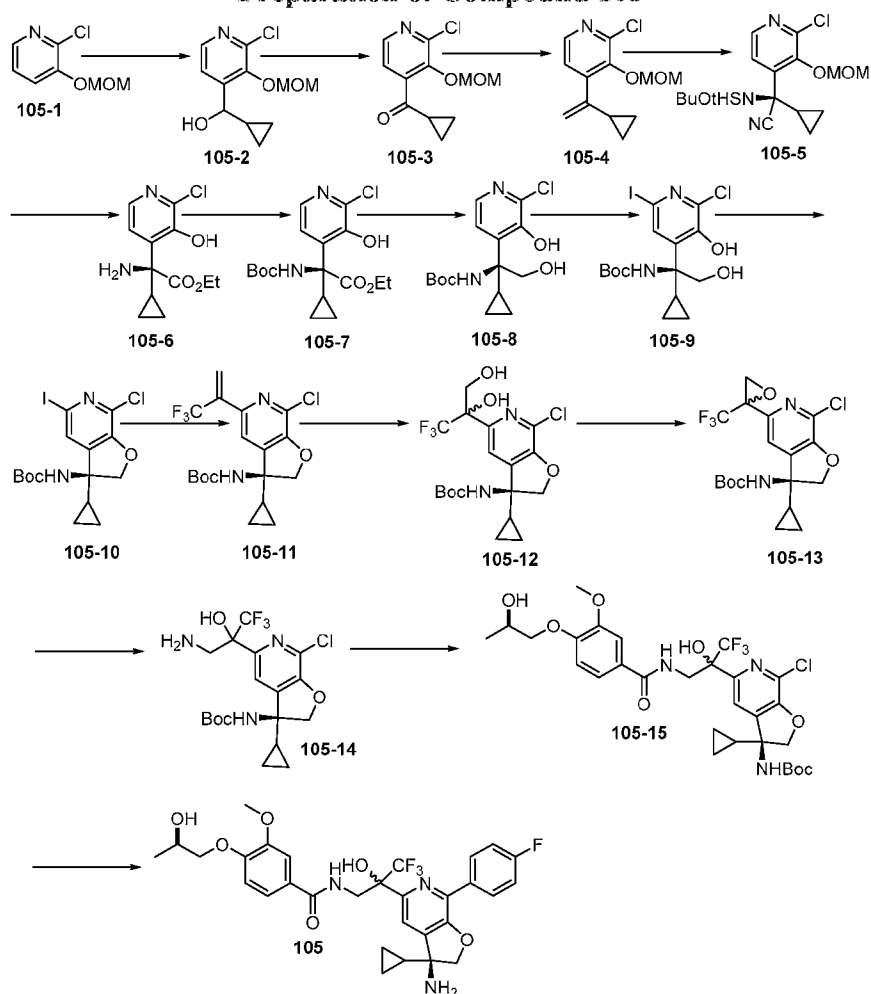
[0495] To a stirring mixture of acid (21 mg), HATU (38 mg) in DMF (1.0 mL) at RT was added DIPEA (26 µL). The mixture was stirred for 10 mins before a solution of crude **103-15** in DMF (0.5 mL) was added. The mixture was stirred for 20 mins. The reaction was quenched with a 10% aqueous NaHCO₃ solution and diluted with EtOAc. A normal aqueous work up with EtOAc was followed. The crude mixture was purified via a silica gel and then further purified via HPLC to afford **103-16**. LC/MS 634.1 m/z [M+H]⁺.

[0496] To a stirring mixture of **103-16** (13 mg) in DME (1.5 mL/0.1 mL, 10:1, deoxygenated prior to use) were added boronic acid (12 mg), Cs₂CO₃ (34 mg), and PdCl₂(dppf) (13.2 mg). The mixture was carried out under microwave irradiation reaction at 110 °C for 2 h. The mixture was diluted with water and EtOAc. A normal aqueous work up with EtOAc was followed. The crude mixture was purified via a silica gel to afford **103-17**. LC/MS 694.3 m/z [M+H]⁺.

[0497] Compound **103-17** was dissolved in a solution of HCl in dioxane (5 mL). The mixture was stirred at RT for several hours until all the starting material was consumed. The crude product mixture was concentrated under reduced pressure and purified via HPLC to afford **103** as a white solid. LCMS 594.1 m/z [M+H]⁺.

EXAMPLE 86**Preparation of Compound 104**

[0498] Compound **104** was prepared using methods similar to those for preparing compound **539** of US 2015/0065504. LCMS: 606.2 m/z [M+H]⁺.

EXAMPLE 87**Preparation of Compound 105**

[0499] Compound **105-2** was prepared using methods similar to those for preparing **103-3**. LCMS: 244.0 m/z [M+H]⁺. Compound **105-3** was prepared using methods

similar to those for preparing **103-4**. LCMS: 242.1 m/z $[M+H]^+$. Compound **105-4** was prepared using methods similar to those for preparing **103-5**. LCMS: 345.1 m/z $[M+H]^+$.

[0500] To a stirring mixture of Et_2AlCN in toluene (12.4 mL, 1.0 M) in DCM (10.5 mL) at 0 °C was added iPrOH (0.95 mL). The mixture was stirred at 0 °C for 10 mins and quickly warmed up to RT. The mixture was stirred for 1 h and then cooled to 0 °C. To this mixture was added a solution of **105-4** (1.07 g, 3.11 mmol) in DCM (2 mL). The mixture was stirred at 0 °C for 3 h before it was warmed up to RT overnight. The reaction was quenched slowly with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$. The mixture was stirred at RT for 20 mins before it was filtered through a plug of celite. The crude product was concentrated under reduced pressure and purified via a silica gel column to afford the desired product as a colorless oil. LC/MS: 371.95 m/z $[M+H]^+$.

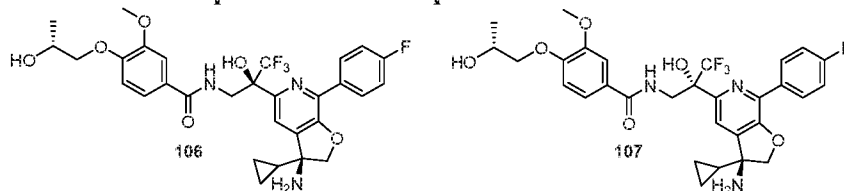
[0501] Compound **105-7** was prepared using methods similar to those for preparing **103-7** and **103-8**. LCMS: 371.1 m/z $[M+H]^+$.

[0502] To a stirring mixture of **105-7** (320 mg, 1 eq.) in THF (3 mL) at RT was added dropwise a solution of LiBH_4 (3.4 mL) in THF. The mixture was stirred at RT for several hours before it was quenched with a saturated NH_4Cl solution at RT. The mixture was heated at reflux for 2 mins before it was cooled to RT and diluted with EtOAc. A normal aqueous workup with EtOAc was followed. The crude product was purified via a silica gel column to afford **105-8** as a colorless oil. LC/MS: 327.1 m/z $[M+H]^+$.

[0503] Compound **105** was prepared using methods similar to those for preparing **103**. LCMS 606.1 m/z $[M+H]^+$.

EXAMPLE 88

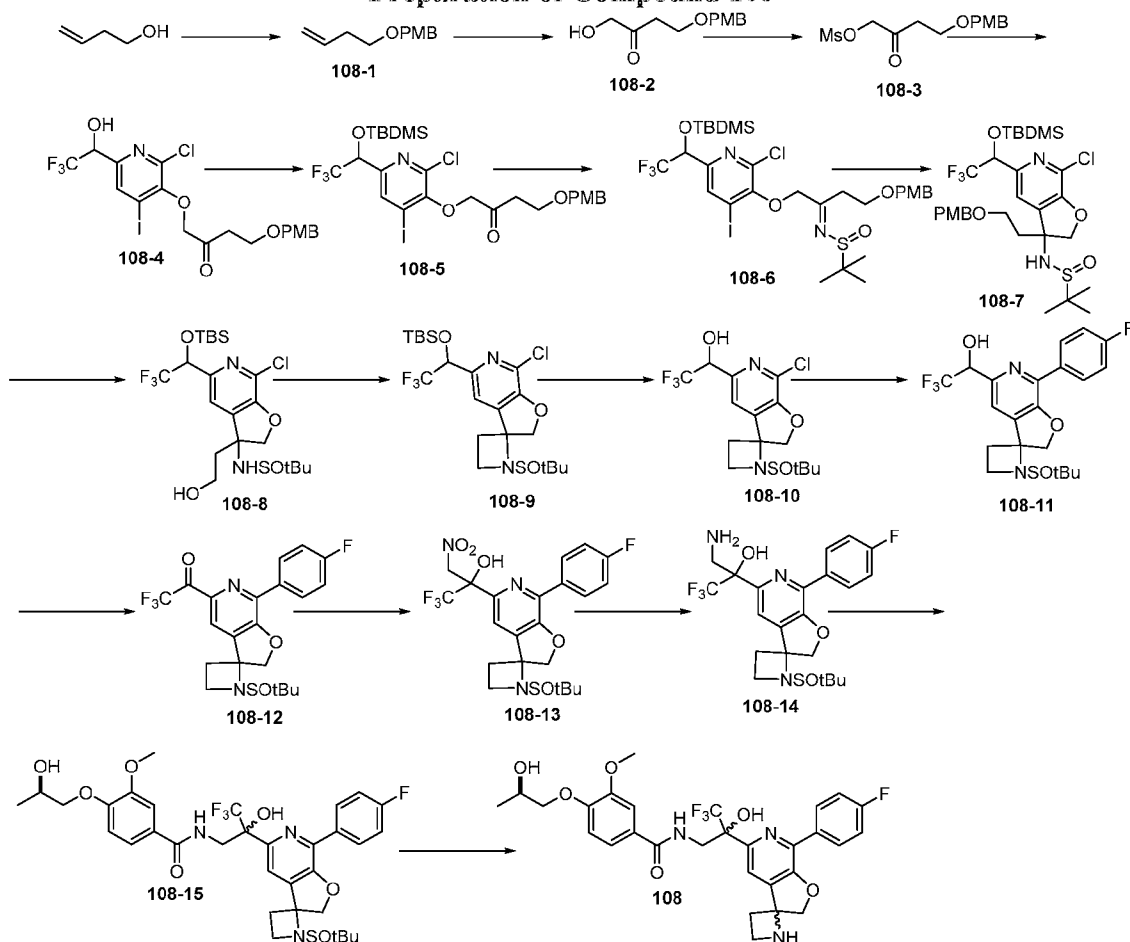
Preparation of Compounds 106 and 107



[0504] The racemic mixture of **105** (115 mg) was separated by SFC using as follows: Column: Chiralpak AD-3 150×4.6mm I.D., 3 μm Mobile phase: A: CO_2 B: isopropanol (0.05% DEA), Gradient: from 5% to 40% of B in 5.0 mins and hold 40% for 2.5 mins, then 5% of B for 2.5 mins Flow rate: 2.5 mL/min. After SFC separation, the solution

was concentrated and re-purified by prep-HPLC (HCl condition) to give **106** (12 mg, 10.4%) as a white solid and **107** (13 mg, 10.5%) as a white solid. **106**: MS: m/z 628.0 [M+Na]⁺. **107**: MS: m/z 628.0 [M+Na]⁺. Compounds **106** and **107** are shown above with relative stereochemistry arbitrarily assigned.

EXAMPLE 89 Preparation of Compound 108



[0505] 3-Butene-1-ol (2.0 mL, 23 mmol) was added dropwise to a solution of sodium hydride (1.0 g, 26 mmol) in THF at 0 °C, and the solution was stirred at RT for 30 mins. Tetrabutylammonium iodide (0.85 g, 2.3 mmol) and para-methoxybenzyl chloride (3.3 mL, 30 mmol) were added, and the reaction was stirred overnight. The reaction was quenched with NH₄Cl and extracted with EA. The organic layer was washed with brine, dried and concentrated. **108-1** (1.69 g, 26%) was purified by flash chromatography (hexane:EA). ¹H NMR (400 MHz, CDCl₃): δ 7.24 (d, J = 8.8, 2H), 6.56 (d, J = 8.8, 2H),

5.78-5.85 (m, 1H), 5.00-5.10 (m, 1H), 4.44 (s, 2H), 3.78 (s, 3H), 3.58 (7, J = 6.4 2H), 2.32-2.37 (m, 2H).

[0506] Potassium permanganate (1.08 g, 6.8 mmol) in acetone (12.8 mL) and water (4.2 mL) was added dropwise to a solution of **108-1** (0.82 g, 4.3 mmol) in acetone (34 mL), water (7.6 mL) and acetic acid (1.6 mL). The solution was stirred at RT for 3 h. EtOH (1 mL) was added, and the solids were removed by filtration. The reaction was concentrated. The residue was dissolved in EA, washed with sodium bicarbonate and brine, dried and concentrated to afford **108-2** (0.34 g, 35%). ¹H NMR (400 MHz, CDCl₃): δ 7.22 (2, J = 8.8, 2H), 6.85 (d, J = 8.8, 2H), 4.42 (s, 2H), 4.25 (d, J = 4.0, 2H), 3.78 (s, 3H), 3.72 (t, j = 6.0, 2H), 2.65 (t, J = 6.0, 2H).

[0507] Methanesulfonyl chloride (1.8 mL, 23 mmol) was added dropwise to a solution of **108-2** (2.0 g, 19 mmol) and DIEA (5.0 mL, 29 mmol) in dichloromethane (100 mL) at 0 °C, and the reaction was stirred at RT for 1 h. The reaction was diluted with EA, washed with 1N HCl and brine, dried and concentrated. **108-3** (1.25 g) was purified by flash chromatography (hexane:EA). ¹H NMR (400 MHz, CDCl₃): δ 7.21 (d, J = 8.8, 2H), 6.87 (d, J = 8.8, 2H), 4.82 (s, 2H), 4.42 (s, 2H), 3.78 (s, 3H), 3.70 (t, J = 6.0 2H), 3.14 (s, 3H), 2.68 (t, J = 6.0, 3H).

[0508] Compound **108-4** was prepared using similar method for preparing **50-2**. LC/MS: m/z 559.95 [M+H]⁺. Compound **108-5** was prepared using methods similar to those for preparing **34**. LC/MS: m/z 674.10 [M+H]⁺. Compound **108-6** was prepared using similar method for preparing **50-3**. LC/MS: m/z 777.10 [M+H]⁺. Compound **108-7** was prepared using similar method for preparing **50-4**. LC/MS: m/z 651.20 [M+H]⁺.

[0509] To a stirring mixture of **108-7** (410 mg, 1.0 eq.) in dichloromethane:water (9 mL:0.4 mL) at RT was added DDQ (286 mg, 2.0 eq.). The mixture was stirred for 1 h. An additional 1 equivalent of DDQ was added. The mixture was stirred for 1 h. The reaction was quenched with a saturated NaHCO₃ solution. A normal aqueous work up with DCM was followed. The crude product mixture was purified via a silica gel column to afford **108-8** (220 mg, 66%) as a colorless oil. LC/MS: m/z 531.2 [M+H]⁺.

[0510] To a stirring mixture of **108-8** (210 mg, 1 eq.) in THF (5.6 mL) at RT was added PPh₃ (155 mg, 1.5 eq.) followed by DIAD (156 μL, 2 eq.). The mixture was heated at

reflux for 1 h. The mixture was concentrated under reduced pressure and purified via a silica gel column to afford **108-9** as a colorless oil. LC/MS: m/z 513.2 [M+H]⁺.

[0511] To a stirring mixture of **108-9** (168 mg, 1 eq.) in THF (3.2 mL) at RT was added a solution of TBAF (632 μ L, 2 eq.). The mixture was stirred at RT for 30 mins. The mixture was diluted with EtOAc and quenched a saturated NaHCO₃ solution. A normal aqueous workup with EtOAc was followed, and the crude product mixture was purified via a silica gel column to afford **108-10** as a white solid (100 mg, 80%). LC/MS: m/z 399.1 [M+H]⁺.

[0512] To stirring mixture of **108-10** (100 mg, 1 eq.) in DME:water (1.5 mL:0.4 mL, deoxygenated prior to use) were added (4-fluorophenyl)boronic acid (53 mg, 1.5 eq.), PdCl₂(dppf) (55 mg, 0.075 eq.), and Cs₂CO₃ (325 mg, 4 eq.). The mixture was carried under a microwave irradiation condition at 110 °C for 2 h. The mixture was concentrated under reduced pressure and purified via a silica gel column to afford **108-11** as a white foam. LC/MS: m/z 459.1 [M+H]⁺.

[0513] To a stirring mixture of **108-11** (70 mg, 1 eq.) in DCM (1.8 mL) at RT was added DMP (77 mg, 1.2 eq.). The mixture was stirred at RT for 20 mins before it was quenched with a 10% Na₂S₂O₃ solution and a saturated NaHCO₃ solution. A normal aqueous work up with DCM was followed. The crude product was purified via a silica gel column to afford **108-12**. LC/MS: m/z 475.1 [M+H+H₂O]⁺.

[0514] To a stirring mixture of **108-12** (60 mg, 1 eq.) in MeNO₂ (0.5 mL) at RT was added Et₃N (25 μ L). The mixture was stirred at RT for 30 mins before it was directly loaded into a silica gel column to afford **108-13** as a white solid (45 mg, 70%). LC/MS: m/z 518.1 [M+H]⁺.

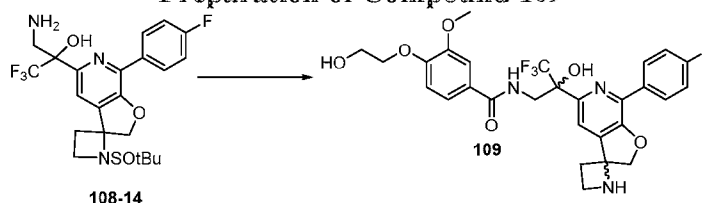
[0515] To a stirring mixture of **108-13** (35 mg, 1 eq.) in MeOH (0.45 mL) at 0 °C were added NaBH₄ (31 mg) and NiCl₂·6H₂O (16.1 mg). The mixture was stirred at 0 °C for 15 mins before it was quenched with a saturated NaHCO₃ solution and diluted with EtOAc. A normal aqueous work up with EtOAc was followed, and the crude product was purified via a silica gel column to afford **108-14** as a white solid (28 mg, 85%). LC/MS: m/z 488.0 [M+H]⁺.

[0516] To a stirring mixture of (R)-4-(2-hydroxypropoxy)-3-methoxybenzoic acid (12 mg, 1.0 eq.) in DMF (0.26 mL) at RT were added HATU (20 mg, 1 eq.) and DIPEA (20 μ L, 2 eq.). The mixture was stirred at RT for 20 mins before a solution of **108-14** (25 mg, 1 eq.) in DMF (0.25 mL) was added. The mixture was stirred at RT for 15 mins before it was quenched with a 10% aq. NaHCO_3 solution and diluted with DCM. A normal aqueous work up with DCM was followed. The crude product was purified via HPLC column to afford **108-15** as a white solid (20 mg, 56%). LC/MS: 696.2 m/z $[\text{M}+\text{H}]^+$.

[0517] To a stirring mixture of **108-15** (20 mg) in MeOH (1.0 mL) was added a solution of HCl in dioxane (0.2 mL). The mixture was stirred at RT for 10 min before it was concentrated under reduced pressure, and the crude product was purified via HPLC column to afford **108** as a white solid. LC/MS: 592 m/z $[\text{M}+\text{H}]^+$.

EXAMPLE 90

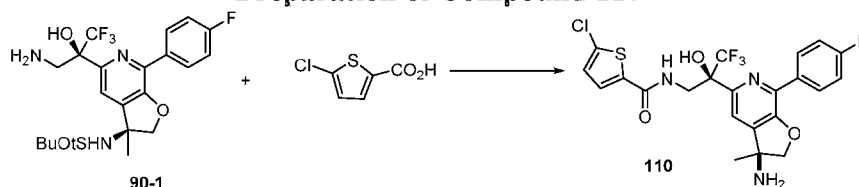
Preparation of Compound 109



[0518] Compound **108-14** was coupled with 4-(2-hydroxyethoxy)-3-methoxybenzoic using methods similar to those for preparing **108** to afford **109** as a white solid. LC/MS: m/z 578.1 $[\text{M}+\text{H}]^+$.

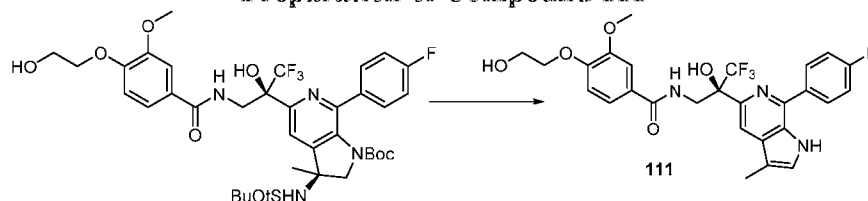
EXAMPLE 91

Preparation of Compound 110



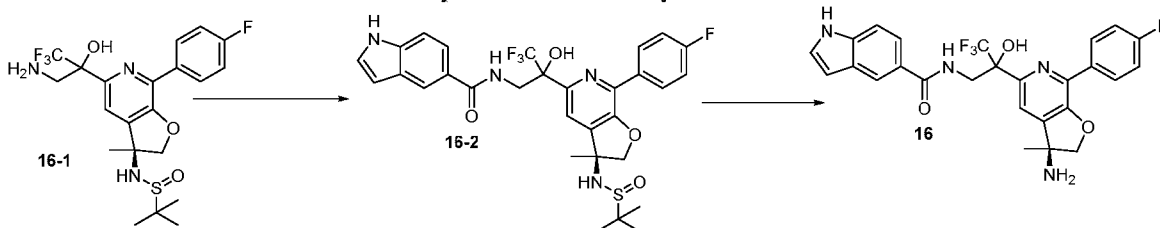
[0519] Compound **90-1** was coupled with 5-chlorothiophene-2-carboxylic acid using methods similar to those for preparing **108** to afford **110** as a white solid. LC/MS: m/z 516.0 $[\text{M}+\text{H}]^+$.

EXAMPLE 92
Preparation of Compound 111



[0520] Compound **111** was obtained as a byproduct during the deprotection step using HCl in MeOH of **51**. LCMS: 548.0 m/z [M+H]⁺.

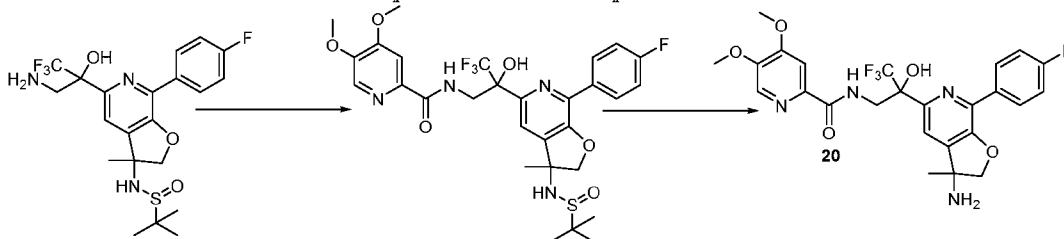
EXAMPLE 93
Preparation of Compound 16



[0521] Triethylamine (35 μ L, 0.25 mmol) was added to a solution of **16-1** (40 mg, 0.084 mmol), indole-5-acetic acid (27 mg, 0.17 mmol) and HATU (67 mg, 0.18 mmol) in DMF (1 mL). The reaction was stirred at RT for 1 h. The crude reaction product was purified by HPLC to afford **16-2** (41 mg, 78%). LC/MS: m/z 619.20 [M+H]⁺.

[0522] HCl in dioxane (4N, 0.2 mL) was added to a solution of **16-2** (41 mg, 0.066 mmol) in methanol (1 mL), and the reaction was stirred at RT for 10 mins. The reaction was concentrated, and the crude product purified by HPLC to afford **16** (35.4 mg, 95%). LC/MS: m/z 515.15 [M+H]⁺.

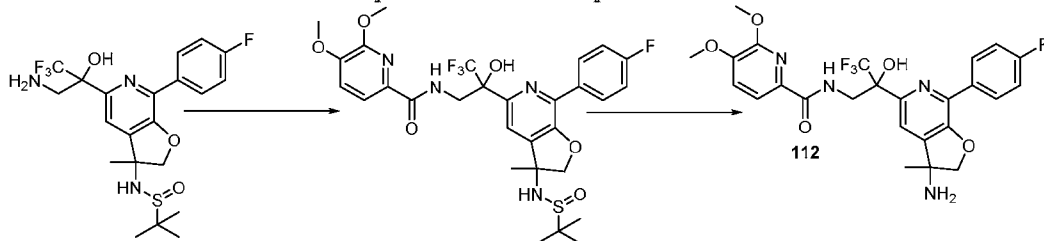
EXAMPLE 94
Preparation of Compound 20



[0523] Compound **20** was prepared in a similar manner to **16**, by substituting 4,5-dimethoxypicolinic acid in the coupling step. LC/MS: m/z 537.15 $[M+H]^+$.

EXAMPLE 95

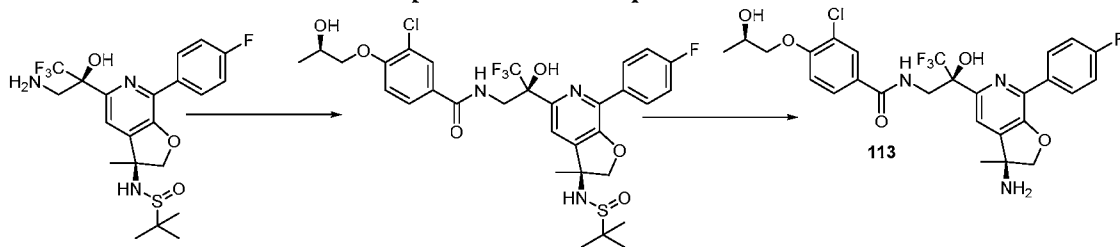
Preparation of Compound 112



[0524] Compound **112** was prepared in a similar manner to **16**, by substituting 5,6-dimethoxypicolinic acid in the coupling step. LC/MS: 537.15 $[M+H]^+$.

EXAMPLE 96

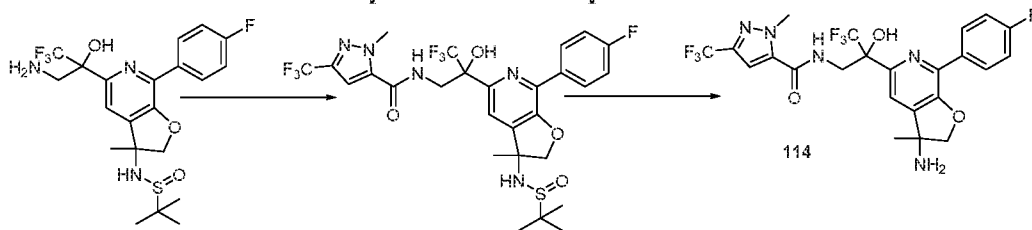
Preparation of Compound 113



[0525] Compound **113** was prepared in a similar manner to **16**, by substituting (R)-3-chloro-4-(2-hydroxypropoxy)benzoic acid in the coupling step. LC/MS: m/z 583.95 $[M+H]^+$.

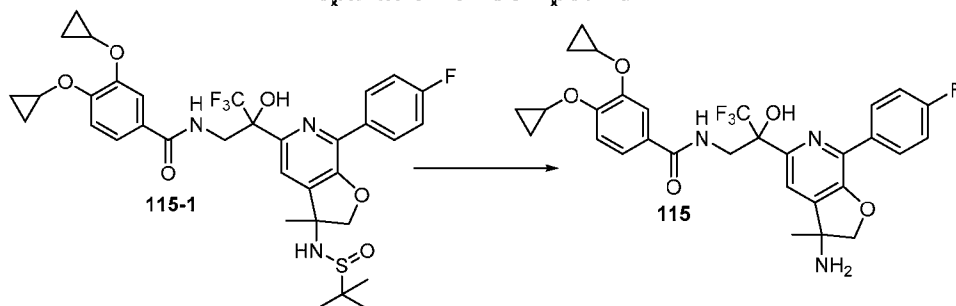
EXAMPLE 97

Preparation of Compound 114



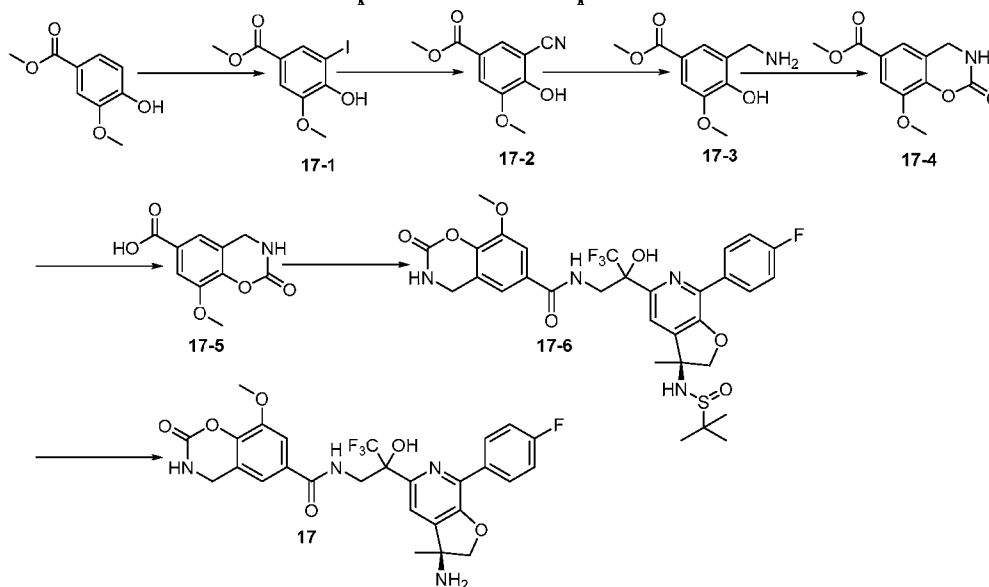
[0526] Compound **114** was prepared in a similar manner to **16**, by substituting 1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid in the coupling step. LC/MS: m/z 548.15 $[M+H]^+$.

EXAMPLE 98
Preparation of Compound 115



[0527] Compound **115** was prepared by deprotecting **115-1** (an intermediate in the synthesis of **25**) in a similar manner to **16**. LC/MS: m/z 558.05 $[M+H]^+$.

EXAMPLE 99
Preparation of Compound 17



[0528] N-Iodosuccinimide (1.2 g, 5.5 mmol) was added portion wise to a solution of methyl vanillate (1.0 g, 5.5 mmol) in trifluoroacetic acid (10 mL). The reaction was monitored by LC/MS and judged complete after 3 h. The reaction was concentrated to remove the TFA then diluted with EA. The organic layer was washed with sodium

thiosulfate and brine, dried and concentrated to afford **17-1** (0.50 g, 29%). LC/MS: m/z 308.95 [M+H]⁺.

[0529] Copper cyanide (250 mg, 3.0 mmol) and sodium cyanide (50 mg, 1.0 mmol) were added to a solution of **17-1** (0.33 g, 1.0 mmol) in DMF (1 mL). The reaction was flushed with argon and heated at 100 °C for 5 h. The mixture was diluted with EA, washed with water and brine, dried and concentrated. The crude product was purified by chromatography (hexane:EA) to yield **17-2** (46 mg, 22%). LC/MS: m/z 206.10 [M-H]⁻.

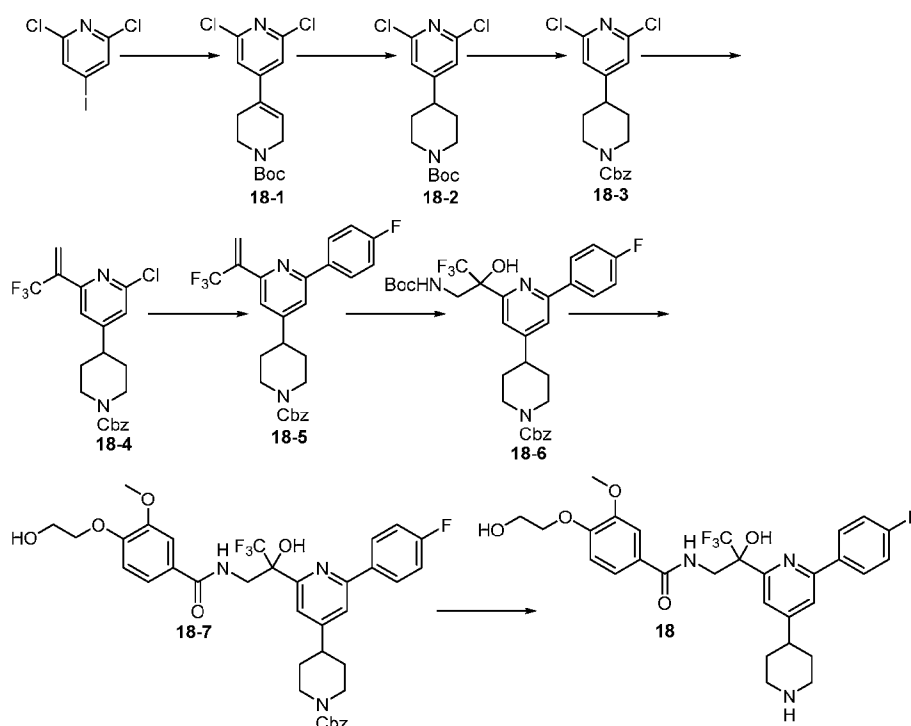
[0530] Compound **17-2** (46 mg, 0.22 mmol) was reduced over 10% Pd/C (40 mg) for 2 h. The catalyst was removed by filtration, and the product was concentrated. **17-3** was used without further purification. LC/MS: m/z 212.15 [M+H]⁺.

[0531] Carbonyldiimidazole (50 mg, 0.33 mmol) was added to a solution of **17-3** (50 mg, 0.298 mmol) and triethylamine (0.11 mL, 0.83 mmol) in DMF. The mixture was stirred at RT for 2 h. The mixture was diluted with EA and washed with 1M HCl and brine, dried and concentrated. The product was purified by flash chromatography (hexane:EA) to afford **17-4** (12 mg, 17%). LC/MS: m/z 238.05 [M+H]⁺.

[0532] Concentrated HCl (0.5 mL) was added to a solution of **17-4** (12 mg, 0.051 mmol) in 4N HCl/dioxane (0.5 mL), and the reaction was heated at 100 °C for 1 h. The mixture was concentrated, and crude **17-5** was used without purification. LC/MS: m/z 221.75 [M-H]⁻.

[0533] Compounds **17-6** and **17** were prepared using a similar methodologies for preparing **16**. **17-6**: LC/MS: m/z 681.20 [M+H]⁺. **17**: LC/MS: m/z 515.15 [M+H]⁺.

EXAMPLE 100
Preparation of Compound 18



[0534] Pd(dppf)Cl_2 (0.27 g, 0.37 mmol) was added to a solution of 2,6-dichloro-4-iodopyridine (2.0 g, 7.3 mmol), 1-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (2.1 g, 7.3 mmol) and cesium carbonate (7.1 g, 22 mmol) in dimethoxyethane (10 mL) and water (1 mL). The reaction was flushed with argon and heated under microwave irradiation at 110 °C for 1 h. The reaction was diluted with EA, washed with water and brine, dried and concentrated. **18-1** (1.62 g, 67%) was purified by flash chromatography (hexane:EA). LC/MS: m/z 329.05 $[\text{M}+\text{H}]^+$.

[0535] **18-1** (1.62 g, 4.9 mmol) was treated with PtO_2 (0.16 g) under a H_2 atmosphere for 1 h. The catalyst was removed by filtration, and **18-2** (1.46g, 90%) was used without further purification. LC/MS: m/z 331.10 $[\text{M}+\text{H}]^+$.

[0536] 4N HCl/dioxane (10 mL) was added to **18-2** (1.46 g, 4.4 mmol), and the reaction was stirred for 1 h. The reaction was concentrated and immediately re-suspended in dichloromethane. Benzyl chloroformate (0.75 mL, 5.3 mmol) and triethyl amine (1.5 mL, 11 mmol) were added, and the reaction was stirred at RT for 1 h. The reaction was washed with

1N HCl and brine, dried and concentrated. The product was purified by flash chromatography (hexane:EA) to afford **18-3** (0.84 g, 52%). LC/MS: m/z 365.05 [M+H]⁺.

[0537] Pd(dppf)Cl₂ (84 mg, 0.11 mmol) was added to a solution of **18-3** (0.84 g, 2.3 mmol), 1-(trifluoromethyl)vinylboronic acid hexylene glycol ester (0.51 g, 2.3 mmol) and cesium carbonate (2.2 g, 6.9 mmol) in dimethoxyethane (6 mL) and water (0.6 mL). The reaction was flushed with argon and heated under microwave irradiation at 110 °C for 30 mins. The reaction was worked up and purified as described above for **18-1** to afford **18-4** (0.266 g, 27%). LC/MS: m/z 425.10 [M+H]⁺.

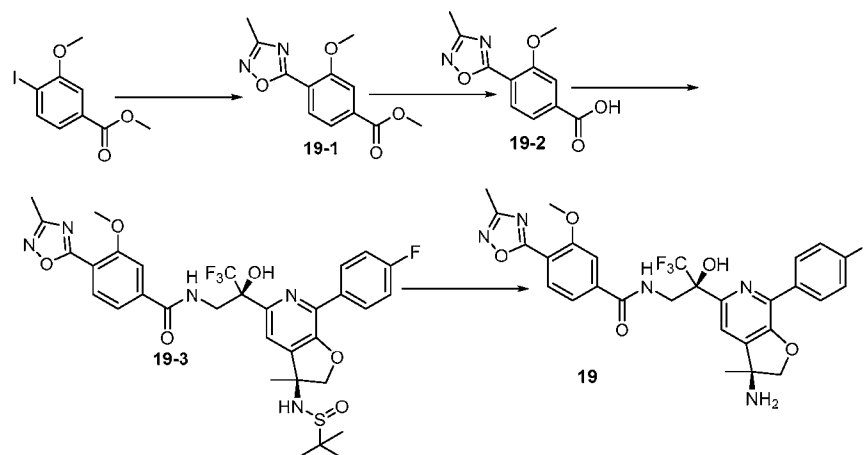
[0538] Pd(dppf)Cl₂ (23 mg, 0.031 mmol) was added to a solution of **18-4** (0.266 g, 0.63 mmol), 4-fluorophenyl boronic acid (88 mg, 0.63 mmol) and cesium carbonate (0.61 g, 1.9 mmol) in dimethoxyethane (2 mL) and water (0.2 mL). The reaction was flushed with argon and heated under microwave irradiation at 110 °C for 90 mins. The reaction was worked up and purified as described above for **18-1** to afford **18-5** (0.27 g, 88%). LC/MS: m/z 485.15 [M+H]⁺.

[0539] Potassium osmate (41 mg, 0.11 mmol) was added to a solution of **18-5** (0.27 g, 0.56 mmol) and *tert*-butyl tosyloxycarbamate (0.30 g, 1.1 mmol) in *t*-butanol (2 mL) and water (0.6 mL). The reaction was stirred at RT overnight. The crude mixture was applied directly to a flash column and **18-6** (45 mg, 13%) was eluted with hexane:EA. LC/MS: m/z 618.30 [M+H]⁺.

[0540] Compound **18-7** was prepared in a manner similar to **16-2**. LC/MS: m/z 712.25 [M+H]⁺.

[0541] Compound **18-7** (17 mg) was hydrogenated over 10% Pd/C (5 mg) in EtOH (5 mL) for 1 h. The catalyst was removed by filtration, and the product purified by HPLC to afford **18** (5.7 mg). LC/MS: m/z 578.02 [M+H]⁺.

EXAMPLE 101
Preparation of Compound 19



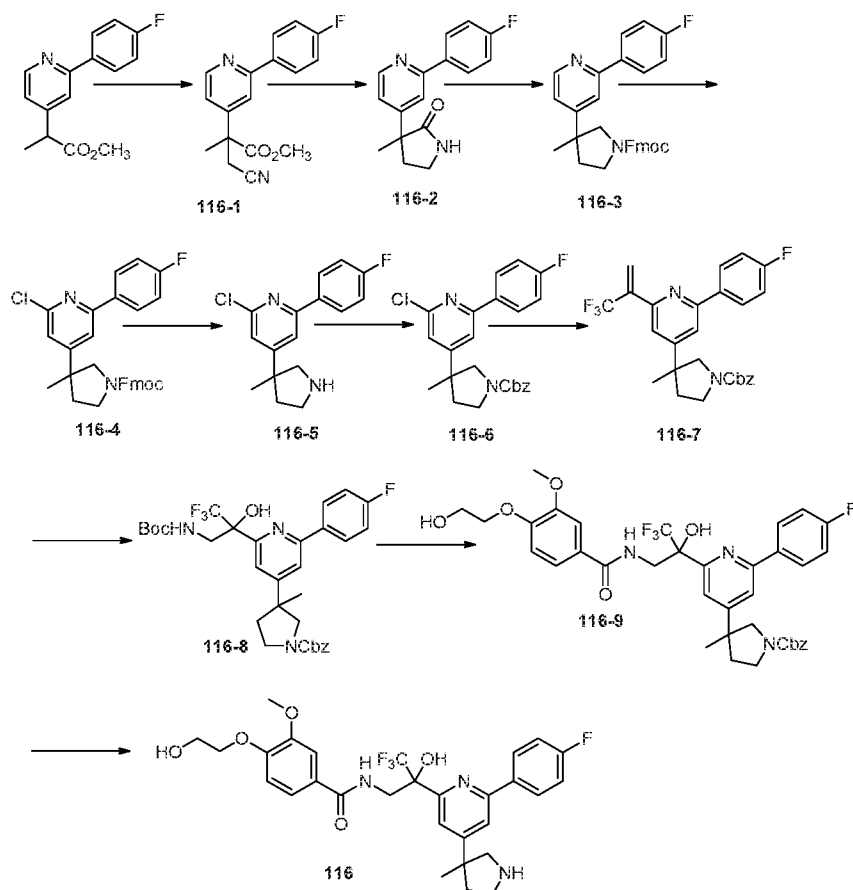
[0542] $\text{PdCl}_2(\text{PPh}_3)_2$ (0.12 g, 0.17 mmol) was added to a solution of methyl 4-iodo-3-methoxybenzoate (1.0 g, 3.4 mmol), (Z)-N'-hydroxyacetimidamide (0.7 g, 10 mmol), and trimethylamine (0.95 mL, 6.8 mmol) in toluene (20 mL). The reaction was flushed with argon, then carbon monoxide was bubbled through the solution for 5 mins. The reaction was heated at reflux under carbon monoxide atmosphere overnight. The reaction was diluted with EA and washed with brine, dried and concentrated. **19-1** (60 mg 7%) was purified by flash chromatography (hexane:EA). ^1H NMR (400 MHz, CDCl_3): δ 8.07 (d, $J = 8.8$, 1H), 7.71-7.73 (m, 2H), 4.03 (s, 3H), 3.95 (s, 3H), 2.49 (s, 3H).

[0543] Sodium hydroxide (2 N, 1 mL) was added to a solution of **19-1** (60 mg, 0.24 mmol) in methanol (4 mL), and the mixture stirred at RT for 2 h. The reaction was acidified with 2N HCl. The product was extracted with EA, washed with brine, dried and concentrated to afford **19-2** (42 mg, 75%). LC/MS: m/z 235.10 $[\text{M}+\text{H}]^+$.

[0544] Compound **19-3** was prepared in a manner similar to **16-2**. LC/MS: m/z 692.20 $[\text{M}+\text{H}]^+$.

[0545] Compound **19** was prepared in a similar manner to **16**. LC/MS: m/z 588.15 $[\text{M}+\text{H}]^+$.

EXAMPLE 102
Preparation of Compound 116



[0546] To a stirring mixture of methyl 2-(2-(4-fluorophenyl)pyridin-4-yl)propanoate (320 mg, 1.234 mmol) in THF (4.6 mL) at -78°C were added dropwise a solution of LiHMDS in THF (1.87 mL, 1.85 mmol). The mixture was stirred at -78°C for 30 mins before a solution of bromoacetonitrile (178 mg, 1.48 mmol) in THF (0.5 mL) was added. The mixture was stirred at -78°C for 1 h before it was warmed to RT for 1 h. The reaction was quenched with water and diluted with EtOAc. A normal aqueous work up with EtOAc was followed. The crude product was purified via a silica gel column to afford **116-1** as a colorless oil (150 mg); LC/MS: m/z 299.10 $[\text{M}+\text{H}]^{+}$.

[0547] Compound **116-1** (1.13 g, 3.8 mmol) was hydrogenated at 50 psi over PtO_2 (200 mg) in EtOH (20 mL) and 1N HCl (1 mL) for 4 h. The catalyst was removed by filtration, and the reaction was concentrated to 5 mL. Saturated sodium bicarbonate was added until the reaction was basic, and the mixture was heated at reflux for 1 h. The mixture

was diluted with EA, washed with water and brine, dried and concentrated. **116-2** (0.30 g, 26%) was purified by flash chromatography (EA).

[0548] Lithium aluminum hydride (2 mL, 2.0 mmol) was added to a solution of **116-2** (0.30 g, 0.99 mmol) in THF (3 mL), and the solution was heated at reflux for 1 h. The reaction was cooled to RT and quenched with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$. The solids were removed by filtration, and washed with EA. The filtrate was concentrated and used immediately. The crude amine from step 1 was dissolved in dichloromethane. To this stirring mixture was added DIEA (0.52 mL, 3.0 mmol) and 9-fluorenylmethylchloroformate (0.51g, 1.9 mmol). The solution was stirred at RT for 3 h. The reaction mixture was diluted with EA, washed with 1N HCl and brine, dried and concentrated. **116-3** (0.30 g, 64%) was purified by flash chromatography. LC/MS: m/z 479.20 $[\text{M}+\text{H}]^+$.

[0549] *meta*-Chloroperbenzoic acid (0.30 g, 1.1 mmol) was added to a solution of **116-3** (0.30 g, 0.63 mmol) in dichloromethane (3 mL), and the reaction was stirred at RT overnight. The reaction was diluted with EA and washed with sodium carbonate and brine, dried and concentrated. The crude N-oxide was immediately dissolved in POCl_3 (10 mL) and heated at 60 °C for 4 h. The solvent was removed by evaporation, and the residue was dissolved in EA. The organic layers were washed with NaHCO_3 and brine, dried and concentrated. **116-4** (0.16g, 49%) was purified by flash chromatography (hexane:EA). LC/MS: m/z 513.15 $[\text{M}+\text{H}]^+$.

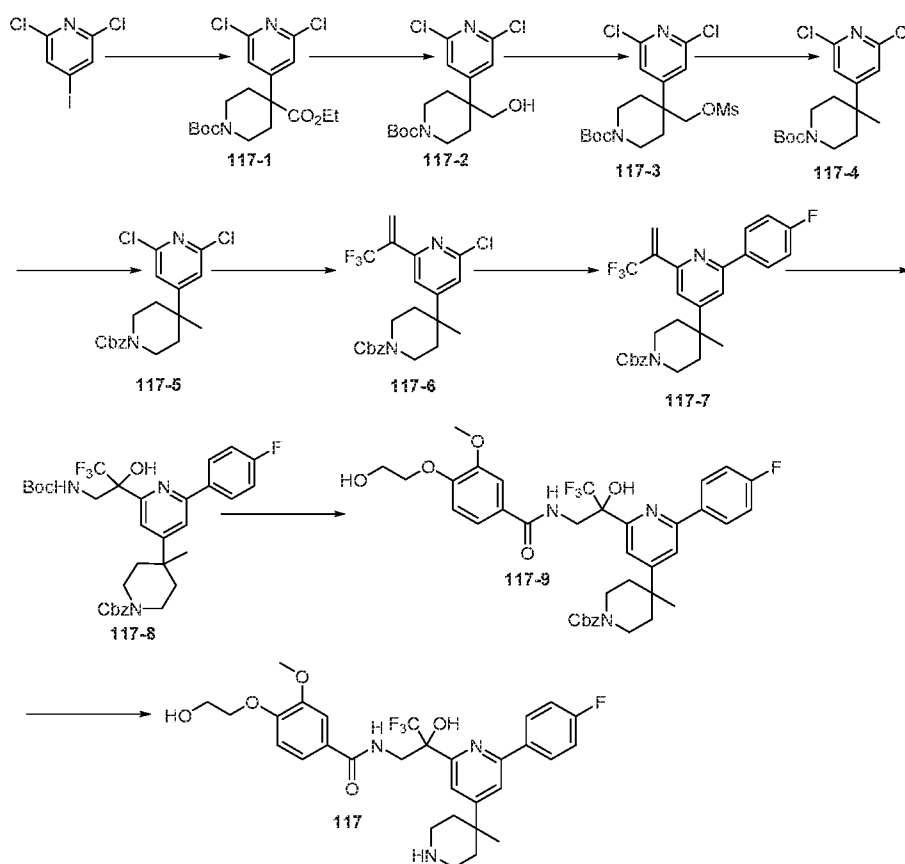
[0550] Piperidine (0.2 mL) was added to a solution of **116-4** (0.16 g, 0.31 mmol) in DMF (1 mL), and the mixture stirred at RT for 10 mins. **116-5** (0.064 g, 71%) was purified by HPLC. LC/MS: m/z 291.10 $[\text{M}+\text{H}]^+$.

[0551] Benzyl chloroformate (0.047 mL, 0.33 mmol) was added to a solution of **116-5** (64 mg, 0.22 mmol) and DIEA (0.11 mL, 0.66 mmol) in CH_2Cl_2 (1 mL), and the solution was stirred at RT for 1 h. The reaction was diluted with EA, washed with 1N HCl, bicarbonate and brine, dried and concentrated. **116-6** (53 mg, 55%) was purified by flash chromatography (hexane:EA). LC/MS: m/z 425.10 $[\text{M}+\text{H}]^+$.

[0552] Compound **116-7** was prepared in a similar manner to **18-4**. LC/MS: m/z 485.15 $[\text{M}+\text{H}]^+$. Compound **116-8** was prepared in a similar manner to **18-6**. LC/MS: m/z 618.25 $[\text{M}+\text{H}]^+$. Compound **116-9** was prepared in a similar manner to **18-7**. LC/MS: m/z 712.25 $[\text{M}+\text{H}]^+$.

[0553] Compound **116** was prepared in a similar manner to **18**. LC/MS: m/z 578.25 $[M+H]^+$.

EXAMPLE 103
Preparation of Compound 117



[0554] NaHMDS (10.0 mL, 10 mmol) was added dropwise to a solution of 1-tert-butyl-4-ethyl piperidine-1,4-dicarboxylate (2.0 g, 7.8 mmol) in THF (5 mL) at 0 °C. The mixture was allowed to stir at 0 °C for 30 mins. The anion was added to a solution of 2,6-dichloro-4-iodopyridine (2.0 g, 7.8 mmol) in THF (5 mL) at 0 °C, and the reaction was stirred for 1.5 h. The reaction was quenched with 1N HCl and extracted with EA. The organic layers were washed with brine, dried and concentrated. **117-1** (1.21 g, 41%) was purified by flash chromatography (hexane:EA). LC/MS: m/z 425.10 $[M+Na]^+$.

[0555] Sodium borohydride (0.36 g, 9.4 mmol) was added to a solution of **117-1** (0.76 g, 1.9 mmol) in EtOH (15 mL) at RT, and the mixture was stirred at RT overnight. The mixture was concentrated slightly and diluted with EA. The organic layers were washed

with brine, dried and concentrated. **117-2** (0.59 g, 84%) was purified by flash chromatography (hexane:EA). LC/MS: m/z 380.05 $[M+Na]^+$.

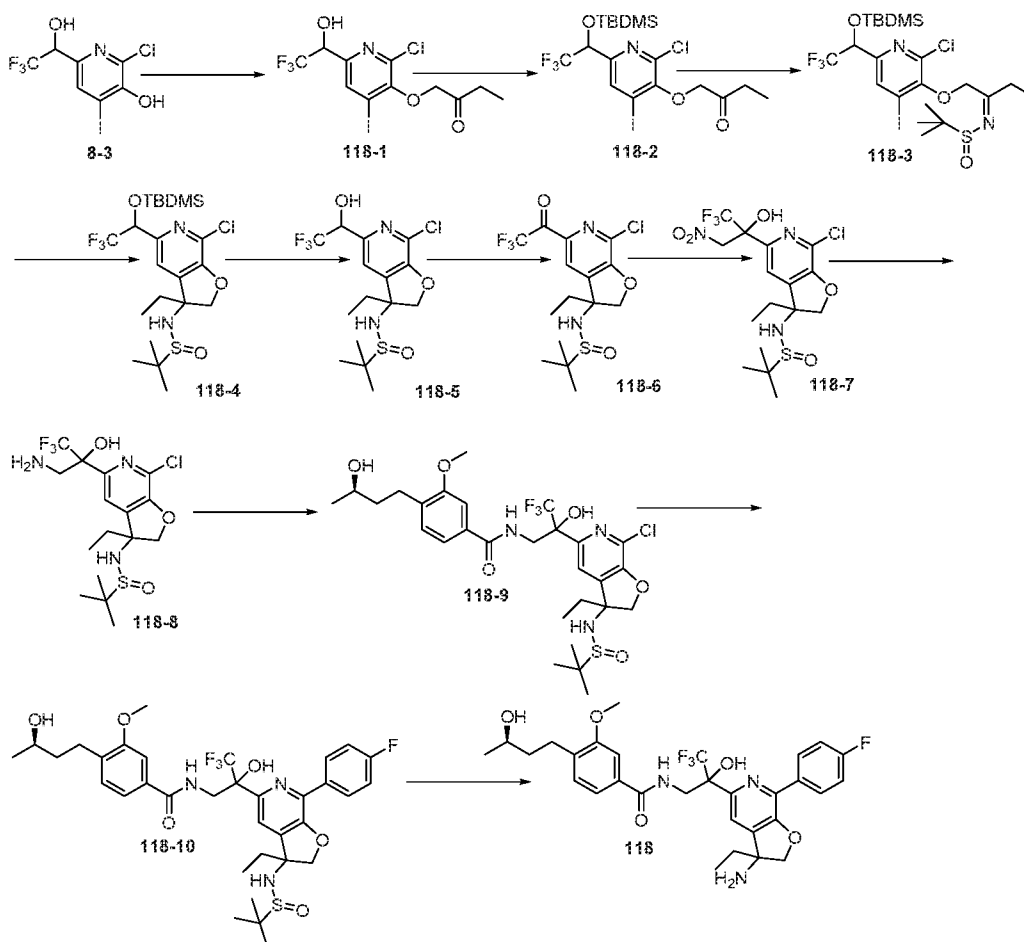
[0556] Methanesulfonyl chloride (0.18 mL, 2.3 mmol) was added to a solution of **117-2** (0.59 g, 1.6 mmol) and DIEA (0.56 mL, 3.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at 0 °C for 45 min. The mixture was diluted with CH_2Cl_2 and washed with 1N HCl and brine, dried and concentrated. **117-3** (0.498 g, 58%) was purified by flash chromatography (hexane:EA). LC/MS: m/z 461.10 $[M+Na]^+$.

[0557] Zn (0.89 g, 14 mmol) was added to a solution of **117-3** (0.435 g, 0.92 mmol) and sodium iodide (0.69g, 4.6 mmol) in DMF (2 mL), and the mixture stirred at 110 °C overnight. The mixture was diluted with EA and washed with water and brine, dried and concentrated. **117-4** (0.165 g, 52%) was purified by flash chromatography (hexane:EA). LC/MS: m/z 366.95 $[M+Na]^+$.

[0558] Compound **117-5** was prepared in a similar manner to **18-3**. LC/MS: m/z 378.95 $[M+H]^+$. Compound **117-6** was prepared in a similar manner to **18-4**. LC/MS: m/z 438.95 $[M+H]^+$. Compound **117-7** was prepared in a similar manner to **18-5**. LC/MS: m/z 499.00 $[M+H]^+$. Compound **117-8** was prepared in a similar manner to **18-6**. LC/MS: m/z 632.10 $[M+H]^+$. Compound **117-9** was prepared in a similar manner to **18-7**. LC/MS: m/z 726.15 $[M+H]^+$.

[0559] Compound **117** was prepared in a similar manner to **18**. LC/MS: m/z 529.15 $[M+H]^+$.

EXAMPLE 104
Preparation of Compound 118



[0560] Compound **118-1** was prepared from **8-3** in a similar manner to **8-4**. LC/MS: m/z 423.75 $[M+H]^+$.

[0561] Tert-butyldimethylsilyl chloride (1.2 g, 8.0 mmol) was added to a solution of **118-1** (1.7 g, 4.0 mmol) and imidazole (0.82 g, 8.0 mmol) in DMF (8 mL), and the mixture was stirred at RT for 8 h. The mixture was diluted with EA and washed with water and brine. The solvent was removed by filtration, and **118-2** (1.53 g, 70%) purified by flash chromatography (hexane:EA). LC/MS: m/z 537.90.

[0562] Compound **118-3** was prepared in a similar manner to **8-5**. LC/MS: m/z 640.90 $[M+H]^+$. Compound **118-4** was prepared in a similar manner to **8-6**. LC/MS: m/z 515.00 $[M+H]^+$.

[0563] Tetrabutylammonium fluoride (1.6 mL, 1.6 mmol) was added to a solution of **118-4** (0.76 g, 1.48 mmol) in THF (10 mL), and the solution was stirred at RT for 1 h.

The mixture was concentrated, and **118-5** (0.52 g, 80%) purified by flash chromatography. LC/MS: m/z 400.95 [M+H]⁺.

[0564] Compound **118-6** was prepared in a similar manner to **8-7**. LC/MS: m/z 398.95 [M+H]⁺.

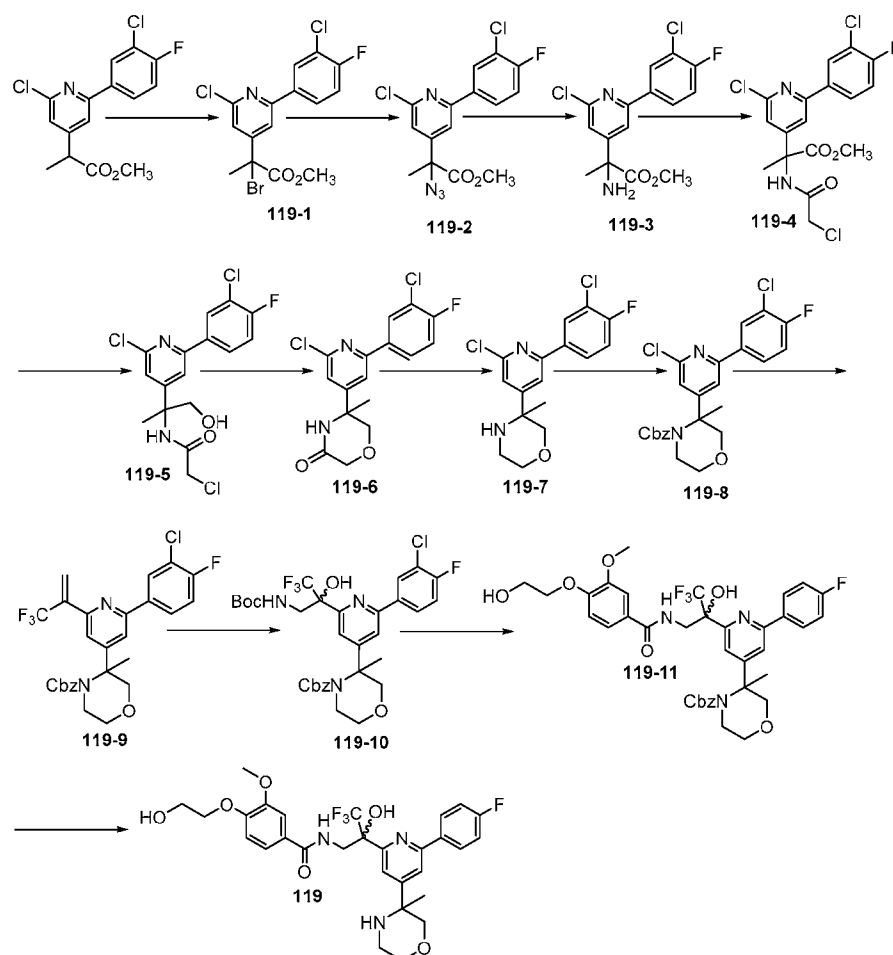
[0565] Triethylamine (0.18 mL, 1.3 mmol) was added dropwise to a solution of **118-6** (90.44 g, 1.1 mmol) in nitromethane (4 mL), and the solution was stirred at RT for 1 h. The crude material was loaded directly onto a flash column and **118-7** (0.47 g, 91%) was eluted (hexane:EA). LC/MS: m/z 459.95 [M+H]⁺.

[0566] Sodium borohydride (0.46 g, 12 mmol) was added to a solution of **118-7** (0.47 g, 1.0 mmol) and NiCl₂ (0.24 g, 1.0 mmol) in MeOH (7 mL) at 0 °C. The mixture was stirred at 0 °C for 30 minx. The reaction was quenched with sodium bicarbonate and extracted with EA. **118-8** was used without further purification. LC/MS: m/z 429.95 [M+H]⁺.

[0567] Compound **118-9** was prepared in a similar manner to **16-2**. LC/MS: m/z 638.00 [M+H]⁺. Compound **118-10** was prepared in a similar manner to **18-5**. LC/MS: m/z 698.10 [M+H]⁺.

[0568] Compound **118** was prepared in a similar manner to **8**. LC/MS: m/z 594.10 [M+H]⁺.

EXAMPLE 105
Preparation of Compound 119



[0569] Bromine (42 μ L, 0.84 mmol) was added to a solution of methyl 2-(2-chloro-6-(3-chloro-4-fluorophenyl)pyridine-4-yl) propanoate (0.213 mg, 0.76 mmol) in acetic acid (1 mL), and the solution was heating at 100 $^{\circ}$ C, for 1 h. The solvent was removed, and the mixture was concentrated. The mixture was then diluted with EA, washed with $\text{Na}_2\text{S}_2\text{O}_3$, NaHCO_3 and brine. **119-1** (0.224 g, 72%) was purified by flash chromatography (EA:hexane). LC/MS: m/z 407.80 $[\text{M}+\text{H}]^+$.

[0570] Sodium azide (5 eq) was added to a solution of **119-1** (0.224g, 0.69 mmol) in MeOH (3 mL), and the mixture was heated at 60 $^{\circ}$ C for 5 h. The mixture was diluted with EA, washed with brine, dried and concentrated. Crude **119-2** (0.32 g) was purified by flash chromatography (hexane:EA). LC/MS: m/z 414.80 $[\text{M}+\text{H}]^+$.

[0571] Compound **119-2** (0.32 g, 0.87) was hydrogenated over 10% Pd/C (30 mg) in EtOH for 1 h. The catalyst was removed by filtration, and **119-3** was used without further purification. LC/MS: m/z 342.85 [M+H]⁺.

[0572] Chloroacetylchloride (68 μ L, 8.9 mmol) was added to a solution of **119-3** (0.27 g, 0.78 mmol) and DIEA (0.20 mL, 1.2 mmol) in CH₂Cl₂ at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was diluted with EA, washed with 1N HCl and brine, dried and concentrated to afford **119-4**. LC/MS: m/z 419.80 [M+H]⁺.

[0573] Compound **119-4** was reduced with sodium borohydride in MeOH at RT for 1 h. The reaction was quenched with 1N HCl and extracted with EA. The crude product was purified by flash chromatography (EA) to provide **119-5**. LC/MS: m/z 392.75 [M+H]⁺.

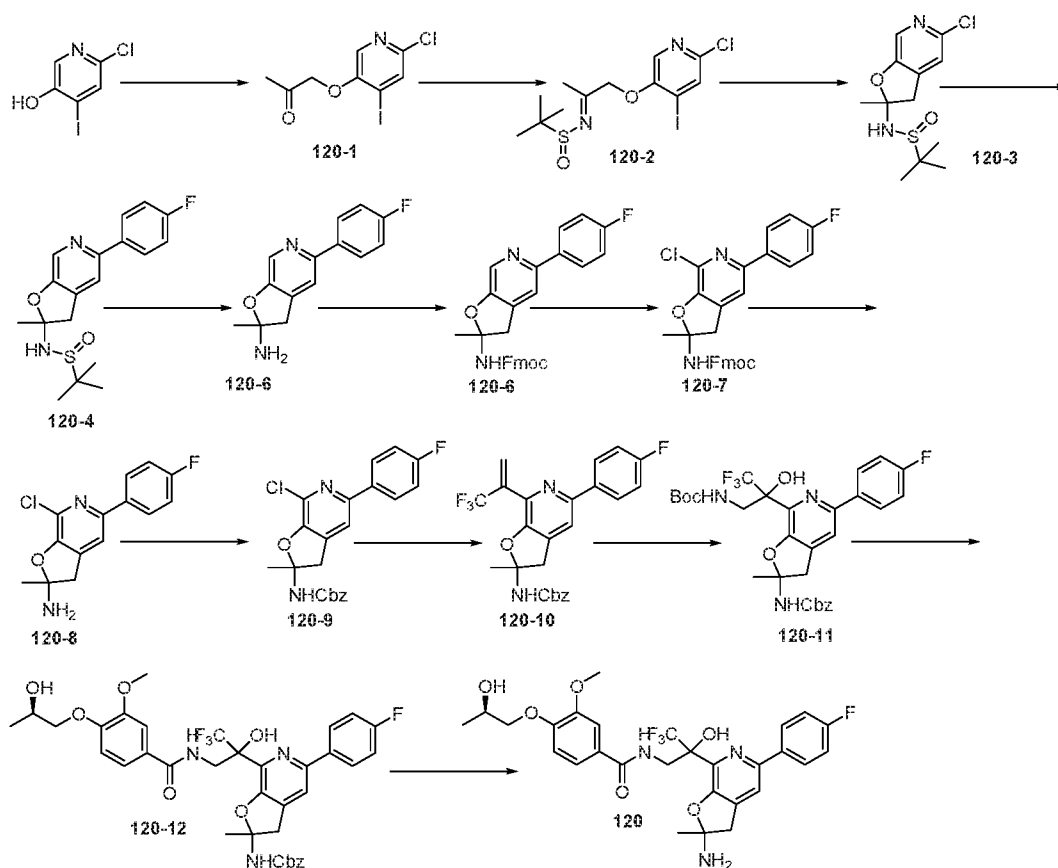
[0574] Potassium t-butoxide (10 mg) was added to a solution of **119-5** in THF (1 mL), and the mixture stirred at RT for 1 h. The reaction was quenched with 1N HCl and extracted with EA. The product was purified by flash chromatography (hexane:EA) to afford **119-6** (30 mg). LC/MS: m/z 354.90 [M+H]⁺.

[0575] Borane-dimethyl sulfide (10 μ L, 0.006 mmol) was added to a solution of **119-6** (30 mg, 0.088 mmol) in THF (2 mL), and the mixture was heated at reflux for 30 mins. The reaction was cooled to RT and quenched with MeOH and 3 drops conc. HCl. The mixture was heated at reflux for 1.5 h to break up the borate complex. The reaction was concentrated to remove the solvents, and **119-7** used without further purification. LC/MS: m/z 342.85 [M+H]⁺.

[0576] Compound **119-8** was prepared in a similar manner to **18-3**. LC/MS: m/z 474.95 [M+H]⁺. Compound **119-9** was prepared in a similar manner to **18-4**. LC/MS: m/z 535.00 [M+H]⁺. Compound **119-10** was prepared in a similar manner to **18-6**. LC/MS: m/z 668.05 [M+H]⁺. Compound **119-11** was prepared in a similar manner to **16-2**. LC/MS: m/z 762.10 [M+H]⁺.

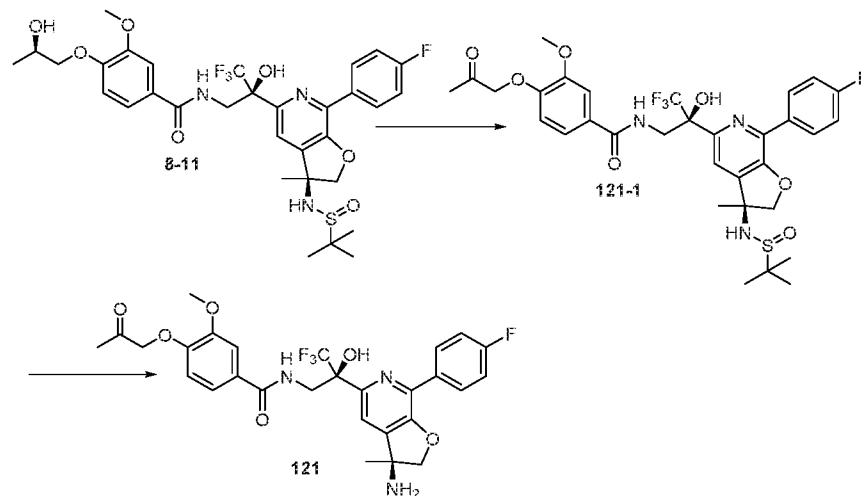
[0577] Compound **119** was prepared in a similar manner to **18**. LC/MS: m/z 594.05 [M+H]⁺.

EXAMPLE 106
Preparation of Compound 120



[0578] Compound **120-1** was prepared in a similar manner to **8-4**. LC/MS: m/z 255.85 $[M+H]^+$. Compound **120-2** was prepared in a similar manner to **8-5**. LC/MS: m/z 414.80 $[M+H]^+$. Compound **120-3** was prepared in a similar manner to **8-6**. LC/MS: m/z 288.95 $[M+H]^+$. Compound **120-4** was prepared in a similar manner to **18-5**. LC/MS: m/z 349.00 $[M+H]^+$. Compound **120-5** was prepared in a similar manner to **16**. Compound **120-6** was prepared in a similar manner to **116-3**. LC/MS: m/z 467.05 $[M+H]^+$. Compound **120-7** was prepared in a similar manner to **116-4**. LC/MS: m/z $[M+Na]^+$.523.00. Compound **120-8** was prepared in a similar manner to **116-5**. LC/MS: m/z 266.05 $[M+H]^+$. Compound **120-9** was prepared in a similar manner to **116-6**. LC/MS: m/z 412.95 $[M+H]^+$. Compound **120-10** was prepared in a similar manner to **18-4**. LC/MS: m/z 473.00 $[M+H]^+$. Compound **120-11** was prepared in a similar manner to **18-6**. LC/MS: m/z 507.00 $[M+H]^+$. Compound **120-12** was prepared in a similar manner to **18-7**. LC/MS: m/z 714.10 $[M+H]^+$. Compound **120** was prepared in a similar manner to **18**. LC/MS: m/z 580.05 $[M+H]^+$.

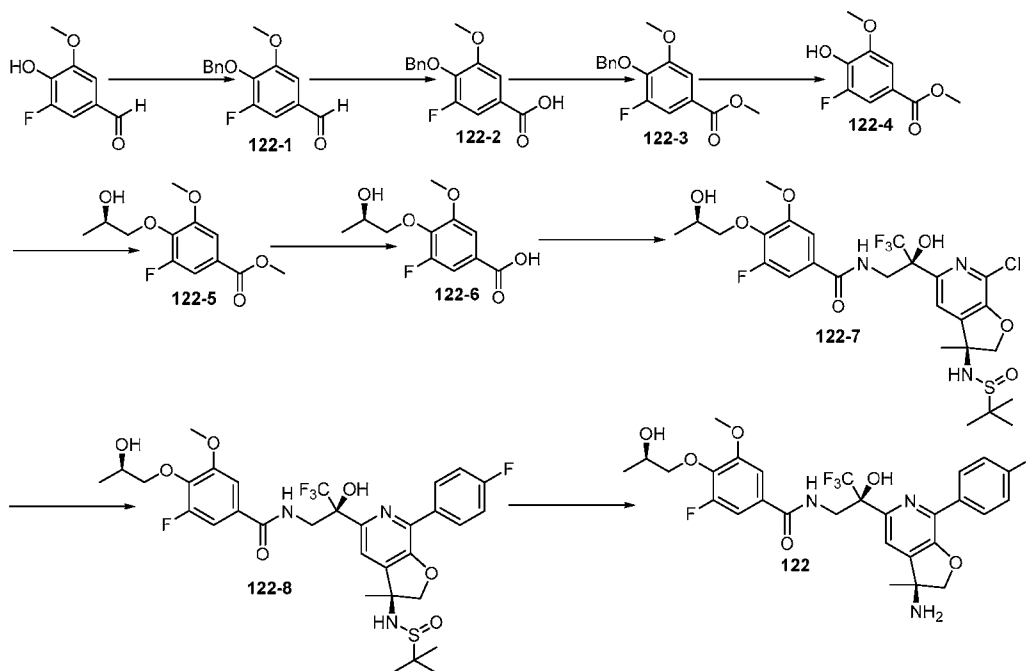
EXAMPLE 107
Preparation of Compound 121



[0579] Dess-Martin periodinane (25 mg, 0.061 mmol) was added to a solution of **8-11** (32 mg, 0.047 mmol) in dichloromethane (1 mL). The mixture was stirred at RT for 2 h. The reaction was diluted with EA, washed with Na₂CO₃ and brine, dried and concentrated. **121-1** was used crude in the next reaction. LC/MS: *m/z* 682.25 [M+H]⁺.

[0580] Compound **121-1** was deprotected in a similar manner to **16** to provide **121**. LC/MS: *m/z* 578.00 [M+H]⁺.

EXAMPLE 108
Preparation of Compound 122



[0581] Benzyl bromide (0.64 mL, 5.4 mmol) was added to a solution of 3-fluoro-4-hydroxy-5-methoxybenzaldehyde (0.70 g, 4.12 mmol) and potassium carbonate (1.7g, 12 mmol) in acetonitrile (10 mL). The solution was stirred at RT overnight. The reaction was diluted with EA, washed with water and brine, dried and concentrated. **122-1** (0.37 g, 34%) was purified by flash chromatography (hexane:EA). ^1H NMR (400 MHz, CDCl_3): δ 9.81 (d, $J=1.2$, 1H), 7.42-7.44 (m, 2H), 7.31-7.34 (m, 2H), 7.19-7.30 (m, 2H), 7.42 (s, 2H), 3.92 (s, 3H).

[0582] Compound **122-1** (0.37 g, 1.4 mmol) in acetone (2 mL) was added dropwise to a solution of potassium permanganate (0.29 g, 2.1 mmol) in water (2 mL). The solution was stirred at RT for 1 h. The reaction was quenched with saturated sodium bisulfite solution and acidified with HCl. **122-2** (0.34 g, 86%) was extracted with EA and used without further purification. ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.45 (m, 4H), 7.24-7.34 (m, 3H), 5.20 (s, 2H), 3.90 (s, 3H).

[0583] Acetyl chloride (1.0 mL) was added to MeOH (15 mL) dropwise at 0 °C. This solution was added to **122-2** (0.34 g, 1.2 mmol), and the mixture was heated at reflux overnight. The solvent was removed by evaporation and **122-3** (0.172 g, 42%) was purified

by flash chromatography (hexane:EA). ^1H NMR (400 MHz, CDCl_3): δ 7.30-7.44 (m, 7H), 5.17 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H).

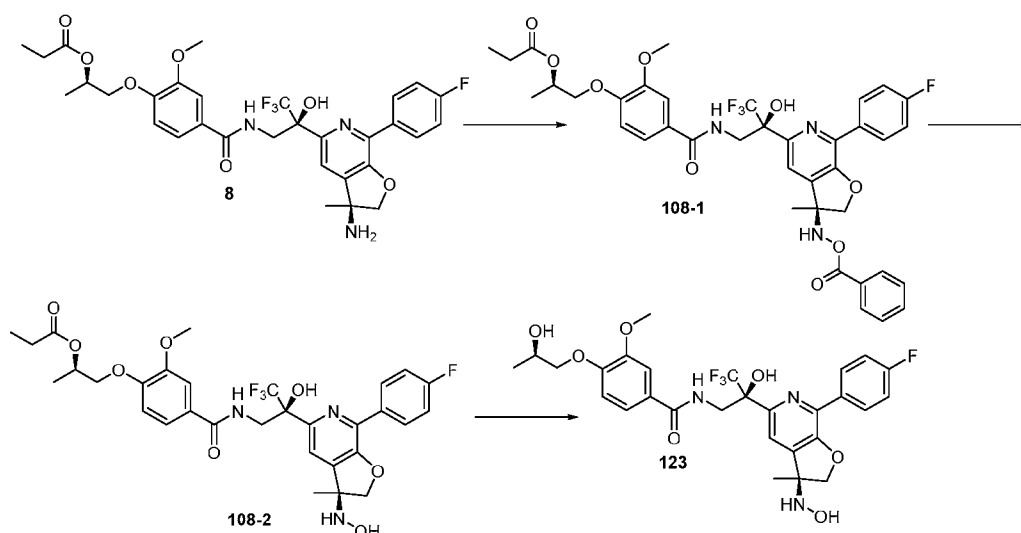
[0584] Compound **122-3** (0.172 g, 0.59 mmol) was hydrogenated over 10% Pd/C (25 mg) in ethanol (20 mL) for 1 h. The catalyst was removed by filtration, and the reaction was concentrated. **122-4** (0.104 g, 88%) was used without further purification. ^1H NMR (400 MHz, CDCl_3): δ 7.45 (dd, J = 16.1, 10.8, 1H), 7.36 (m, 1H), 3.94 (s, 3H), 3.87 (s, 3H).

[0585] (R)-Propyleneoxide (0.18 mL, 2.6 mmol) was added to a solution of **122-4** (0.104 g, 0.52 mmol) and potassium carbonate (0.14 g, 1.0 mmol) in DMF (2 mL). The reaction was heated at 80 °C overnight. The reaction was diluted with EA, washed with water and brine, dried and concentrated. **122-5** (20 mg, 15%) was purified by flash chromatography (hexane:EA). ^1H NMR (400 MHz, CDCl_3): δ 7.24-7.44 (m, 2H), 4.20-4.21 (m, 1H), 4.02-4.07 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.76-3.86 (m, 1H), 1.17 (d, J = 6.0, 3H).

[0586] Compound **122-6** was prepared in a similar manner to **19-2**. Compound **122-7** was prepared in a similar manner to **18-7**. LC/MS: m/z 442.15 $[\text{M}+\text{H}]^+$. Compound **122-8** was prepared in a similar manner to **18-5**. LC/MS: m/z 702.25 $[\text{M}+\text{H}]^+$.

[0587] Compound **122-8** was deprotected in a similar manner to **16-2** to provide **122**. LC/MS: m/z 599.05 $[\text{M}+\text{H}]^+$.

EXAMPLE 109 Preparation of Compound 123

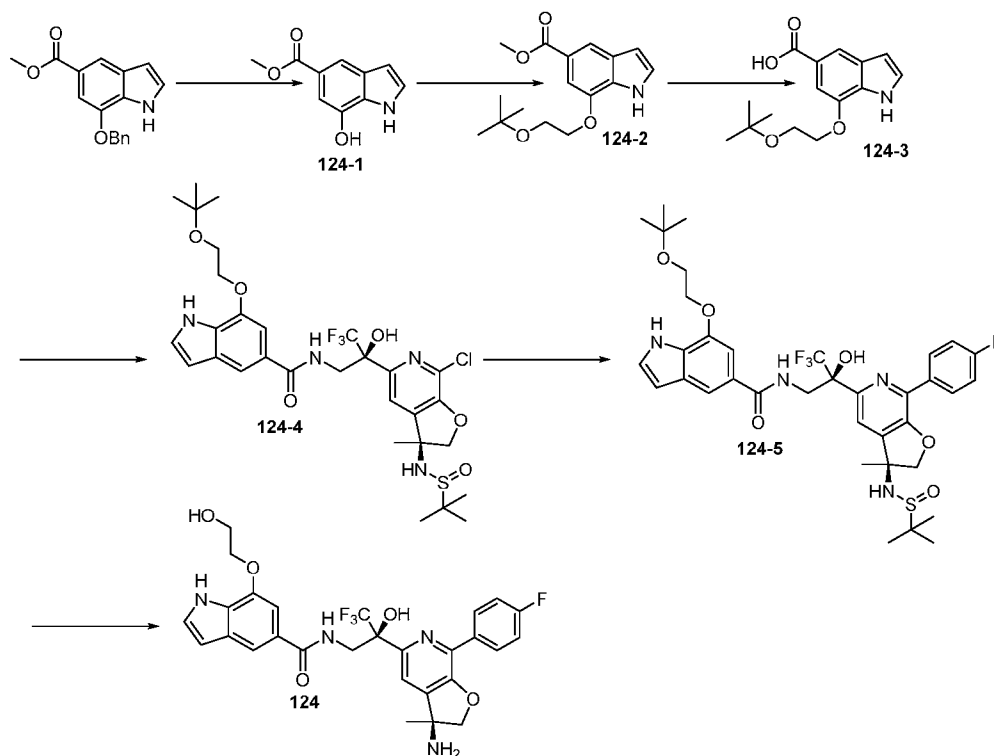


[0588] Benzoyl peroxide (0.25 g, 1.0 mmol) was added to a solution of **8** (131 mg, 0.21 mmol) and K_2HPO_4 (0.25g, 1.4 mmol) in DMF (1 mL). The reaction was stirred at RT overnight. The reaction was diluted with ethyl acetate, washed with water and brine, dried and concentrated. **123-1** (0.15 g, 90%) was purified by flash chromatography (hexane:EA). LC/MS: m/z 756.25 $[M+H]^+$.

[0589] Hydrazine hydrate (0.5 mL) was added to a solution of **123-1** (250 mg, 0.32 mmol) in THF (0.5 mL), and the mixture was stirred overnight at RT. The reaction was diluted with ethyl acetate, washed with brine, dried and concentrated. **123-2** was used without purification. LC/MS: m/z 652.25 $[M+H]^+$.

[0590] 2N HCl (0.1 mL) and conc. HCl (3 drops) were added to a solution of **123-2** (57 mg, 0.088 mmol) in THF (1 mL). The reaction was heated at 50 °C for 20 mins. The reaction was diluted with ethyl acetate, washed with brine, dried and concentrated. The final product was purified by HPLC to provide **123** (7 mg, 16%). LC/MS: m/z 596.25 $[M+H]^+$.

EXAMPLE 110 Preparation of Compound 124



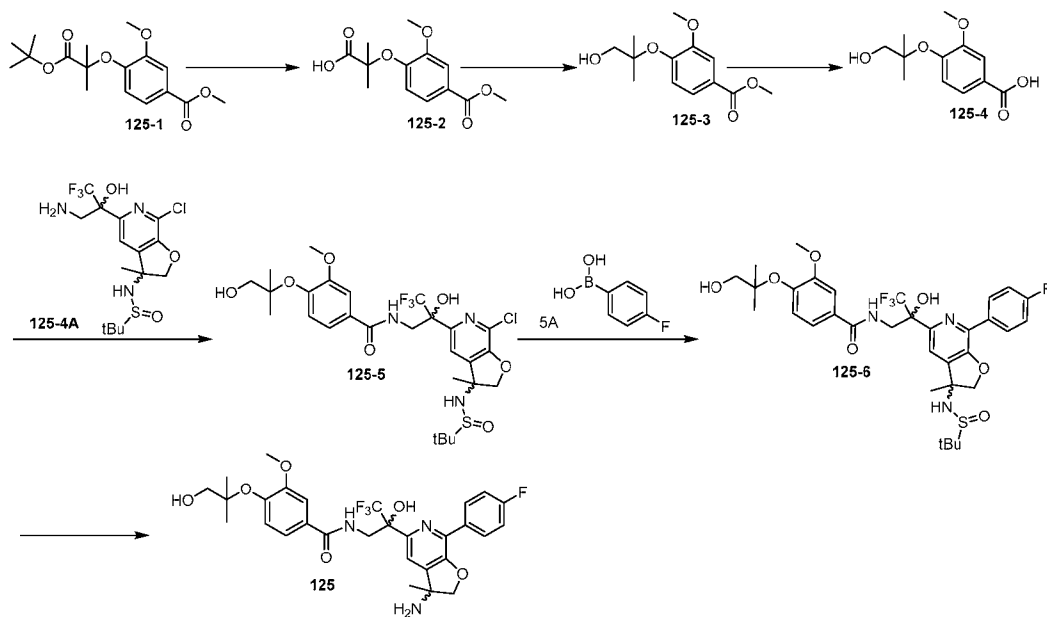
[0591] Methyl 7-(benzyloxy)-1H-indole-5-carboxylate (0.22 g) was hydrogenated over 10% Pd/C (30 mg) in EtOH for 2 h. The catalyst was removed by filtration, and the mixture was concentrated to yield **124-1** (0.13 g 92%), which was used without further purification. ¹H NMR (400 MHz, CDCl₃): δ 8.54 (br. s, 1H), 8.03 (d, J = 0.8, 1H), 7.37 (d, J = 0.8, 1H), 7.25-7.27 (m, 1H), 6.61 – 6.62 (m, 1H), 3.92 (s, 3H).

[0592] Diisopropylazodicarboxylate (53 μL, 0.27 mmol) was added drop wise to a solution of **109-1** (47 mg, 0.25 mmol), 2-(*tert*-butoxy)ethanol (44 mg, 0.27 mmol) and triphenylphosphine (71 mg, 0.27 mmol). The reaction was stirred at RT for 2 h. The reaction was concentrated and the product **124-2** (50 mg, 68%) purified by flash chromatography (hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ 9.31 (br. s, 1H), 8.08 (s, 1H), 7.37 (s, 1H), 7.19-7.20 (m, 1H), 6.58-6.59 (m, 1H), 5.28 (t, J = 5.2, 2H), 3.89 (s, 3H), 3.77 (t, J = 5.2, 2H), 1.26 (s, 9H).

[0593] Compound **124-3** was prepared in a similar manner to **19-2**. Compound **124-4** was prepared in a similar manner to **18-7**. LC/MS: m/z 675.20 [M+H]⁺. Compound **124-5** was prepared in a similar manner to **18-5**. LC/MS: m/z 735.30[M+H]⁺.

[0594] Compound **124** was prepared in a similar manner to **16**. LC/MS: m/z 575.00[M+H]⁺.

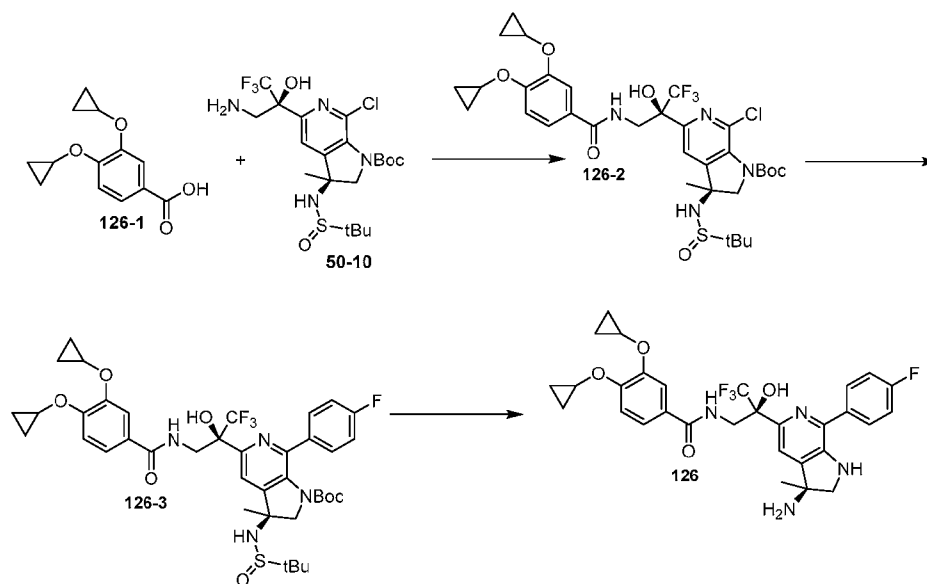
EXAMPLE 111
Preparation of Compound 125



[0595] Compound **125-1** was prepared using methods similar to those provided in WO 2010/71813 A1, and Compound **125-4A** was prepared using methods similar to those provided in WO 2015/26792 A1.

[0596] Compound **125** (5 mg, a white solid) was prepared using methods similar to those for preparing **21** using **125-1**. MS: m/z 594.0 $[M+H]^+$.

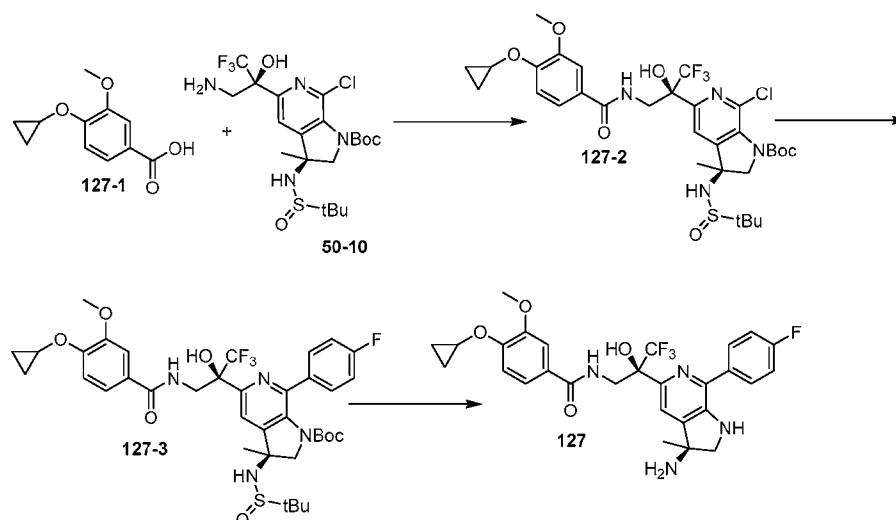
EXAMPLE 112
Preparation of Compound 126



[0597] Compound 126-1 was prepared using as described in the preparation of 25.

[0598] Compound 126 (11 mg, a pale yellow solid) was prepared using methods similar to those for preparing 21 using 126-1 and 50-10. MS: m/z 609.1 $[M+Na]^+$.

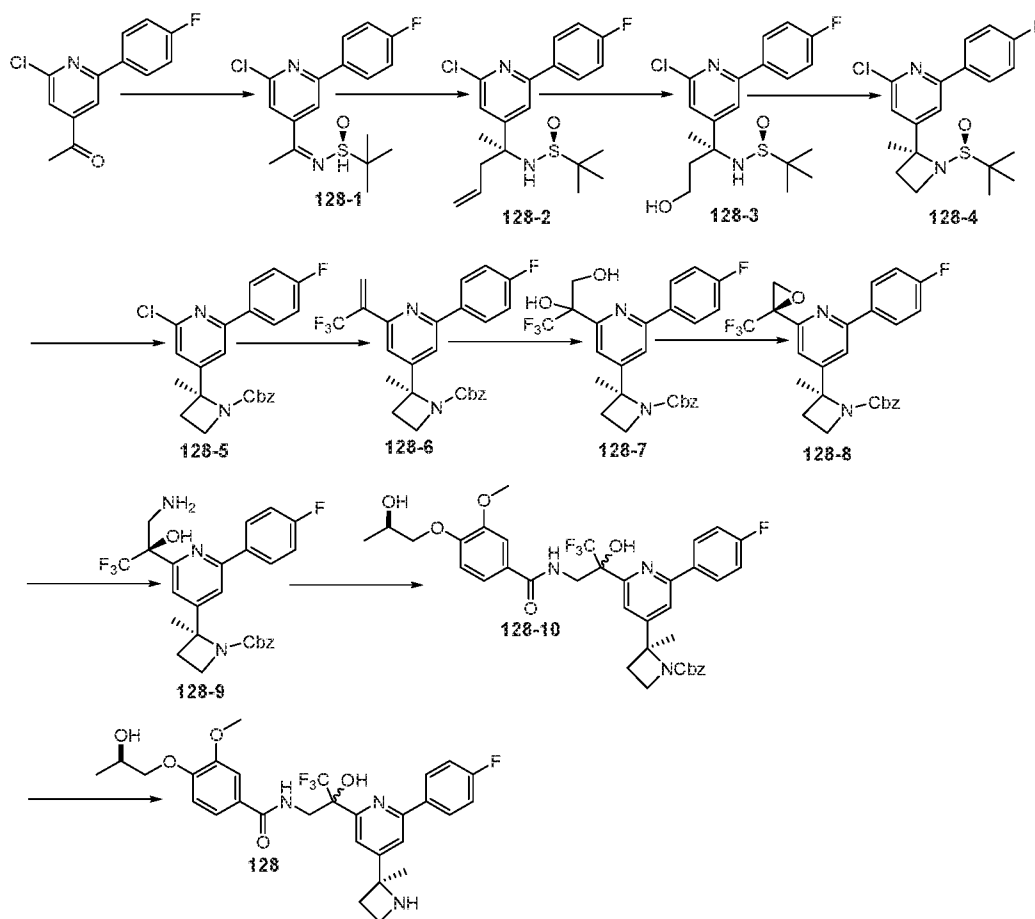
EXAMPLE 113
Preparation of Compound 127



[0599] Compound 127-1 was prepared using methods similar to those provided in WO 2015/26792 A1.

[0600] Compound **127** (46 mg, a yellow solid) was prepared using methods similar to those for preparing **21** using **127-1** and **50-10**. MS: m/z 561.1 $[M+H]^+$.

EXAMPLE 114
Preparation of Compound 128



[0601] Compound **128-1** was prepared using similar methods for preparing **103-5**. LC/MS: m/z 353.0 $[M+H]^+$.

[0602] To a stirring mixture of **128-1** (6 g, 1 eq.) in THF (85 mL) at RT was added allyl bromide (6.2 g, 3 eq.), Zn (3.3 g, 3 eq.), and $\text{In}(\text{OTf})_3$ (12.4 g, 1.3 eq.). The mixture was stirred at RT overnight. The reaction was quenched with a saturated NH_4Cl solution and diluted with EtOAc. The mixture was stirred at RT for 20 mins before it was filtered through a plug of celite. A normal aqueous work up with EtOAc was followed. The crude product was purified via a silica gel to afford **128-2**. LC/MS: m/z 395.1 $[M+H]^+$.

[0603] To a stirring mixture of **128-2** (6.7 g) in acetone/water (80 mL, 3:1) at RT were added $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (680 mg) and NMO (4.0 g). The mixture was stirred several hours at RT. The reaction was quenched with a saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution and diluted with EtOAc. A normal aqueous work up with EtOAc was followed. The crude diol was taken directly to the next reaction without further purification. LC/MS: m/z 429.1 $[\text{M}+\text{H}]^+$.

[0604] The crude diol was dissolved in acetonitrile (60 mL). To this mixture was added $\text{Pb}(\text{OAc})_4$ (9.1 g) in portionwise over 5 mins. After 1 h of stirring at RT, celite was added. The mixture was stirred for 1 h before it was filtered through a plug of celite. The filtrate was concentrated under reduced pressure. The crude product was taken directly to the next reaction without further purification. LC/MS: m/z 397.1 $[\text{M}+\text{H}]^+$.

[0605] To a stirring mixture of the crude aldehyde in MeOH (30 mL) at 0 °C was added NaBH_4 (1.16 g) in 2 portions over 10 mins. The mixture was stirred at 0 °C for 10 mins before it was warmed to RT for 20 mins. The mixture was diluted with EtOAc and quenched with a saturated NH_4Cl solution. A normal aqueous work up with EtOAc was followed. The crude product was purified via a silica gel column to afford **128-3** as a white solid (3.56 g, 52% in 3 steps). LC/MS: 399.1 m/z $[\text{M}+\text{H}]^+$.

[0606] To a stirring mixture of **128-3** (3.56 g) in THF (112 mL) at RT were added PPh_3 (3.5 g) and DIAD (3.5 mL). The mixture was stirred at reflux for 1 h before it was concentrated under reduced pressure to afford **128-4**. LC/MS: m/z 381.1 $[\text{M}+\text{H}]^+$.

[0607] To a stirring mixture of **128-4** in MeOH (25 mL) at RT was added a solution of HCl in dioxane (5 mL). The mixture was stirred at RT for 10 mins before it was concentrated under reduced pressure and purified via a silica gel column.

[0608] To a stirring mixture of the HCl salt in DCM (30 mL) at 0 °C were added DIPEA (3.2 mL) and CbzCl (2.67 mL). The mixture was stirred at 0 °C for 10 mins and slowly warmed to RT for 30 mins. The reaction was quenched with a cold saturated NaHCO_3 solution and diluted with EtOAc. A normal aqueous work up with EtOAc was followed. The crude product was purified via a silica gel column to afford the N-Cbz protected amine (2.5 g). LC/MS: m/z 411.1 $[\text{M}+\text{H}]^+$.

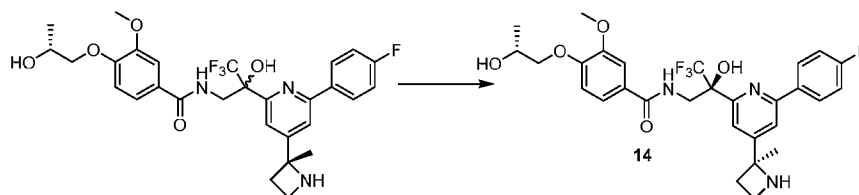
[0609] Compound **128-6** was prepared using similar methods for preparing **103-12**. LC/MS: m/z 471.1 $[\text{M}+\text{H}]^+$.

[0610] To a stirring mixture of **128-6** (680 mg) in tBuOH/water (2.4 mL each) at 0 °C were added NH₂SO₂Me (146 mg) and AD-mix β (4.2 g). The mixture was stirred at 0 °C for 5 h and slowly warmed to RT over the weekend. The crude product was diluted with EtOAc and quenched with a 10% aqueous solution of Na₂S₂O₃. A normal aqueous work up with EtOAc was followed. The crude product was purified via a silica gel column to afford the desired product as a colorless oil. LC/MS: m/z 505.2 [M+H]⁺.

[0611] Compound **128-8** was prepared using similar methods for preparing **103-14**. LC/MS: m/z 487.1 [M+H]⁺. Compound **128-9** was prepared using similar methods for preparing **103-15**. LC/MS: m/z 504.1 [M+H]⁺. Compound **128-10** was prepared using similar methods for preparing **103-16**. LC/MS: m/z 712.3 [M+H]⁺.

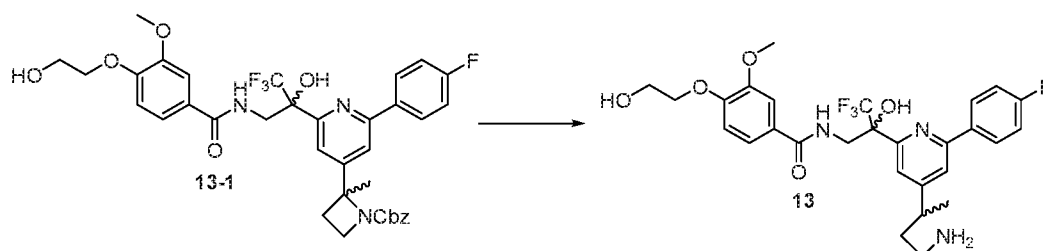
[0612] To a stirring mixture of **128-10** (30 mg) in MeOH (0.7 mL) at RT were added Pd/C (7 mg) and Et₃SiH (51 mg total in 3 portions over 10 mins). The mixture was stirred at RT for 20 mins before it was filtered through a plug of celite. The filtrate was concentrated under reduced pressure and further purified via HPLC to afford **128** as a white solid. LCMS: m/z 578.2 [M+H]⁺.

EXAMPLE 115 Preparation of Compound 14



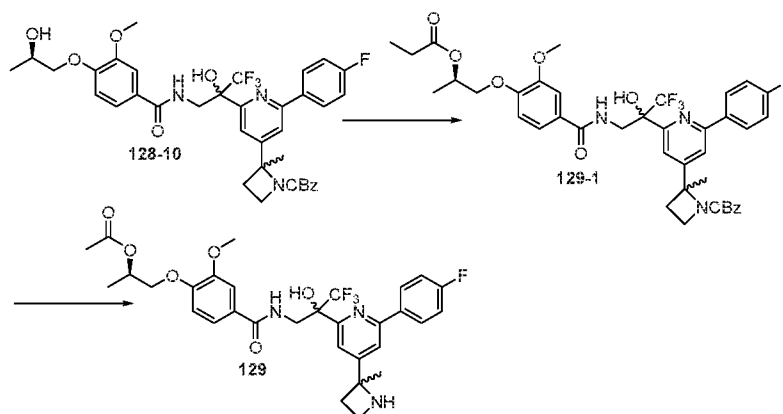
[0613] The racemic mixture of **128** (120 mg) was separated by SFC using method showed below: "Column: Chiralpak AD-H 250×4.6mm I.D., 5 μm Mobile phase: A: CO₂, B: ethanol(0.05% DEA) Gradient: from 5% to 40% of B in 4.2 mins and hold 40% for 3 mins, then 5% of B for 2.8 mins Flow rate: 2.5mL/min". After separation, the solution was concentrated, and re-purified by prep-HPLC (HCl condition) to give **14** (14 mg, 11.7%) as a light yellow solid. LCMS: m/z 578.0 [M+H]⁺.

EXAMPLE 116
Preparation of Compound 13



[0614] Compound **13-1** was synthesized using similar procedures as provided for **128**. Compound **13** was obtained as a byproduct during the removal the N-Cbz protected amine using Et_3SiH , Pd/C in MeOH. LCMS: m/z 566.2 $[\text{M}+\text{H}]^+$.

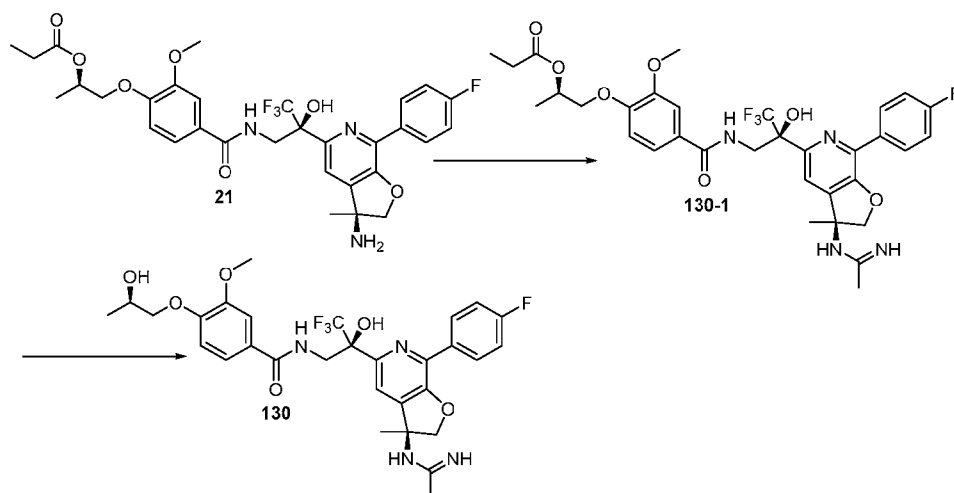
EXAMPLE 117
Preparation of Compound 129



[0615] To stirring mixture of **128-10** (30 mg) and propionic acid (9.3 mg) in THF (1 mL) at RT were added a solution of DCC (60% in xylenes, 48 μL , 3 eq.) and DMAP (1 mg). The mixture was stirred at RT for 2 h before it was filtered. The filtrate was concentrated under reduced pressure. The crude product was purified via HPLC to afford **129-1** (28 mg, 88%). LC/MS: m/z 768.3 $[\text{M}+\text{H}]^+$.

[0616] To a stirring mixture of **129-1** (28 mg, 1 eq.) and Pd/C (6.3 mg) in MeOH (280 μL) was added Et_3SiH (13 mg) dropwise over 10 mins. The mixture was stirred for 15 mins before it was filtered and concentrated under reduced pressure. The crude product was purified via HPLC to afford **129** as a white solid. LC/MS: m/z 634.3 $[\text{M}+\text{H}]^+$.

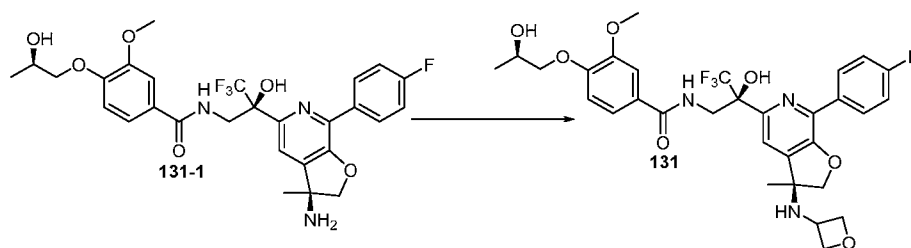
EXAMPLE 118
Preparation of Compound 130



[0617] Trimethylaluminum (2M in hexane, 1.6 mL, 5.8 mmol) was added to a solution of **21** (0.403 g, 0.63 mmol) in acetonitrile (12 mL), and the solution was heating at 90 °C in a sealed tube for 1 h. The mixture was cooled to 0 °C, quenched with MeOH, and concentrated. Crude **130-1** (50 mg, 13%) was purified by HPLC. LC/MS: m/z 677.10 [M+H]⁺.

[0618] HCl (2N, 0.1 mL) was added to a solution of **130-1** (50 mg, 0.074 mmol) in THF (3 mL). The solution was heated at 60 °C for 3 h. The reaction was concentrated and **130** (11.0 mg, 23%) was purified by HPLC. LC/MS: m/z 621.15 [M+H]⁺.

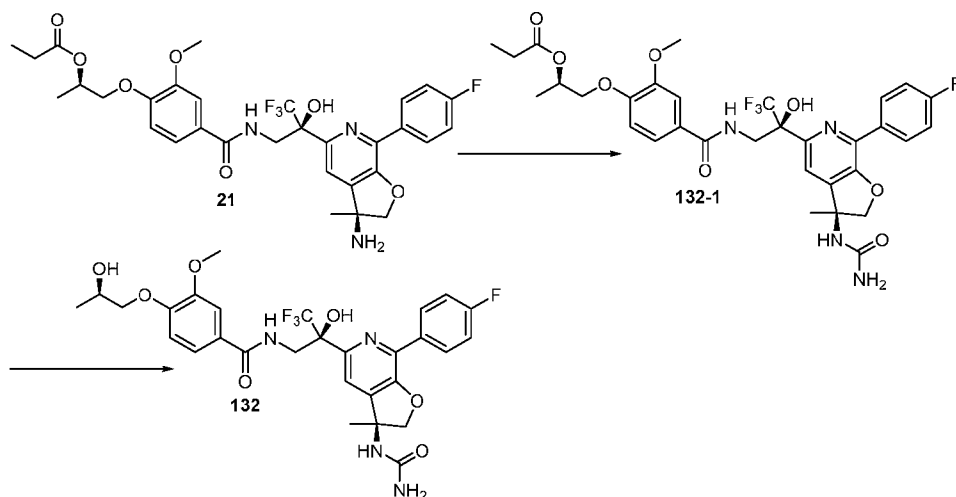
EXAMPLE 119
Preparation of Compound 131



[0619] Sodium triacetoxyborohydride (93 mg, 0.24 mmol) was added to a solution of **131-1** (126 mg, 0.22 mmol), acetic acid (13 μL, 0.22 mmol) and 3-oxetanone (13 μL, 0.22 mmol) in dichloroethane (2 mL). The reaction was stirred at RT for 1 h, at which point additional reagents were added. The reaction was stirred at RT overnight. The

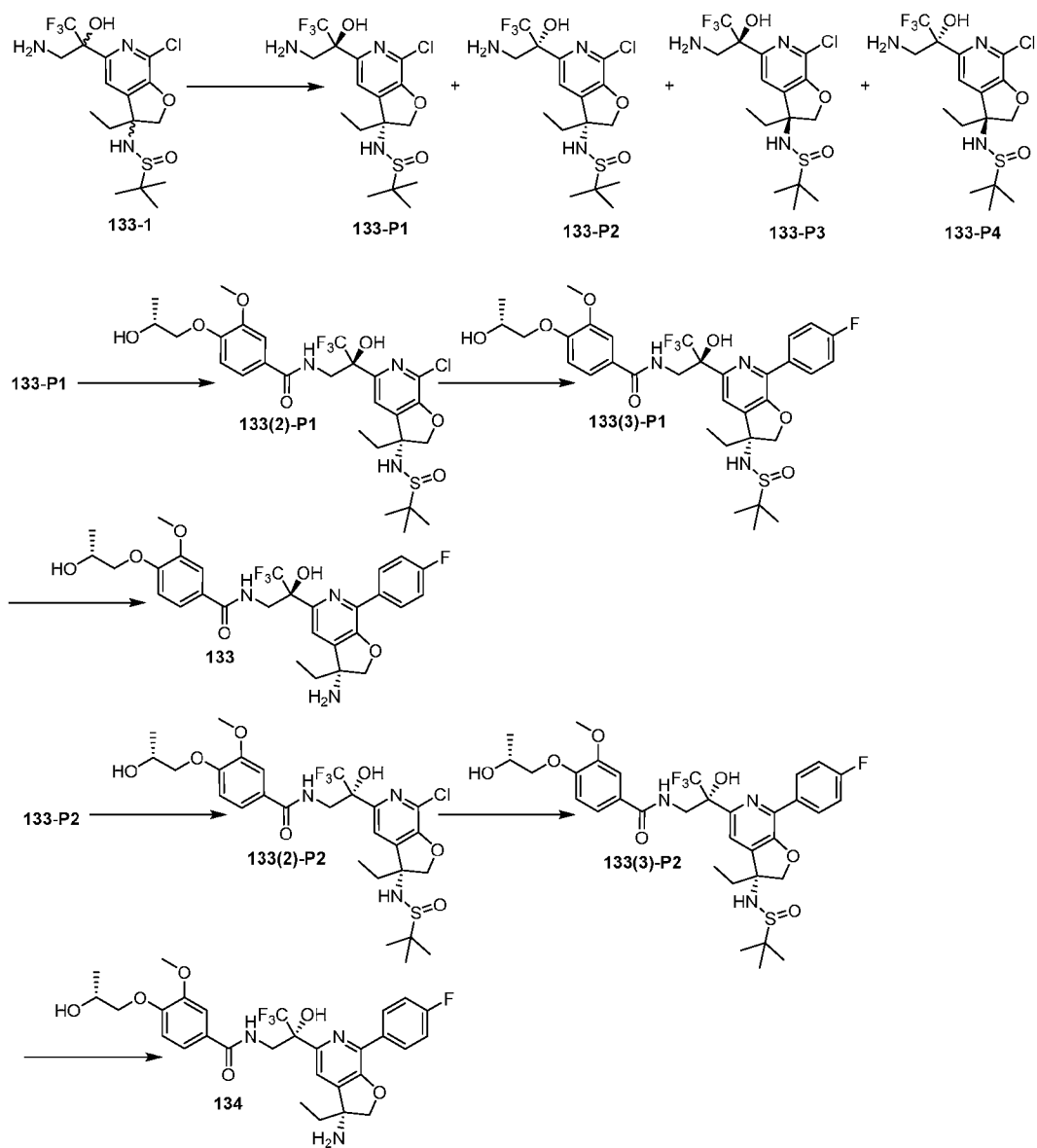
reaction was diluted with EA, washed with 1N HCl and brine, dried and concentrated. Compound **131** (11mg, 8%) was purified by HPLC. LC/MS: m/z 621.15 $[M+H]^+$.

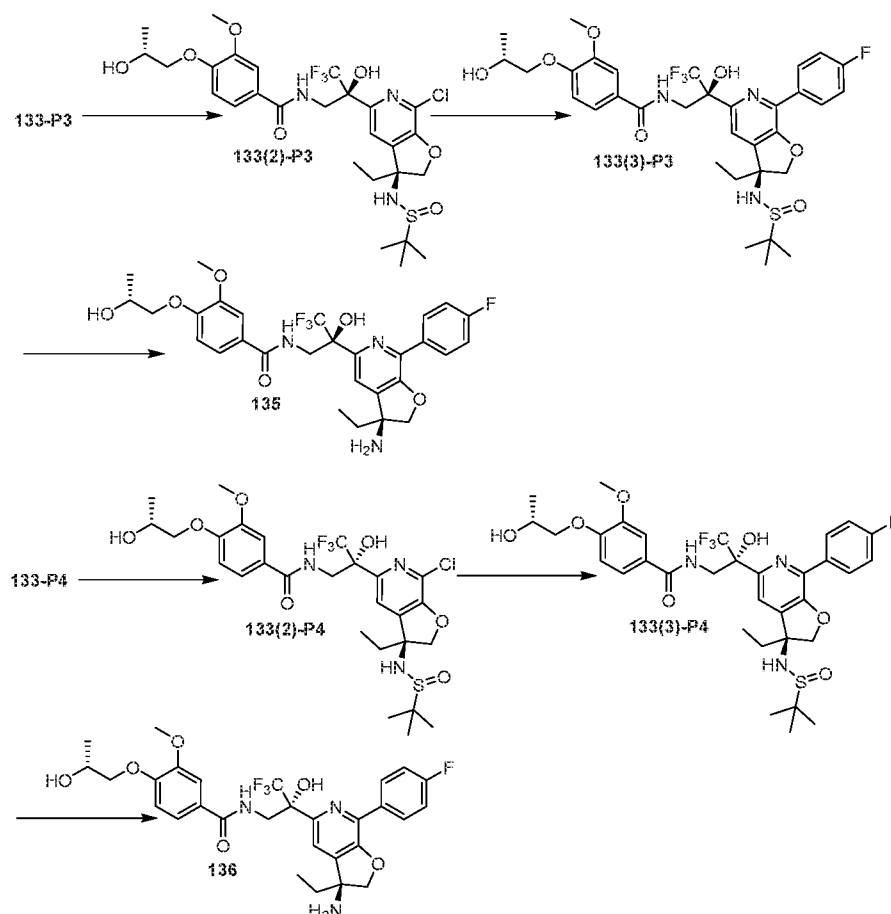
EXAMPLE 120
Preparation of Compound 132



[0620] Ethyl-2-thiopseudourea hydrobromide (0.32 g, 1.7 mmol) was added to a solution of **21** (109 mg, 0.17 mmol) in EtOH (5 mL). The solution was heated at reflux for 2 days. The reaction was concentrated, and **132-1** (28 mg, 24%) was purified by HPLC. LC/MS: m/z 679.10 $[M+H]^+$.

[0621] Compound **132** was prepared using methods similar to those for preparing **123** using **132-1**. MS: m/z 623.05 $[M+H]^+$.

EXAMPLE 121**Preparation of Compounds 133, 134, 135 and 136**



[0622] Compound **133-1** was prepared using methods similar to those provided in WO 2015/26792 A1.

[0623] Compound **133-1** (500 mg) was separated by prep-HPLC (FA condition). The separated solution was concentrated to give four desired isomers: **133-P1** (15.8 mg), **133-P2** (45 mg), **133-P3** (40 mg) and **133-P4** (68 mg) were obtained as a colorless oil. MS: m/z 429.9 $[M+H]^+$.

[0624] To a mixture of (*R*)-4-(2-hydroxypropoxy)-3-methoxybenzoic acid (15.8 mg, 0.07 mmol, WO 2015/26792 A1) and DIPEA (14 mg, 0.1 mmol) in DMF (1 mL) was added HATU (13.3 mg, 0.035 mmol). The mixture was stirred at 25 °C for 5 mins and **133-P1** (15 mg, 0.035 mmol) was added. After stirring at 25 °C for 30 mins, the reaction was quenched with H₂O (5 mL) and extracted with EA (10 mL). The organic layer was concentrated to give crude **133(2)-P1** (12 mg) as a colorless oil. MS: m/z 638.0 $[M+H]^+$.

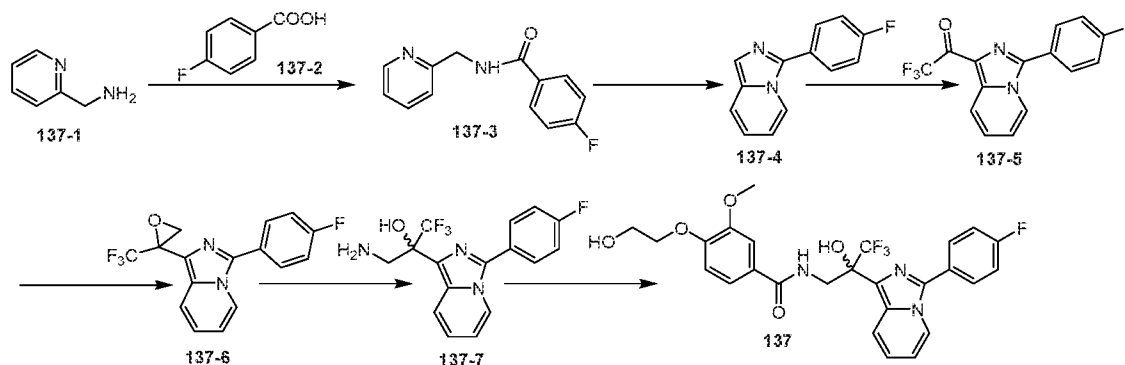
[0625] A mixture of **133(2)-P1** (12 mg, crude), 4-Fluorophenylboronic acid (10 mg, 0.07 mmol), Cs₂CO₃ (46.8 mg, 0.14 mmol) and Pd(dppf)Cl₂ (5 mg) in dioxane (2

mL):H₂O (0.2 mL) was heated at 120 °C for 30 mins under microwave. The mixture was concentrated, and the residue was purified by prep-TLC (EA) to give **133(3)-P1** (9.5 mg) as a colorless oil. MS: m/z 698.2 [M+H]⁺.

[0626] To a solution of **133(3)-P1** (10 mg) in MeOH (0.5 mL) was added HCl/MeOH (4M, 0.5 mL). The mixture was stirred at 25 °C for 15 mins and concentrated. The residue was purified by prep-HPLC (HCl condition) to give **133** (2.5 mg) as a white solid. MS: m/z 594.1 [M+H]⁺.

[0627] Compound **134** (9.3 mg, a white solid) **135** (32.1 mg, a white solid) and **136** (14.2 mg, a white solid) were prepared in a similar manner as preparing **133** using **133-P2**, **133-P3** and **133-P4**, respectively. **134**: MS: m/z 594.2 [M+H]⁺. **135**: MS: m/z 594.1 [M+H]⁺. **136**: MS: m/z 594.1 [M+H]⁺.

EXAMPLE 121 Preparation of Compound 137



[0628] To a solution of **137-2** (2.6 g, 18.5 mmol) and DIPEA (4.8 g, 37.2 mmol) in DMF (20 mL) was added HATU (7.03 g, 18.5 mmol) in 1 portion. After stirring for 5 mins, **137-1** (2.0 g, 18.5 mmol) was added. The mixture was stirred at 25 °C for 30 mins. The mixture was poured into water (40 mL) and extracted with EA (2 X 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 15~25% EA in PE as the eluent to give **137-3** (3.0 g, 70.5 %) as light yellow oil. MS: m/z 230.9 [M+H]⁺.

[0629] A mixture of **137-3** (2.8 g, 12.2 mmol) in TFAA (50 mL) was stirred at 50 °C for 3 h. The reaction was quenched by saturated NaHCO₃ and extracted with EA (2 X 50 mL). The combined organic layers were dried, washed with brine (20 mL), dried over

Na₂SO₄ and concentrated. The residue was purified by column chromatography using 5~15% EA in PE to give **137-4** (1.2 g, 46.6%) as a light yellow solid. MS: m/z 212.8 [M+H]⁺.

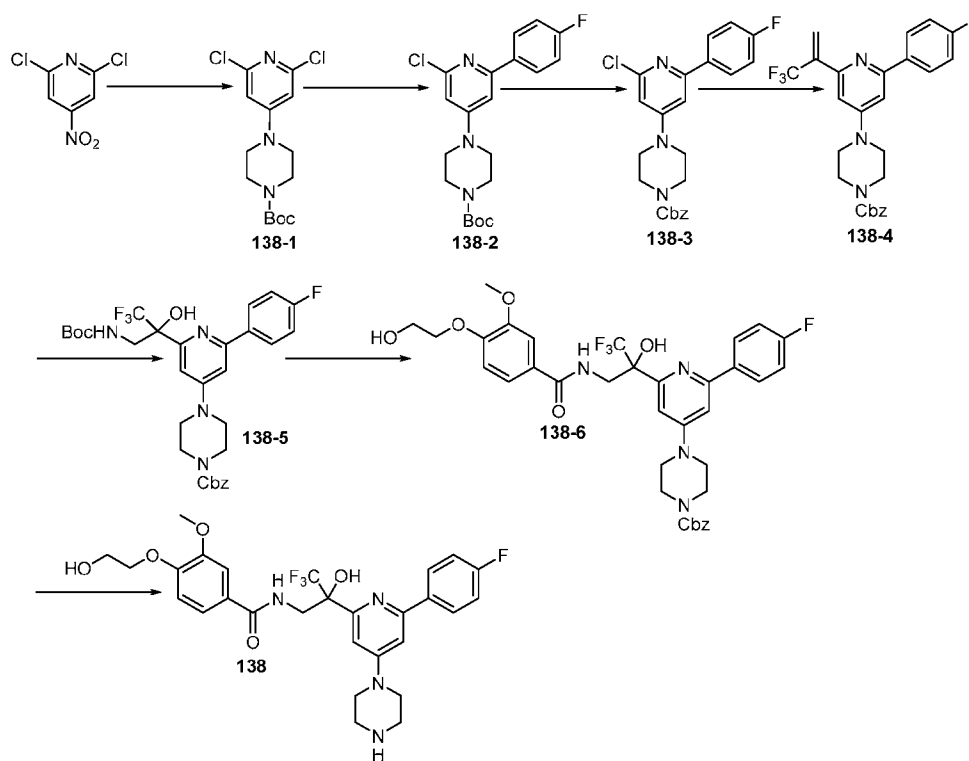
[0630] To a solution of **137-4** (1.0 g, 4.7 mmol) in DMF (25.00 mL) was added TFAA (1.48 g, 7.1 mmol) dropwise. The mixture was stirred at 25 °C for 15 h. The reaction was quenched with saturated NaHCO₃ and extracted with EA (2 X 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated to give **137-5** (1.25 g, 86.1%) as a light yellow solid. MS: m/z 308.9 [M+H]⁺.

[0631] To a mixture of t-BuOK (87 mg, 0.78 mmol) in CH₃CN (8 mL) was added Me₃SOI (143 mg, 0.65 mmol) in 1 portion. The mixture was degassed and stirred at 25 °C for 0.5 h. The clear solution was poured to a solution of **137-5** (200 mg, 0.65 mmol) in CH₃CN (8 mL), and the mixture was stirred at 25 °C for 1 h. The solution was used for the next step directly. MS: m/z 322.8 [M+H]⁺.

[0632] A mixture of **137-6** (crude solution in CH₃CN) in NH₃-EtOH (10 mL, 7M) was stirred at RT for 1.5 h. The mixture was poured into water (40 mL) and extracted with EA (2 X 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-TLC (DCM:MeOH = 20:1) to give **137-7** (75 mg, 34% over 2 steps) as a light yellow gum.

[0633] To a solution of 4-(2-hydroxyethoxyl)-3-methoxybenzoic acid (41 mg, 0.19 mmol), DIEA (50 mg, 0.38 mmol) and **137-7** (65 mg, 0.19 mmol) in DMF (10 mL) was added HATU (73 mg, 0.19 mmol). The mixture was stirred at 25 °C for 2 h, poured into water (15 mL) and extracted with EA (2 X 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC (HCl condition) to give **137** (47 mg) as a white solid. MS: m/z 534.1 [M+H]⁺.

EXAMPLE 122
Preparation of Compound 138



[0634] To a stirring mixture of 2,6-dichloro-4-nitropyridine (940 mg, 1 eq.) in THF:DMF (7.8 mL:2.3 mL) at RT were added Et₃N (670 μ L) and 2,6-dichloro-4-nitropyridine (908 mg, 1 eq.). The mixture was stirred at RT for 2 h before it was concentrated under reduced pressure. The crude product mixture was purified via a silica gel column to afford the desired product as a yellow solid (560 mg, 37%). LC/MS: m/z 332.1 [M+H]⁺.

[0635] To a stirring mixture of tert-butyl 4-(2,6-dichloropyridin-4-yl)piperazine-1-carboxylate (560 mg, 1 eq.) in a solution of TBAF in THF (5.1 mL, 3 eq.) at RT were added PdCl₂(dppf) (124 mg, 0.1 eq.) and (4-fluorophenyl)boronic acid (235 mg, 1 eq.). The mixture was carried under the microwave condition at 90 °C for 1 h. The mixture was concentrated under reduced pressure and purified via a silica gel column to afford the desired product as a white solid. LC/MS: m/z 392.2 [M+H]⁺.

[0636] 2N HCl in dioxane (3 mL) was added to 138-2 (0.11 g, 0.28 mmol), and the solution was stirred at RT for 1 h. The reaction was concentrated and then redissolved in dichloromethane (3 mL). DIEA (0.15 mL, 0.85 mmol) and benzyl chloroformate (52 μ L,

0.37 mmol) were added, and the reaction was stirred at RT for 2 h. The reaction was concentrated, and **138-3** (0.116 g, 96%) was purified by flash chromatography (hexane:EA). LC/MS: $[M+H]^+$ 426.05 $[M+H]^+$.

[0637] Compound **138-4** was prepared using methods similar to preparing **18-4**. LC/MS: m/z 486.15 $[M+H]^+$. Compound **138-5** was prepared using methods similar to preparing **18-6**. LC/MS: m/z 619.25 $[M+H]^+$. Compound **138-6** was prepared using methods similar to preparing **18-7**. LC/MS: m/z 713.25 $[M+H]^+$.

[0638] Compound **138** was prepared by deprotecting **138-6** using methods similar to those for preparing **18**. LC/MS: m/z 579.25 $[M+H]^+$.

EXAMPLE A **RSV Antiviral Assay**

[0639] CPE reduction assays are performed as described by Sidwell and Huffman et al., Appl. Microbiol. (1971) 22(5):797–801 with slight modifications. HEp-2 cells (ATCC#, CCL-23) are seeded at a density of 1,500 cells/30 μ L/well into the 384-well cell plate(s) (Corning#3701) one day prior to the assay. Compounds are added into 384-well cell plates by Labcyte POD 810 Plate Assembler system. Each of the test compounds is provided to duplicate wells of a 384-well cell plate at final concentrations starting from 100 μ M or 1 μ M using 1/3 stepwise dilutions for 9 points. Quick-thaw Respiratory Syncytial Virus (RSV) long strain (ATCC#VR-26) stock in a 37°C water bath. Place on ice until ready to use. Viruses are diluted to the concentration of 100 TCID₅₀/30 μ L with medium and 30 μ L diluted RSV are added into related wells of 384-well cell plates. For each plate, sixteen wells are set aside as uninfected, untreated cell controls (CC), and nine wells per test plate receive virus only as a control for virus replication (VC). The final DMSO concentration of all wells is 1%. Place the plates at 37°C, 5% CO₂ for 5 days.

[0640] After 5 days incubation, observe the CPE of cells in all wells. Cell controls should be natural and have no cell fusion; Cells in the virus control wells should exhibit signs of virus cytopathology (giant cell formation, syncytia). Six μ L of cell counting kit-8 reagent (CCK-8, Dojindo Molecular Technologies Inc., CK04-20) are added to each well, which allows colorimetric assays to determine the number of viable cells through the dehydrogenase activity detection. After 3-4 hour incubation, the absorbance of each well is

measured with a spectrophotometric plate reader at 450 nm wavelength, using a 630 nm filter as background according to manufacturer's instruction. The 50% effective concentration (EC_{50}) is calculated by using regression analysis, based on the mean O.D. at each concentration of compound.

[0641] Compounds of Formula (I) are active in the assay against the RSV virus as demonstrated in Tables A and B. Table A includes compounds with an EC_{50} value that is less than 1 μ M. Table B includes compounds with an EC_{50} value that is equal to or higher than 1 μ M and less than 50 μ M. Other tested compounds disclosed herein had an EC_{50} value of 50 μ M or greater.

Table A

Compound	Compound	Compound	Compound	Compound
1	3	5	7	12
2	4	6	8	

Table B

Compound
10

EXAMPLE B **Cytotoxicity Determination**

[0642] In order to determine the compound cytotoxicity, in parallel, each of the compounds is applied to duplicate wells in a 384-well cell plate at serial final concentrations starting from 100 μ M using 1/2 stepwise dilutions for 7 points without addition of virus. Incubate the cells at 37°C, 5% CO_2 for 5 days. Add 6 μ L CCK-8 into each well and incubate in a CO_2 incubator at 37°C for 3-4 h. Read the plates to obtain the optical densities which are used to calculate 50% cytotoxicity concentration (CC_{50}).

[0643] Compounds of Formula (I) are not cytotoxic as shown in Tables C and D. Table C includes compounds with a CC_{50} value that is greater than 100 μ M. Table D includes compounds with a CC_{50} value that is equal to or less than 100 μ M and greater than 10 μ M. Other tested compounds disclosed herein had a CC_{50} value of less than 10 μ M.

Table C

Compound	Compound	Compound	Compound	Compound
3	12	46	72	130
6	26	51	82	
7	37	67	87	
8	40	71	119	

Table D

Compound	Compound	Compound	Compound	Compound
1	30	62	91	115
2	31	65	92	116
5	34	68	93	117
10	35	69	94	118
11	36	70	95	120
13	38	73	98	121
14	39	74	101	122
15	41	75	102	123
16	43	76	103	124
18	44	79	106	125
19	47	80	107	126
20	48	81	108	127
21	49	83	109	129
22	55	84	110	131
23	57	85	111	132
24	59	86	112	138
25	60	88	113	
27	61	90	114	

EXAMPLE C**RSV Polymerase Inhibition Assay**

[0644] Standard RSV polymerase assays were conducted in the presence of 10 nM recombinant RSV complex in a reaction buffer containing Tris-HCl pH7.5, 6 mM MgCl₂, and other additives and substrates including RNA oligonucleotides and radionucleotides. Standard reactions were incubated in 96-well plate format for 2 h at 30 °C, in the presence of increasing concentration of inhibitor. The reaction was stopped with 90 µL of 0.1M EDTA, and the reaction product was transferred to a "reading" 96-well plate. After washing of the plate, radiolabeled RNA products were detected according to standard procedures with a Trilux Topcount scintillation counter. The compound concentration at

which the enzyme-catalyzed rate was reduced by 50% (IC₅₀) was calculated by fitting the data to a non-linear regression (sigmoidal). The IC₅₀ values were derived from the mean of several independent experiments and are shown in Tables E and F.

[0645] Table E includes compounds with an IC₅₀ of < 1 μ M. Table F includes compounds with an IC₅₀ < 50 μ M.

Table E

Compound	Compound	Compound	Compound	Compound
1	31	59	87	114
2	32	60	88	115
3	33	61	89	116
9	34	65	90	118
11	35	68	91	119
12	36	69	92	120
13	37	70	94	121
14	38	71	95	122
15	39	72	96	123
16	40	73	97	124
17	41	74	98	125
18	42	75	99	126
19	43	76	101	127
20	44	77	102	130
21	47	79	103	131
22	49	80	106	132
23	51	81	108	133
24	53	82	109	137
25	55	83	110	138
27	56	84	111	
28	57	85	112	
30	58	86	113	

Table F

Compound	Compound	Compound	Compound
10	54	78	107
26	62	93	117
48	67	100	

EXAMPLE D
RSV Assay

[0646] The RSV subgenomic replicon 395 HeLa and APC126 were licensed from Apath (Brooklyn, NY) and were originally developed by Dr. Mark Meebles of Center for Vaccines & Immunity, the Research Institute at Nationwide Children's Hospital in Columbus, Ohio. To generate subgenomic RSV replicon, three glycoprotein genes, those for SH, G, and F, from a full-length recombinant GFP-expressing (rg) RSV antigenomic cDNA were deleted. In their place, a blasticidin S deaminase (*bsd*) gene was inserted. Through multiple steps, the RSV replicon was established in HeLa cells (395 HeLa) or BHK cells (APC126). Both 395 HeLa and APC126 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) containing 4500 mg/L D-glucose, L-glutamine, and 110 mg/L sodium pyruvate (Invitrogen, Cat. #11995-040). The medium was further supplemented with 10% (v/v) fetal bovine serum (FBS) (Mediatech, Cat. #35-010-CV), 1% (v/v) penicillin/streptomycin (Mediatech, Cat. #30-002-CI), and 10 µg/mL of Blasticidin (BSD) (Invivogen, Cat. code ant-bl-1). Cells were maintained at 37 °C in a humidified 5% CO₂ atmosphere.

[0647] Determination of 50% inhibitory concentration (EC₅₀), 90% inhibitory concentration (EC₉₀) and 50% cytotoxic concentration (CC₅₀) in RSV replicon cells were performed by the following procedure. On the first day, 5000 RSV replicon cells per well were plated in a 96-well plate. On the following day, compounds to be tested were solubilized in 100% DMSO to 100X the desired final testing concentration. Each compound was serially diluted (1:3) up to 9 distinct concentrations. Compounds in 100% DMSO were reduced to 10% (v/v) DMSO by diluting 1:10 in cell culture media. A 10 µL sample of the compounds diluted to 10% (v/v) DMSO with cell culture media was used to treat the RSV replicon cells in 96-well format. The final DMSO concentration was 1% (v/v). Cells were incubated with compounds for 7 days (for 395Hela) or 3 days (for APC126) at 37 °C in a 5% CO₂ atmosphere. In each assay, positive control that was previously characterized in the RSV replicon assay was included.

[0648] The *Renilla* Luciferase Assay System (Promega, Cat. #E2820) was used to measure anti-RSV replicon activity. Assay plates were set up as stated above. Luminescence was recorded using a Perkin Elmer multilabel counter Victor3V. EC₅₀, the

concentration of the drug required for reducing RSV replicon RNA by 50% in relation to the untreated cell control value, was calculated from the plot of percentage reductions of the optical density (OD) value against the drug concentrations using the Microsoft Excel forecast function.

[0649] 395 HeLa or APC126 cell proliferation assay (Promega; CellTiter-Glo Luminescent Cell Viability Assay, Cat. #G7572) was used to measure cell viability. The CellTiter-Glo[®] Luminescent Cell Viability Assay is a homogeneous method to determine the number of viable cells in culture based on quantitation of the ATP present, which signals the presence of metabolically active cells. Assay plates were set up in the same format as noted above for the replicon assay. CellTiter-Glo reagent (100 μ L) was added to each well and incubated at room temperature for 8 minutes. Luminescence was recorded using a Perkin Elmer multilabel counter Victor3V. The CC₅₀, the concentration of the drug required for reducing viable cells by 50% in relation to the untreated cell control value, was calculated from the plot of percentage reductions of the luminescence value against the drug concentrations using the Microsoft Excel forecast function.

[0650] Table G includes compounds with an EC₅₀ value that is less than 1 μ M. Table H includes compounds with an EC₅₀ value that is equal to or higher than 1 μ M and less than 50 μ M. Other tested compounds disclosed herein had an EC₅₀ value of 50 μ M or greater.

Table G

Compound	Compound	Compound	Compound	Compound
1	18	36	60	76
2	19	37	61	79
3	20	38	62	80
5	21	39	65	81
6	22	40	67	82
7	23	41	68	83
8	24	44	69	84
11	28	47	70	85
12	30	49	71	87
13	31	51	72	88
14	33	55	73	90
15	34	57	74	91
16	35	59	75	92

Compound	Compound	Compound	Compound	Compound
94	103	118	124	131
95	106	119	125	132
96	112	120	126	
97	113	121	127	
98	114	122	129	
101	115	123	130	

Table H

Compound	Compound	Compound	Compound	Compound
10	43	93	107	117
26	86	102	108	138

EXAMPLE E Combination Studies

RSV with Renilla Reporter

[0651] RSV expressing Renilla luciferase (A2-RL-line19F) are generated by Dr. Martin Moore of Emory University, Atlanta, GA, USA. The *in vitro* viral kinetics of A2-RL-line19F is similar to that of wild type RSV (See Hotard, A.L., Virology (2012) 434(1):129--136).

[0652] Host cell HEP-2 are purchased from ATCC (Cat. #CCL-23) and cells are cultured in DMEM/Ham's F-12 50/50 1× containing L-glutamine and 15 mM HEPES (Mediatech, Cat. #10-092-CM). The medium is further supplemented with 5% (v/v) FBS (Mediatech, Cat. #35-010-CV) and 1% (v/v) penicillin/streptomycin (Mediatech, Cat. #30-002-CI). HEP-2 cells are maintained at 37 °C in a humidified 5% CO₂ atmosphere.

Drug Treatment and Viral Dosing

[0653] To determine the effect of a combination of compounds, the following procedure is followed. On the first day, 20,000 HEP-2 cells are plated per well in a 96-well plate. On the following day, test articles are solubilized in 100% DMSO (for chemicals) or 1 x PBS (for biologics) to 200x the desired final testing concentration. Subsequently, Compound (A), or a pharmaceutically acceptable salt thereof, is serially diluted (1:3) to 9 distinct concentrations "horizontally" in a 96-well plate, and Compound (B), or a pharmaceutically acceptable salt thereof, is serially diluted (1:3) to 7 distinct concentrations "vertically" in 96-well plate. The serially diluted 200x test articles are then diluted 1:10 into

cell culture media to generate 20x test articles. A 5 μ L aliquot of the 20x test articles is added in a checkerboard fashion to the cells with 90 μ L existing media. Space is also allotted for titrations of each of the compounds alone to be used as reference controls. After 12 hour pre-incubation of test articles, A2-RL-line19F at an MOI of 0.5 is added to the plate and is further incubated for 2 days at 37 °C in a 5% CO₂.

Determination of Anti-RSV Activity

[0654] The *Renilla* Luciferase Assay System (Promega, Cat. # E2820) is used to measure anti-RSV replicon activity. Assay plates are set up as stated above. Luminescence is recorded using a Perkin Elmer multilabel counter Victor3V.

Cell Viability Assay

[0655] Promega CellTiter-Glo Luminescent Cell Viability Assay, Cat. #G7572) is used to measure cell viability. The CellTiter-Glo[®] Luminescent Cell Viability Assay is a homogeneous method to determine the number of viable cells in culture based on quantitation of the adenosine triphosphate (ATP) present, which signals the presence of metabolically active cells. Assay plates are set up in the same format the anti-RSV assay, except that no virus is added to the cell viability assay. A 100- μ L aliquot of CellTiter-Glo reagent is added to each well and incubated at room temperature for 8 minutes. Luminescence is recorded using a Perkin Elmer multilabel counter Victor3V.

Data Analysis

[0656] Each experiment is performed at N=5 for both anti-RSV activity and cell viability. Mean percent inhibition of the replicon values from the 5 experiments is generated and for anti-RSV activity, it is analyzed using two drug interaction analysis models, Isobologram Analysis and/or Prichard's Model.

Isobologram Analysis

[0657] The effects of drug-drug combinations are evaluated by the Loewe additivity model in which the experimental data are analyzed using CalcuSyn (Biosoft, Ferguson, MO), a computer program based on the method of Chou and Talalay. The combination index (CI) value and the isobologram for each experimental combination are calculated. CI values of <1, 1, and >1 indicate synergy, additive effect, and antagonism, respectively. Under the synergy category, CI<0.1 is considered very strong synergism; CI 0.1-0.3 strong synergism; CI 0.3-0.7 synergism and CI 0.7-0.85 moderate synergism. The

isobologram analysis, which graphically represents additive, synergistic, and antagonistic drug effects, is also used to model the interaction of antiviral activities. In this representation, an effective concentration (EC) value of one drug is plotted on one axis and corresponding EC value of a second drug is plotted on the second axis; the line connecting these two points represents the amount of each drug in a combination that would be required to reach the equivalent EC value, given that their effects are additive.

Prichard's Model (MacSynergy II)

[0658] MacSynergy II software is kindly provided by Dr. M. Prichard (University of Michigan). This program allows the three-dimensional examination of drug interactions of all data points generated from the checkerboard combination of two inhibitors with Bliss-Independence model. Confidence bounds are determined from replicate data. If the 95% confidence limits (CL) do not overlap the theoretic additive surface, then the interaction between the two drugs differs significantly from additive. The volumes of synergy or antagonism can be determined and graphically depicted in three dimensions and represent the relative quantity of synergism or antagonism per change in the two drug concentrations. Synergy and antagonism volumes are based on the Bliss independence model, which assumes that both compounds act independently on different targets. A set of predicted fractional responses $faAB$ under the Bliss independence model is calculated as $faAB = faA + faB - faA \cdot faB$ with faA and faB representing the fraction of possible responses, e.g. % inhibition, of compounds A and B at amounts dA and dB , respectively, and describes the % inhibition of a combination of compounds A and B at amount $(dA+dB)$. If $faAB > faA + faB - faA \cdot faB$ then we have Bliss synergy; if $faAB < faA + faB - faA \cdot faB$ then we have Bliss antagonism. The 95% synergy/antagonism volumes are the summation of the differences between the observed inhibition and the 95% confidence limit on the prediction of $faAB$ under the Bliss independence model. MacSynergy II is used for data analysis.

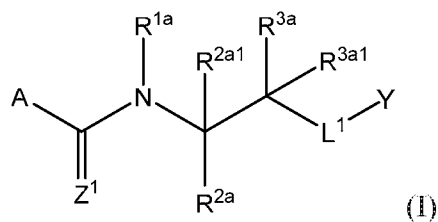
[0659] MacSynergy II Volume Descriptions: $<25 \mu M^2\%$ = Additive; $25-50 \mu M^2\%$ = Minor synergism; $50-100 \mu M^2\%$ = Significant synergism; and $>100 \mu M^2\%$ = Strong synergism.

[0660] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be

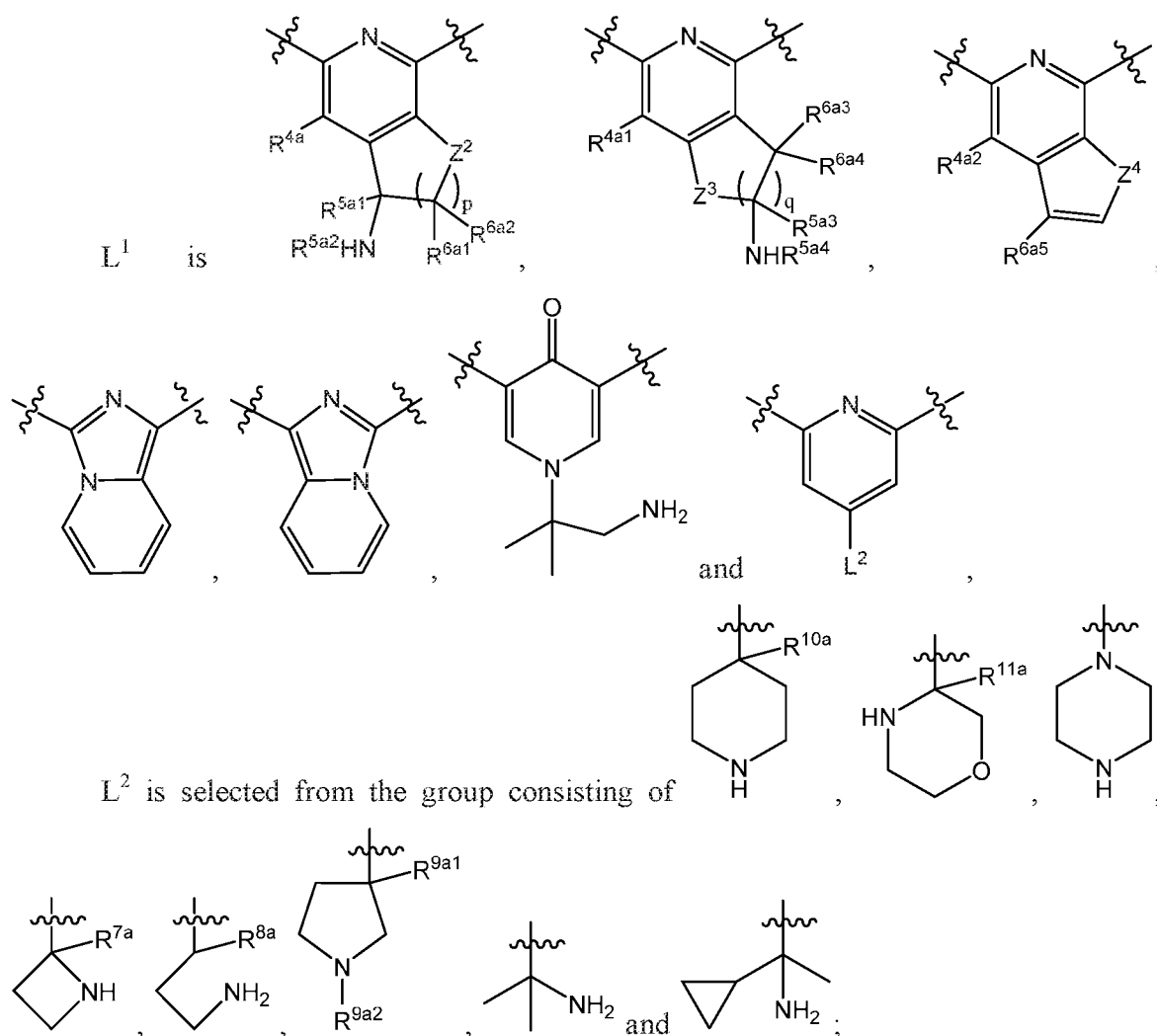
understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



wherein:



A is selected from the group consisting of an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

Y is selected from the group consisting of an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

R^{1a} is hydrogen or an unsubstituted C_{1-4} alkyl;

R^{2a} and R^{2a1} are each independently hydrogen or an unsubstituted C_{1-4} alkyl;

R^{3a} and R^{3a1} are each independently hydroxy, CHF_2 , CF_3 or NH_2 ;

R^{4a} , R^{4a1} and R^{4a2} are independently selected from the group consisting of hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{1-8} alkoxy and haloalkyl;

R^{5a1} and R^{5a3} are independently an unsubstituted C_{1-6} alkyl, an unsubstituted C_{3-6} cycloalkyl, or $-(CH_2)_{1-4}OH$;

R^{5a2} and R^{5a4} are independently hydrogen, hydroxy, an unsubstituted C_{1-6} alkyl, an optionally substituted monocyclic heterocyclyl, $-C(=O)R^{5a5}$, an unsubstituted $-C$ -amido, $-C(=NH)$ -an unsubstituted C_{1-6} alkyl; or

R^{5a1} and R^{5a2} are taken together with the atoms they are attached to form an optionally substituted 4 to 6 membered ring;

R^{5a3} and R^{5a4} are taken together with the atoms they are attached to form an optionally substituted 4 to 6 membered ring;

R^{5a5} is an unsubstituted C_{1-4} alkyl;

each R^{6a1} , each R^{6a2} , each R^{6a3} and each R^{6a4} are independently selected from the group consisting of hydrogen, halogen, an unsubstituted C_{1-6} alkyl and hydroxy;

R^{6a5} is selected from the group consisting of halogen, an unsubstituted C_{1-6} alkyl and hydroxy;

R^{7a} and R^{8a} are each independently an unsubstituted C_{1-6} alkyl;

R^{9a1} , R^{9a2} , R^{10a} and R^{11a} are independently hydrogen or an unsubstituted C_{1-6} alkyl;

Z^1 is O or S;

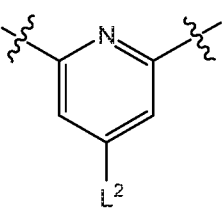
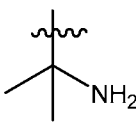
Z^2 is O, NR^Z or $CR^{Z1}R^{Z2}$;

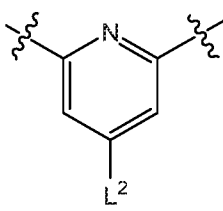
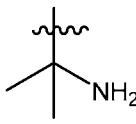
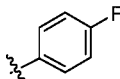
Z^3 is O, NR^{Z3} or $CR^{Z4}R^{Z5}$;

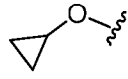
Z^4 is O, NR^{Z6} or $CR^{Z7}R^{Z8}$;

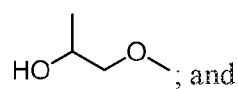
R^Z , R^{Z1} , R^{Z2} , R^{Z3} , R^{Z4} , R^{Z5} , R^{Z6} , R^{Z7} and R^{Z8} are independently hydrogen or an unsubstituted C_{1-4} alkyl;

p and q are independently 1 or 2; and

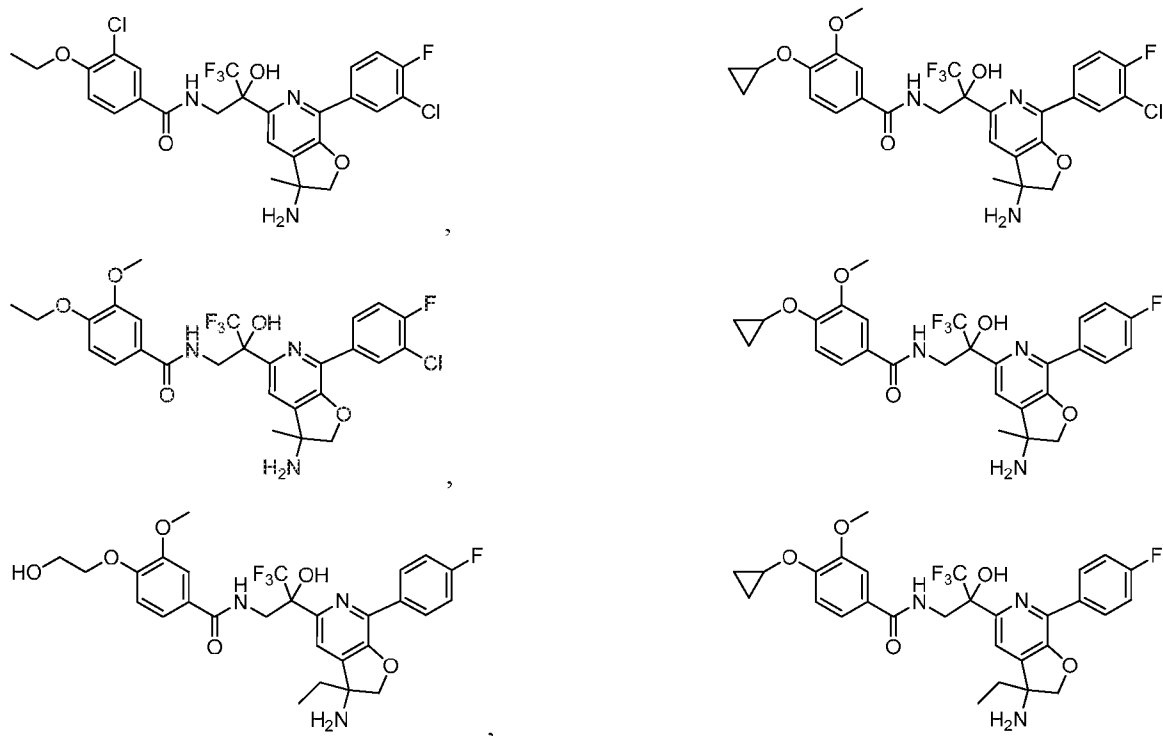
provided that when L^1 is  and L^2 is , then one of R^{3a} and R^{3a1} is NH_2 , and the other of R^{3a} and R^{3a1} is OH ;

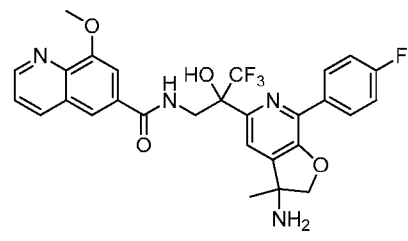
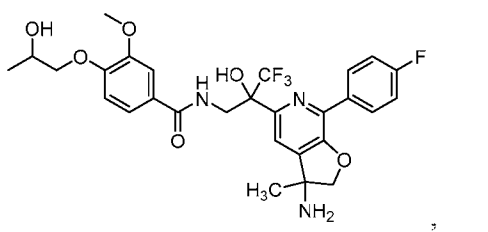
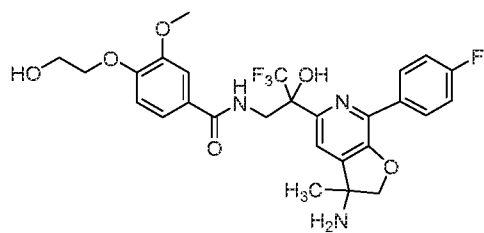
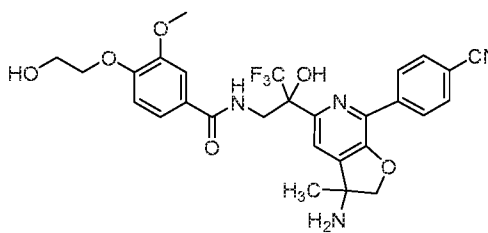
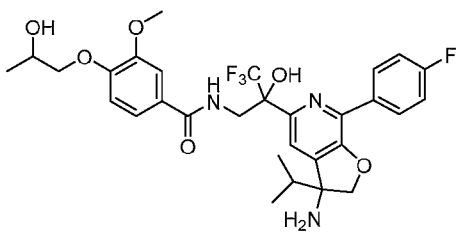
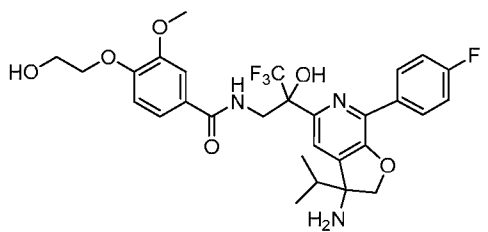
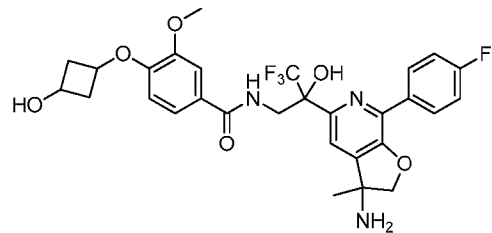
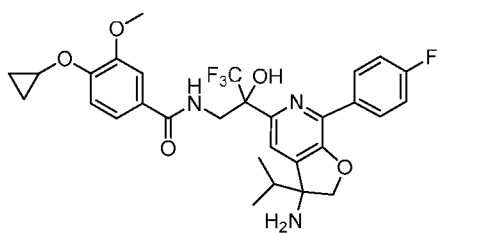
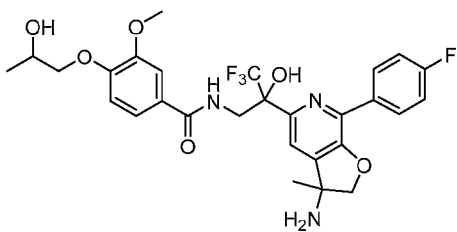
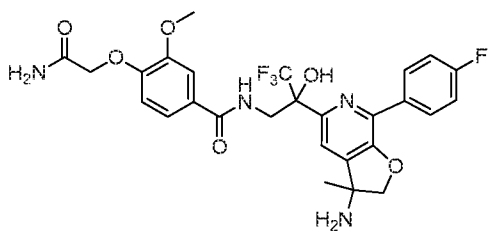
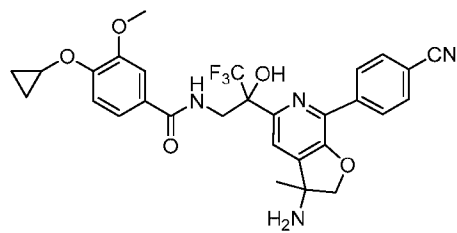
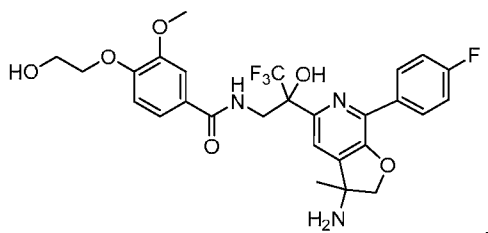
provided that when L^1 is , L^2 is , one of R^{3a} and R^{3a1} is CF_3 , and other of R^{3a} and R^{3a1} is OH , then Y is  and A is a disubstituted phenyl

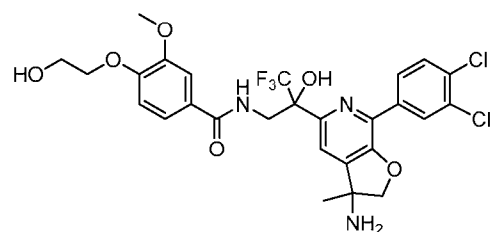
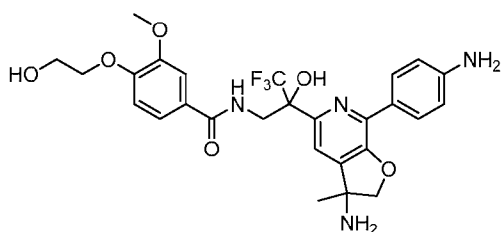
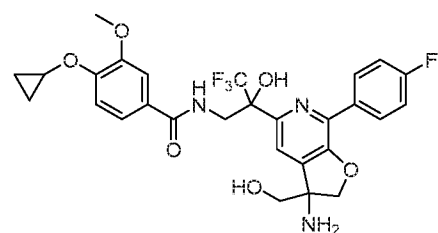
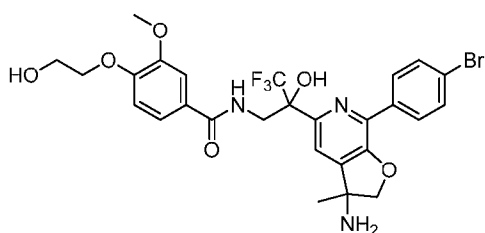
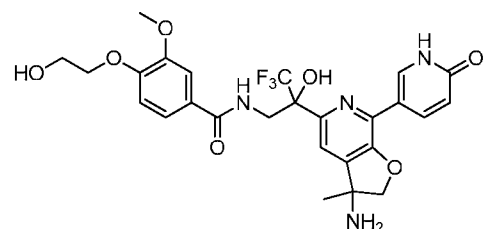
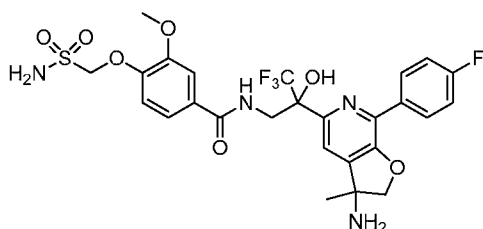
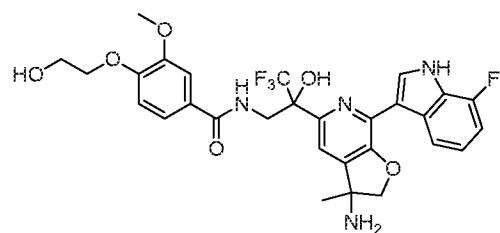
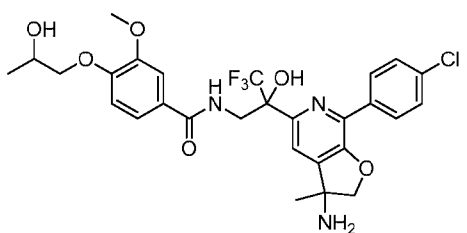
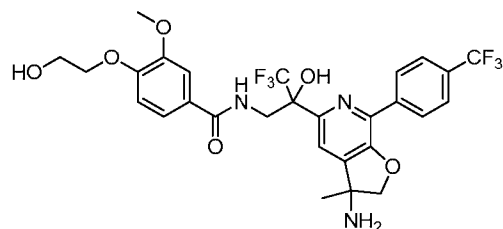
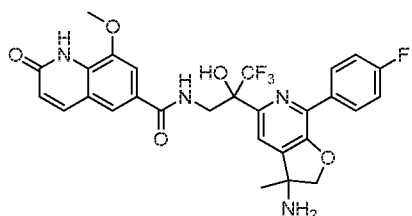
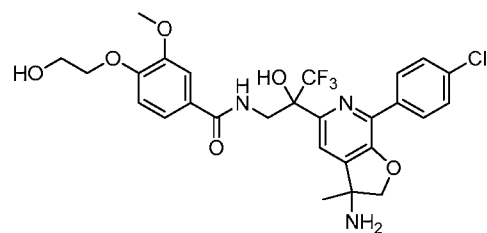
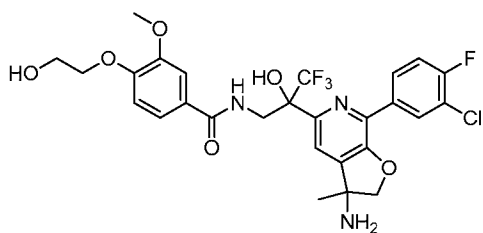
wherein one substituent is  and the other substituent is $-O-(CH_2)_{2-4}OH$ or

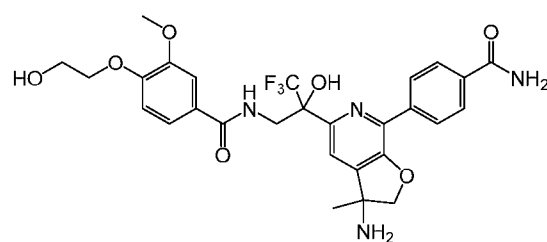
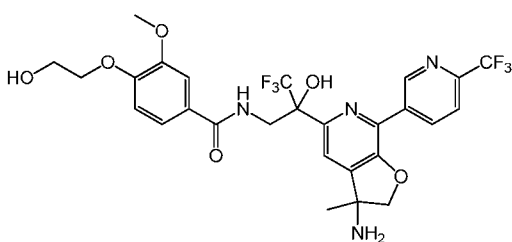
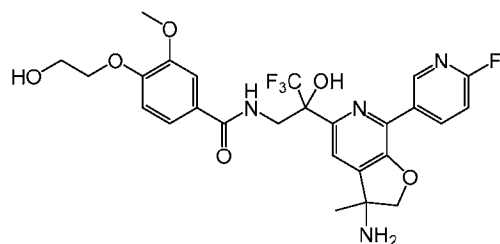
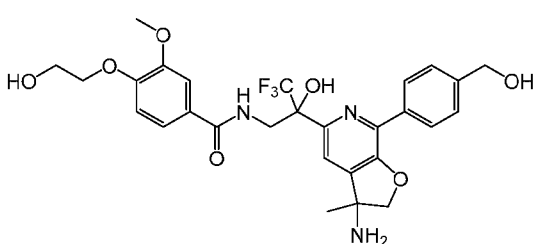
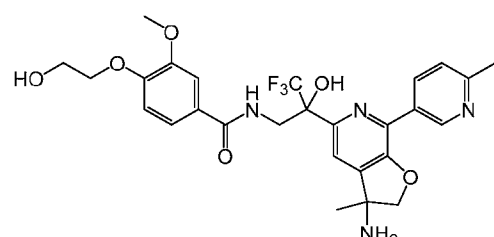
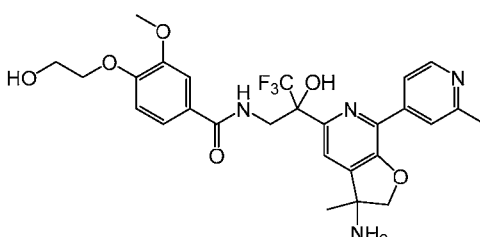
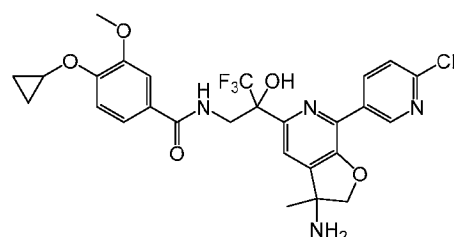
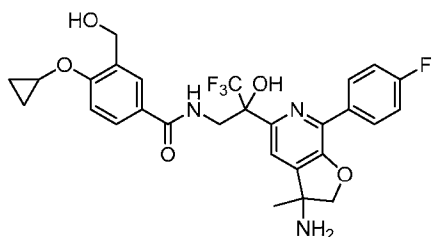
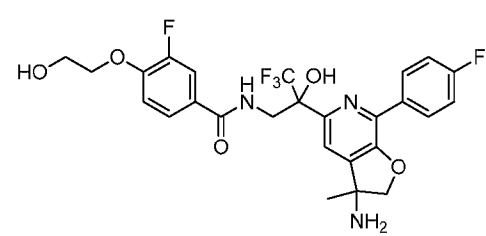
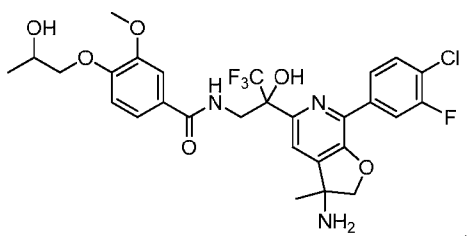
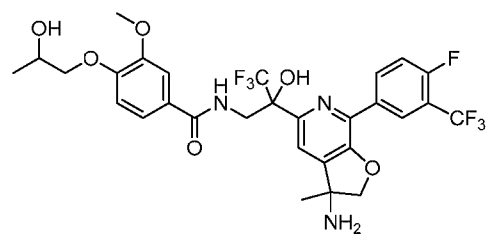
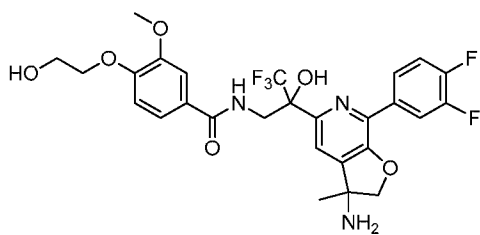


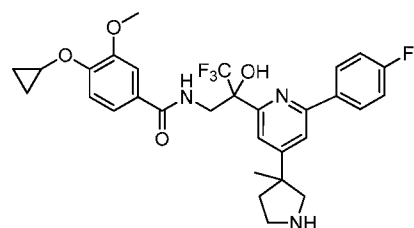
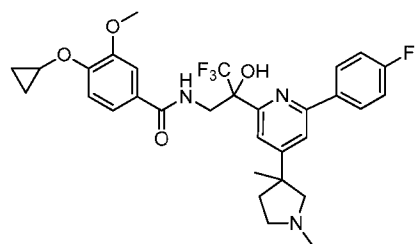
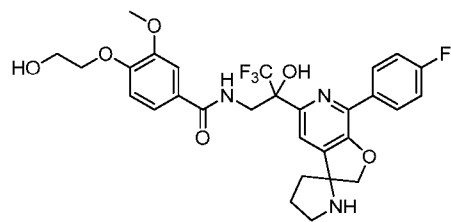
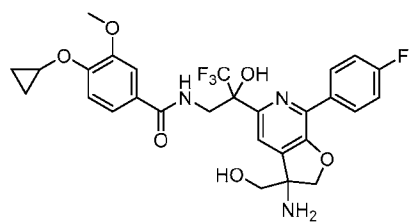
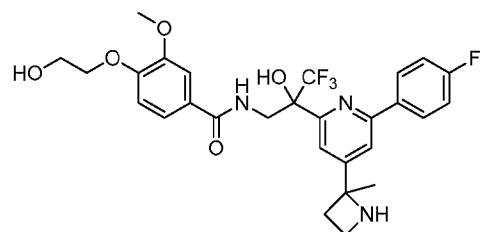
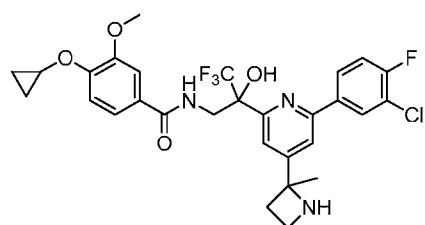
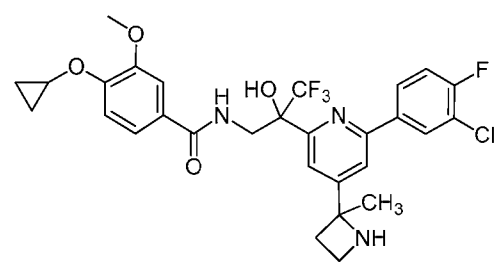
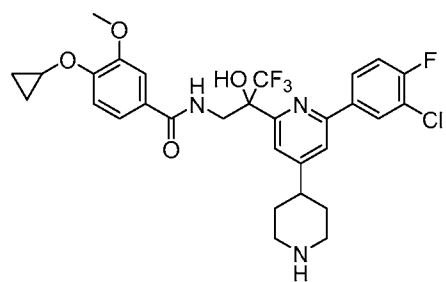
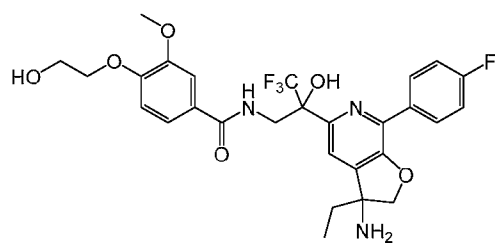
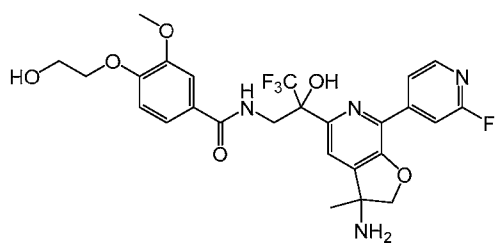
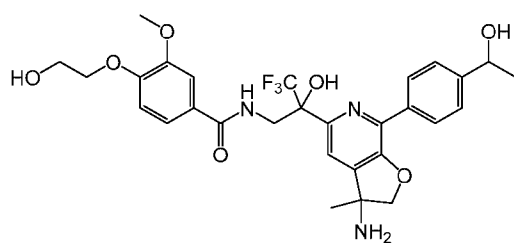
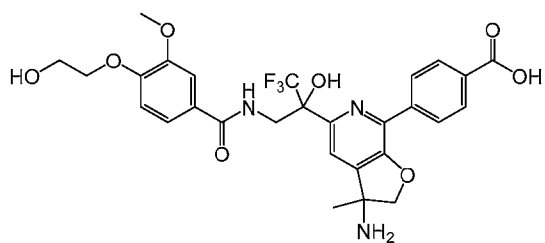
provided the compound of Formula (I) is not any one of the group consisting of:

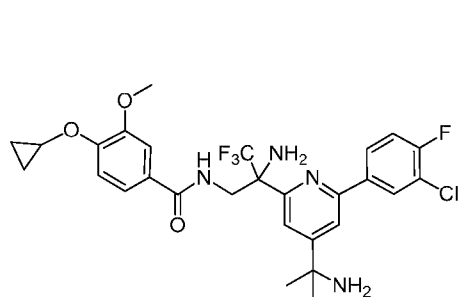




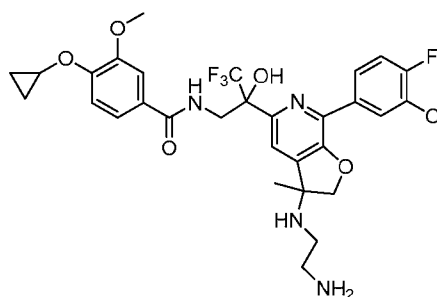








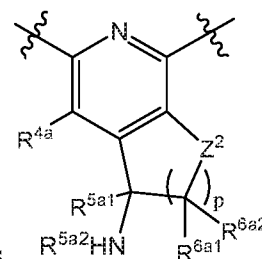
and



, or a

pharmaceutically acceptable salt of the foregoing.

2. The compound of Claim 1, wherein R^{1a} can be hydrogen.
3. The compound of Claim 1, wherein R^{1a} can be an unsubstituted C_{1-4} alkyl.
4. The compound of any one of Claims 1-3, wherein R^{2a} and R^{2a1} are both hydrogen.
5. The compound of any one of Claims 1-3, wherein R^{2a} is hydrogen and R^{2a1} is an unsubstituted C_{1-4} alkyl.
6. The compound of any one of Claims 1-3, wherein R^{2a} and R^{2a1} are both an unsubstituted C_{1-4} alkyl.
7. The compound of any one of Claims 1-6, wherein R^{3a} is hydroxy, and R^{3a1} is CF_3 .
8. The compound of any one of Claims 1-6, wherein R^{3a} is hydroxy, and R^{3a1} is CHF_2 .
9. The compound of any one of Claims 1-6, wherein R^{3a} is hydroxy, and R^{3a1} is NH_2 .



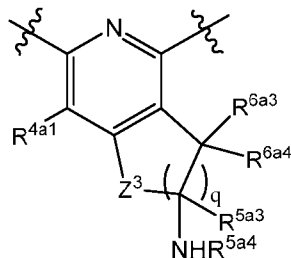
10. The compound of any one of Claims 1-8, wherein L^1 is
11. The compound of Claim 10, wherein R^{5a1} is an unsubstituted C_{1-6} alkyl.
12. The compound of Claim 10, wherein R^{5a1} is an unsubstituted C_{3-6} cycloalkyl.
13. The compound of Claim 10, wherein R^{5a1} is $-(CH_2)_{1-4}OH$.
14. The compound of any one of Claims 10-13, wherein R^{5a2} is hydrogen.
15. The compound of any one of Claims 10-13, wherein R^{5a2} is hydroxy.

16. The compound of any one of Claims 10-13, wherein R^{5a2} is an unsubstituted C_{1-6} alkyl.
17. The compound of any one of Claims 10-13, wherein R^{5a2} is an optionally substituted monocyclic heterocyclyl.
18. The compound of any one of Claims 10-13, wherein R^{5a2} is $-C(=O)R^{5a5}$.
19. The compound of any one of Claims 10-13, wherein R^{5a2} is an unsubstituted $-C$ -amido.
20. The compound of any one of Claims 10-13, wherein R^{5a2} is $-C(=NH)$ -an unsubstituted C_{1-6} alkyl.
21. The compound of Claim 10, wherein R^{5a1} and R^{5a2} are taken together with the atoms they are attached to form an optionally substituted 4 to 6 membered ring.
22. The compound of any one of Claims 10-21, wherein p is 1.
23. The compound of any one of Claims 10-21, wherein p is 2.
24. The compound of any one of Claims 10-21, wherein each R^{6a1} and each R^{6a2} are each hydrogen.
25. The compound of any one of Claims 10-21, wherein at least one of R^{6a1} and R^{6a2} is hydrogen and the other one of R^{6a1} and R^{6a2} is selected from the group consisting of halogen, an unsubstituted C_{1-6} alkyl and hydroxy.
26. The compound of any one of Claims 10-25, wherein R^{4a} is hydrogen.
27. The compound of any one of Claims 10-25, wherein R^{4a} is halogen.
28. The compound of any one of Claims 10-25, wherein R^{4a} is hydroxy.
29. The compound of any one of Claims 10-25, wherein R^{4a} is an optionally substituted C_{1-8} alkyl.
30. The compound of any one of Claims 10-25, wherein R^{4a} is an optionally substituted C_{1-8} alkoxy.
31. The compound of any one of Claims 10-25, wherein R^{4a} is a haloalkyl.
32. The compound of any one of Claims 10-31, wherein Z^2 is O.
33. The compound of any one of Claims 10-31, wherein Z^2 is NR^Z .
34. The compound of Claim 33, wherein R^Z is hydrogen.
35. The compound of Claim 33, wherein R^Z is an unsubstituted C_{1-4} alkyl.
36. The compound of any one of Claims 10-31, wherein Z^2 is $CR^{Z1}R^{Z2}$.

37. The compound of Claim 36, wherein R^{Z1} and R^{Z2} are each hydrogen.

38. The compound of Claim 36, wherein at least one of R^{Z1} and R^{Z2} is an unsubstituted C_{1-4} alkyl.

39. The compound of any one of Claims 1-8, wherein L^1 is



40. The compound of Claim 39, wherein R^{5a3} is an unsubstituted C_{1-6} alkyl.

41. The compound of Claim 39, wherein R^{5a3} is an unsubstituted C_{3-6} cycloalkyl.

42. The compound of Claim 39, wherein R^{5a3} is $-(CH_2)_{1-4}OH$.

43. The compound of any one of Claims 39-42, wherein R^{5a4} is hydrogen.

44. The compound of any one of Claims 39-42, wherein R^{5a4} is hydroxy.

45. The compound of any one of Claims 39-42, wherein R^{5a4} is an unsubstituted C_{1-6} alkyl.

46. The compound of any one of Claims 39-42, wherein R^{5a4} is $-C(=O)R^{5a5}$.

47. The compound of Claim 39, wherein R^{5a3} and R^{5a4} are taken together with the atoms they are attached to form an optionally substituted 4 to 6 membered ring.

48. The compound of any one of Claims 39-47, wherein q is 1.

49. The compound of any one of Claims 39-47, wherein q is 2.

50. The compound of any one of Claims 39-49, wherein each R^{6a3} and each R^{6a4} are each hydrogen.

51. The compound of any one of Claims 39-49, wherein at least one of R^{6a3} and R^{6a4} is hydrogen and the other one of R^{6a1} and R^{6a2} is selected from the group consisting of halogen, an unsubstituted C_{1-6} alkyl and hydroxy.

52. The compound of any one of Claims 39-51, wherein R^{4a1} is hydrogen.

53. The compound of any one of Claims 39-51, wherein R^{4a1} is halogen.

54. The compound of any one of Claims 39-51, wherein R^{4a1} is hydroxy.

55. The compound of any one of Claims 39-51, wherein R^{4a1} is an optionally substituted C_{1-8} alkyl.

56. The compound of any one of Claims 39-51, wherein R^{4a1} is an optionally substituted C_{1-8} alkoxy.

57. The compound of any one of Claims 39-51, wherein R^{4a1} is a haloalkyl.

58. The compound of any one of Claims 39-57, wherein Z^3 is O.

59. The compound of any one of Claims 39-57, wherein Z^3 is NR^{Z3} .

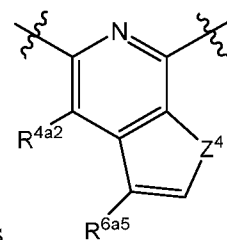
60. The compound of Claim 59, wherein R^{Z3} is hydrogen.

61. The compound of Claim 59, wherein R^{Z3} is an unsubstituted C_{1-4} alkyl.

62. The compound of any one of Claims 39-57, wherein Z^3 is $CR^{Z4}R^{Z5}$.

63. The compound of Claim 62, wherein R^{Z4} and R^{Z5} are each hydrogen.

64. The compound of Claim 62, wherein at least one of R^{Z4} and R^{Z5} is an unsubstituted C_{1-4} alkyl.



65. The compound of any one of Claims 1-8, wherein L^1 is

66. The compound of Claim 65, wherein R^{4a2} is hydrogen.

67. The compound of Claim 65, wherein R^{4a2} is halogen.

68. The compound of Claim 65, wherein R^{4a2} is hydroxy.

69. The compound of Claim 65, wherein R^{4a2} is an optionally substituted C_{1-8} alkyl.

70. The compound of Claim 65, wherein R^{4a2} is an optionally substituted C_{1-8} alkoxy.

71. The compound of Claim 65, wherein R^{4a2} is a haloalkyl.

72. The compound of any one of Claims 65-71, wherein R^{6a5} is halogen.

73. The compound of any one of Claims 65-71, wherein R^{6a5} is an unsubstituted C_{1-6} alkyl.

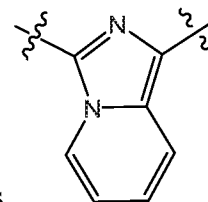
74. The compound of any one of Claims 65-71, wherein R^{6a5} is hydroxy.

75. The compound of any one of Claims 65-74, wherein Z^4 is O.

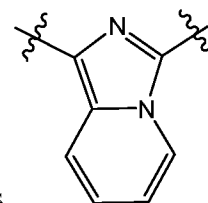
76. The compound of any one of Claims 65-74, wherein Z^4 is NR^{Z6} .

77. The compound of Claim 76, wherein R^{Z6} is hydrogen.

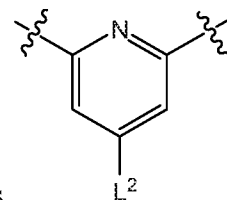
78. The compound of Claim 76, wherein R^{Z6} is an unsubstituted C_{1-4} alkyl.
79. The compound of any one of Claims 65-74, wherein Z^4 is $CR^{Z7}R^{Z8}$.
80. The compound of Claim 79, wherein R^{Z7} and R^{Z8} are each hydrogen.
81. The compound of Claim 79, wherein at least one of R^{Z7} and R^{Z8} is an unsubstituted C_{1-4} alkyl.



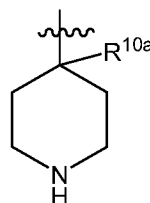
82. The compound of any one of Claims 1-8, wherein L^1 is



83. The compound of any one of Claims 1-8, wherein L^1 is



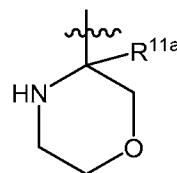
84. The compound of any one of Claims 1-8, wherein L^1 is



85. The compound of Claim 84, wherein L^2 is

86. The compound of Claim 85, wherein R^{10a} is hydrogen.

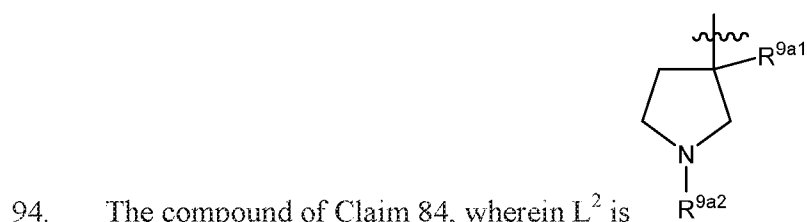
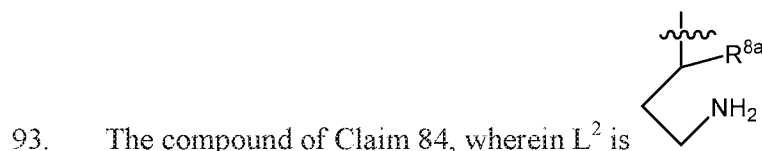
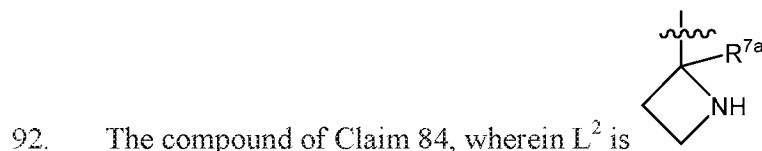
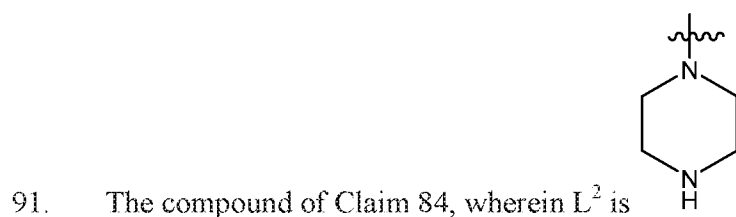
87. The compound of Claim 85, wherein R^{10a} is an unsubstituted C_{1-6} alkyl.



88. The compound of Claim 84, wherein L^2 is

89. The compound of Claim 88, wherein R^{11a} is hydrogen.

90. The compound of Claim 88, wherein R^{11a} is an unsubstituted C_{1-6} alkyl.

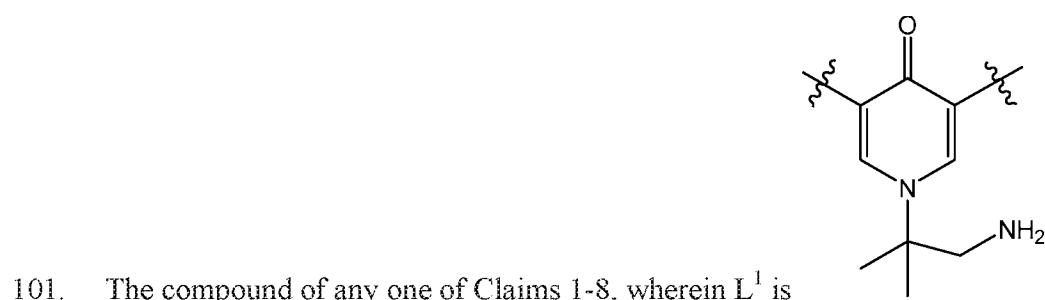
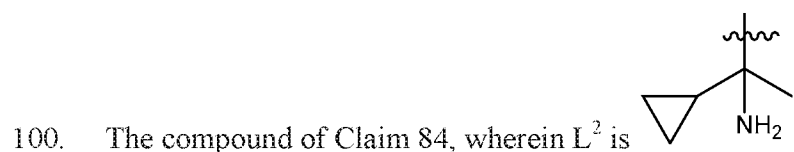
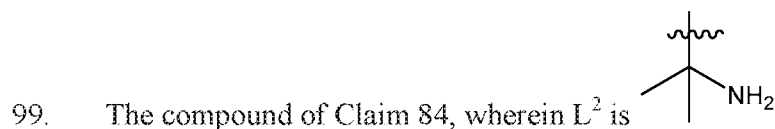


95. The compound of Claim 94, wherein R^{9a1} is hydrogen.

96. The compound of Claim 94, wherein R^{9a1} is an unsubstituted C_{1-6} alkyl.

97. The compound of any one of Claims 94-96, wherein R^{9a2} is hydrogen.

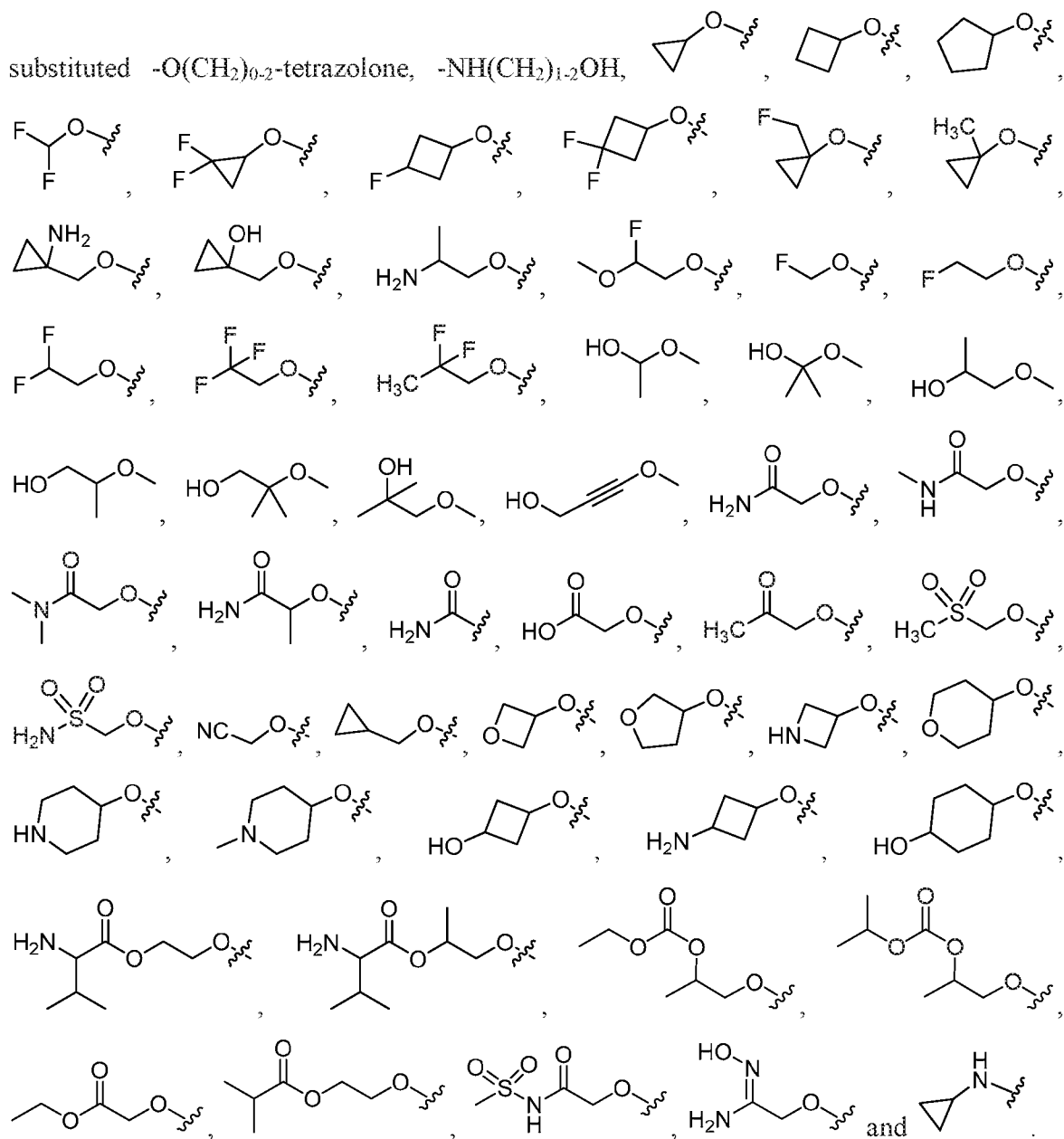
98. The compound of any one of Claims 94-96, wherein R^{9a2} is an unsubstituted C_{1-6} alkyl.



102. The compound of any one of Claims 1-101, wherein A is an optionally substituted phenyl.

103. The compound of Claim 102, wherein A is a phenyl substituted with one or more substituents selected from the group consisting of: an unsubstituted C₁₋₄ alkyl, an optionally substituted C₁₋₄ alkyl, cycloalkyl, hydroxy, an optionally substituted C₁₋₄ alkoxy, C₁₋₄ alkoxy, halogen, haloalkyl, an optionally substituted haloalkoxy, nitro, amino, mono-substituted amino, di-substituted amine, -O-amido, sulfenyl, alkyoxyalkyl, an optionally substituted aryl, an optionally substituted mono-cyclic heteroaryl, an optionally substituted mono-cyclic heterocyclyl, an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted monocyclic heteroaryl(C₁₋₄ alkyl), an optionally substituted monocyclic heterocyclyl(C₁₋₄ alkyl), hydroxyalkyl and aminoalkyl.

104. The compound of Claim 102, wherein A is a phenyl substituted with one or more substituents selected from the group consisting of: methyl, ethyl, propyl, butyl, hydroxy, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, t-butoxy, phenoxy, bromo, chloro, fluoro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, cyano, N,N-di-methyl-amine, N,N-di-ethyl-amine, N-methyl-N-ethyl-amine, N-methyl-amino, N-ethyl-amino, amino, N-amido, N-sulfonamido, alkylthio, an optionally substituted phenyl, an optionally substituted imidazole, an optionally substituted morpholinyl, an optionally substituted pyrazole, an optionally substituted pyrrolidinyl, an optionally substituted pyridinyl, an optionally substituted piperidinyl, an optionally substituted piperidinone, an optionally substituted pyrrolidinone, an optionally substituted pyrimidine, an optionally substituted pyrazine, an optionally substituted 1,2,4-oxadiazole, -(CH₂)₁₋₄-OH, -(CH₂)₁₋₂-NH(CH₃), an optionally substituted -(CH₂)₁₋₂-imidazole, an optionally substituted -(CH₂)₁₋₂-pyrrolidinone, an optionally substituted -(CH₂)₁₋₂-imidazolidinone, -O(CH₂)₂-NH₂, -O(CH₂)₂-NH(CH₃), -O(CH₂)₂-N(CH₃)₂, -O-(CH₂)₂₋₄OH, -O(CH₂)₂OCH₃, an optionally substituted -O(CH₂)₀₋₂-cyclopentanone, an optionally substituted -O(CH₂)₀₋₂pyrrolidinone, an optionally substituted -O(CH₂)₀₋₂-morpholinyl, an optionally substituted -O(CH₂)₀₋₂-triazole, an optionally substituted -O(CH₂)₀₋₂-imidazole, an optionally substituted -O(CH₂)₀₋₂-pyrazole, an optionally substituted -O(CH₂)₀₋₂-tetrahydrofuran, an optionally substituted -O(CH₂)₀₋₂-pyrrolidinone, an optionally substituted -O(CH₂)₀₋₂-tetrazole, an optionally



105. The compound of any one of Claims 102-104, wherein A is a di-substituted phenyl.

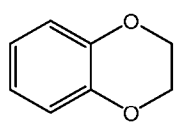
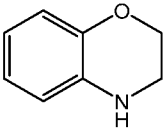
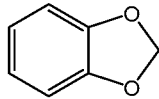
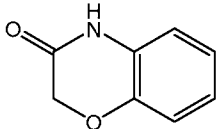
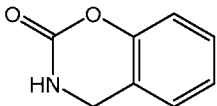
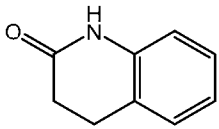
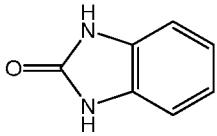
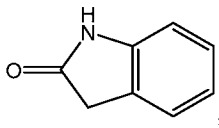
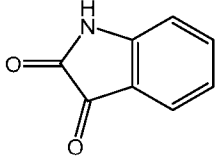
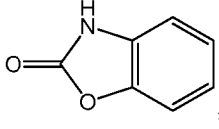
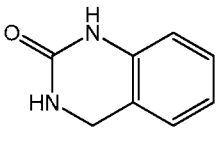
106. The compound of any one of Claims 1-101, wherein A is an optionally substituted heteroaryl.

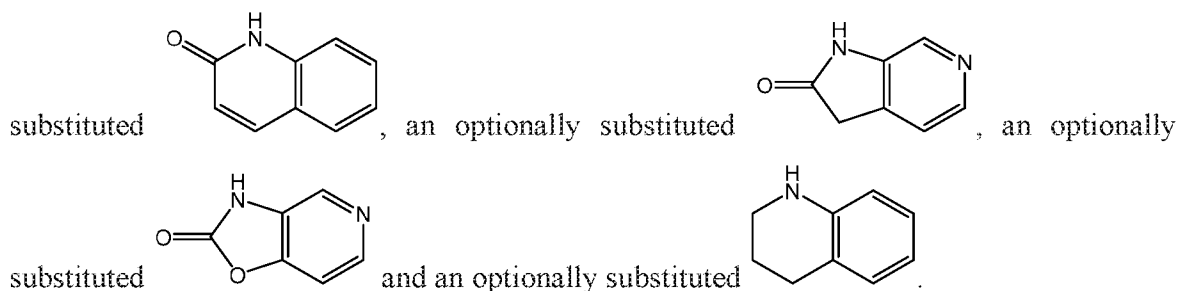
107. The compound of Claim 106, wherein the optionally substituted heteroaryl is selected from the group consisting of: an optionally substituted imidazole, an optionally substituted indole, an optionally substituted thiazole, an optionally substituted furan, an

optionally substituted thiophene, an optionally substituted pyrrole, an optionally substituted pyridine, an optionally substituted pyrimidine, an optionally substituted pyrazine, an optionally substituted pyrazole, an optionally substituted quinolone, an optionally substituted imidazole, an optionally substituted oxazole, an optionally substituted isoxazole, an optionally substituted benzoimidazole, an optionally substituted benzoxazole, an optionally substituted benzothiazole and an optionally substituted imidazo[1,2-a]pyrimidine.

108. The compound of any one of Claims 1-101, wherein A is an optionally substituted heterocyclyl.

109. The compound of Claim 108, wherein the optionally substituted heterocyclyl

is selected from the group consisting of: an optionally substituted , an optionally substituted , an optionally substituted , an optionally substituted , an optionally substituted , an optionally substituted , an optionally substituted , an optionally substituted , an optionally substituted , an optionally substituted , an optionally substituted 



110. The compound of any one of Claims 1-109, wherein Y is an optionally substituted aryl.

111. The compound of Claim 110, wherein Y is a mono-substituted phenyl.

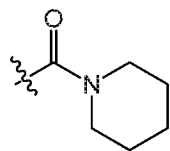
112. The compound of Claim 110, wherein Y is a di-substituted phenyl.

113. The compound of any one of Claims 1-109, wherein Y is an optionally substituted heteroaryl.

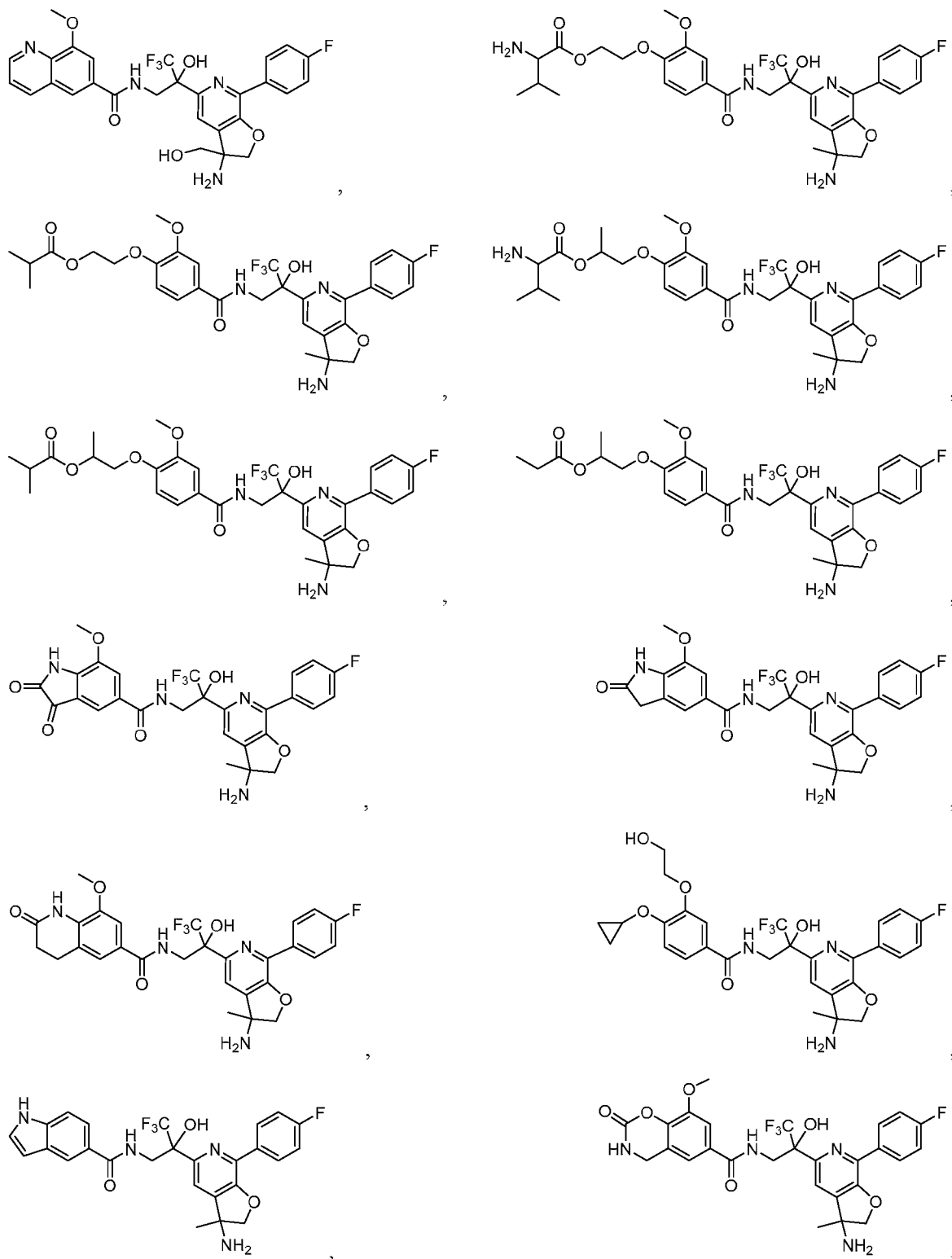
114. The compound of any one of Claims 1-109, wherein Y is an optionally substituted heterocyclyl.

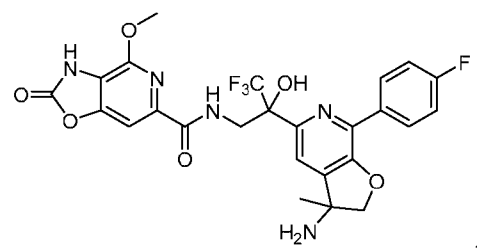
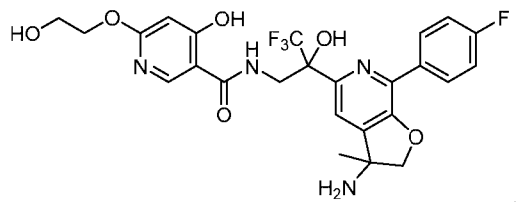
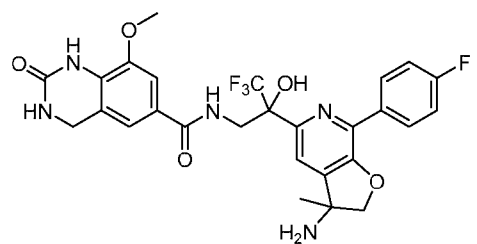
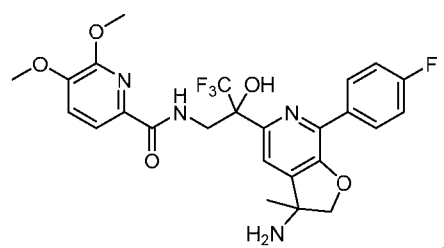
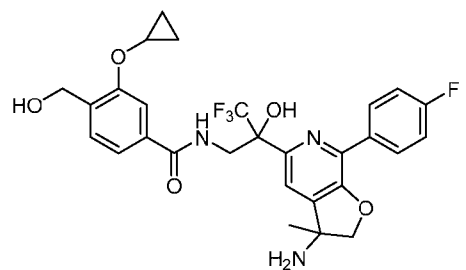
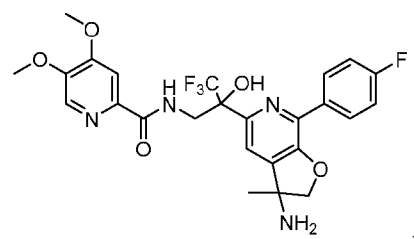
115. The compound of any one of Claims 110-114, wherein Y is substituted with one or more R^B , wherein each R^B is independently selected from the group consisting of: cyano, halogen, an optionally substituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an optionally substituted aryl, an optionally substituted 5 or 6 membered heteroaryl, an optionally substituted 5 or 6 membered heterocyclyl, hydroxy, C_{1-4} alkoxy, alkoxyalkyl, C_{1-4} haloalkyl, haloalkoxy, an unsubstituted acyl, an optionally substituted $-C$ -carboxy, an optionally substituted $-C$ -amido, sulfonyl, carbonyl, amino,

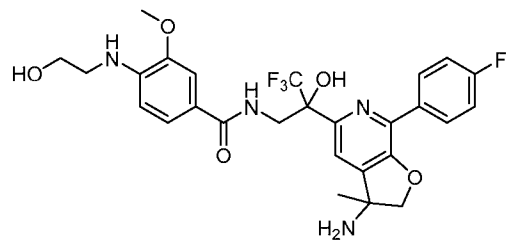
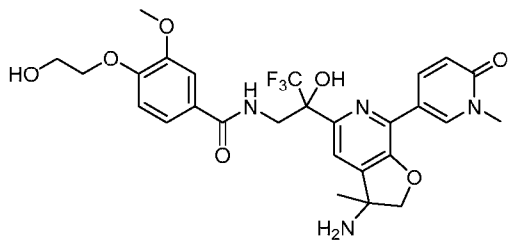
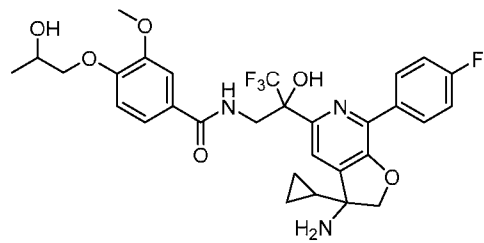
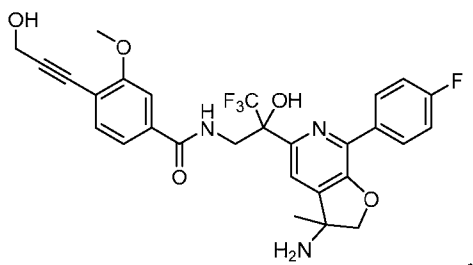
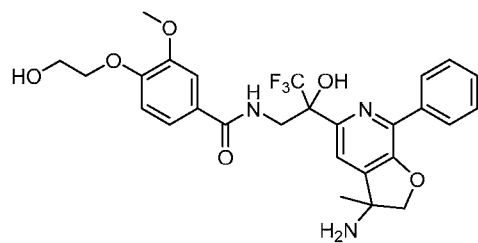
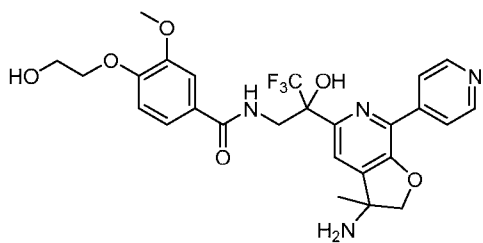
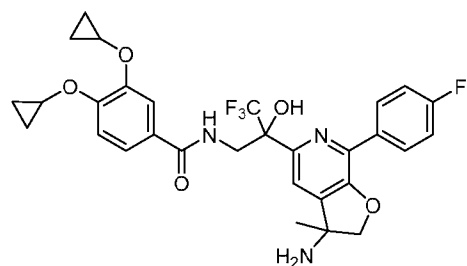
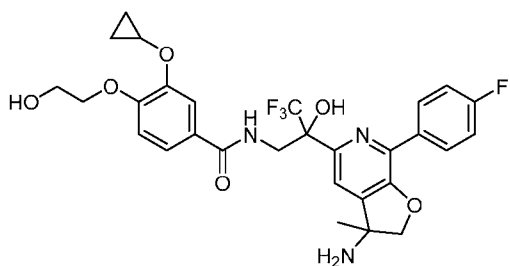
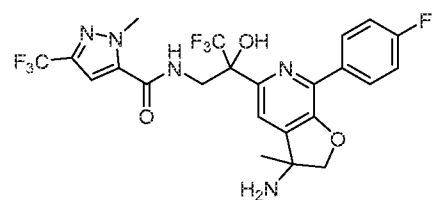
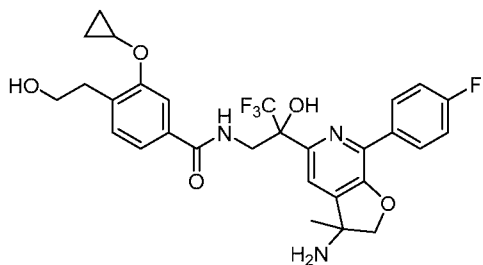
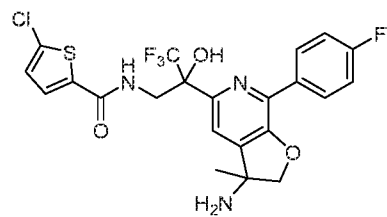
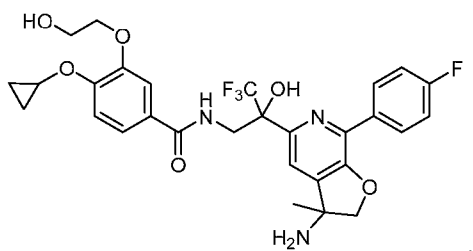
mono-substituted amine, di-substituted amine and

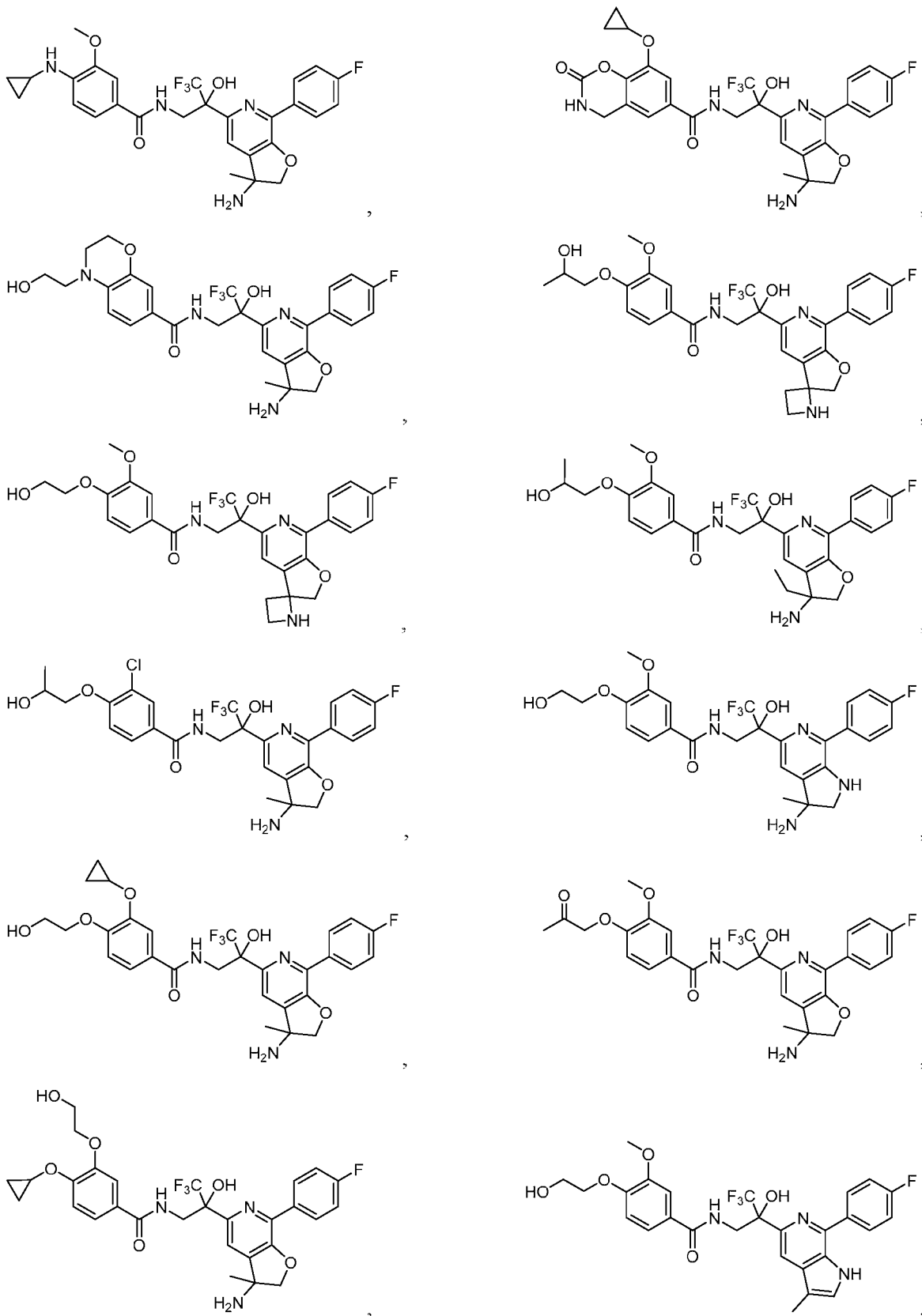


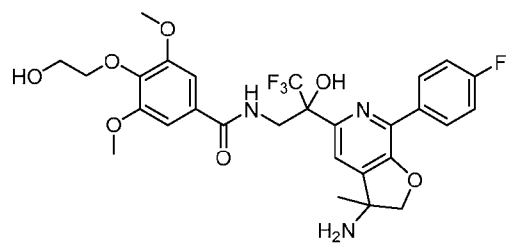
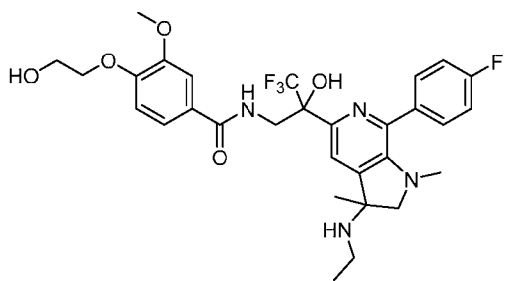
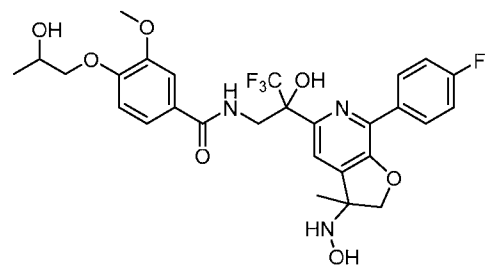
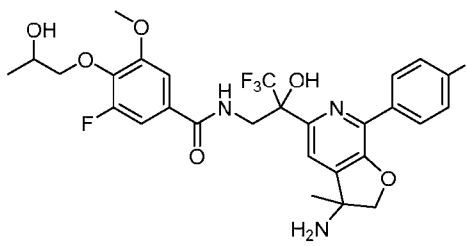
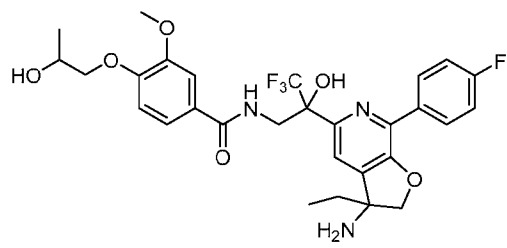
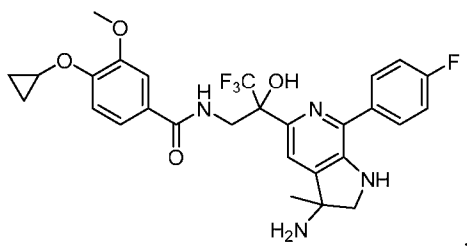
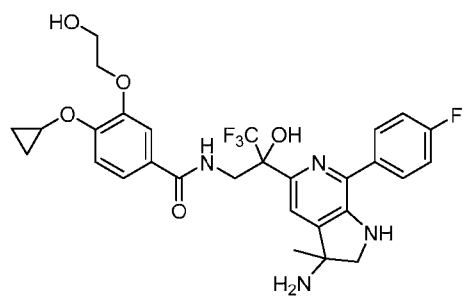
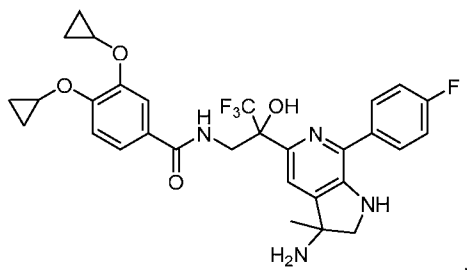
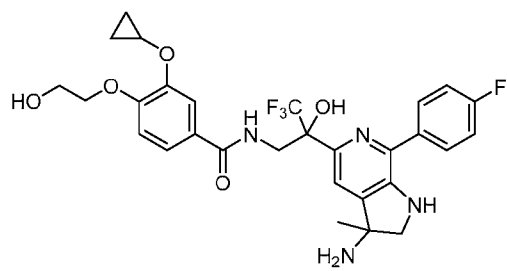
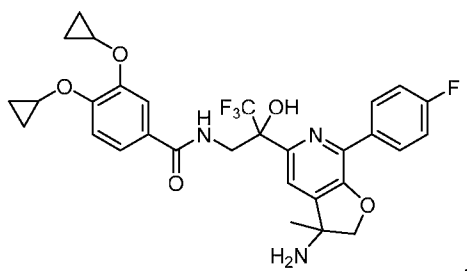
116. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of:

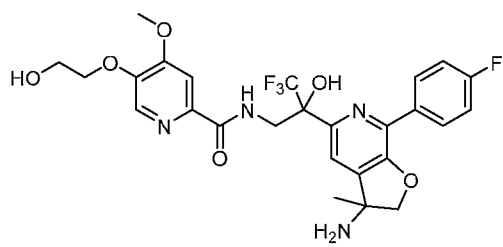
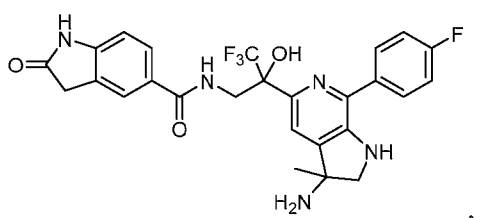
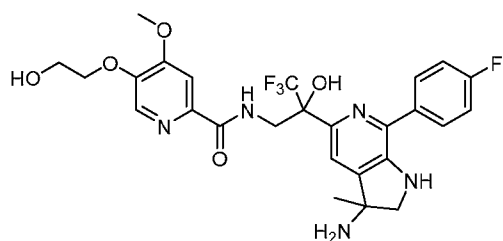
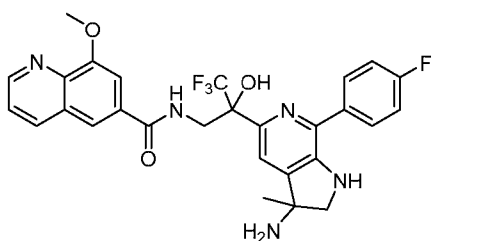
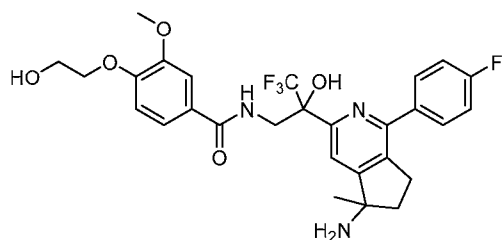
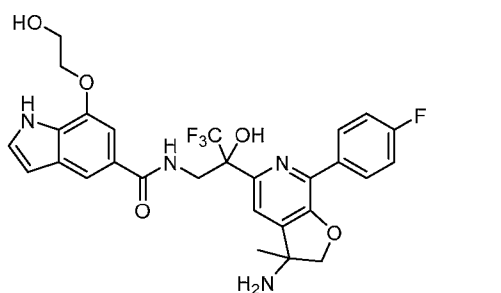
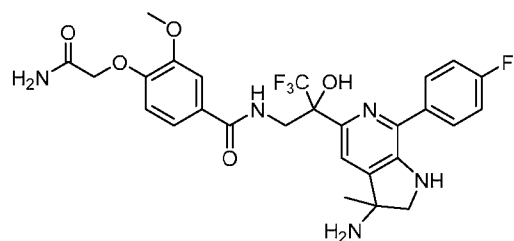
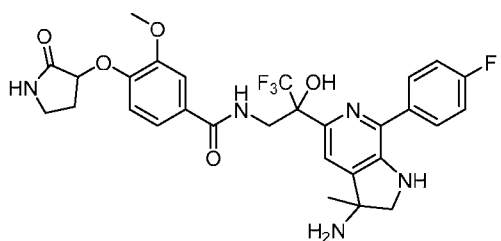
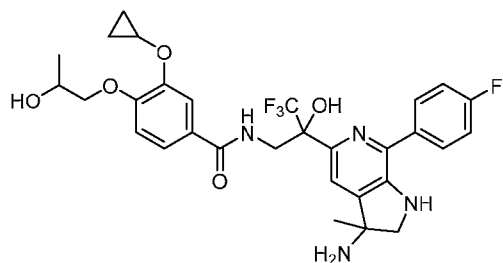
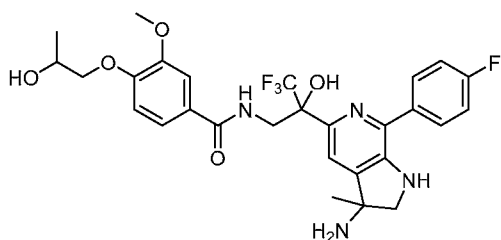
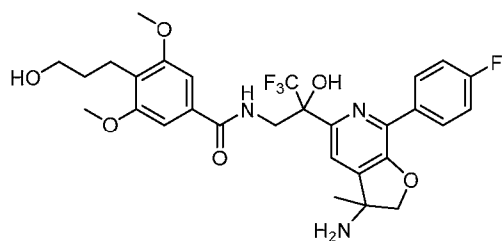
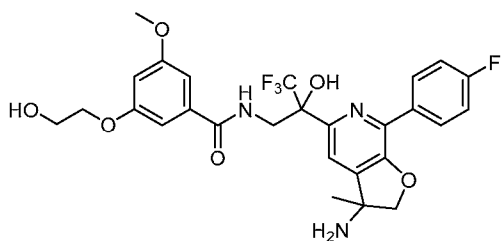


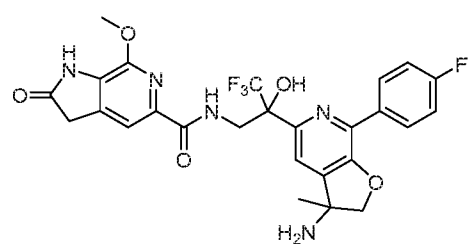
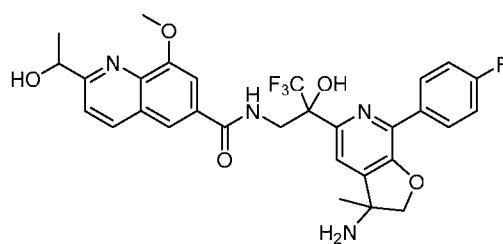
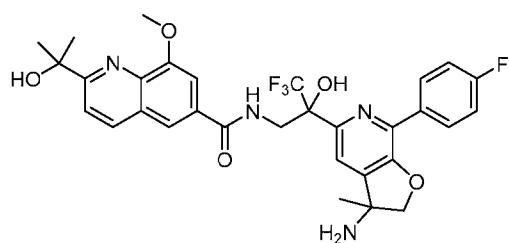
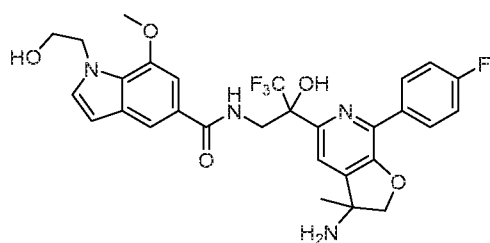
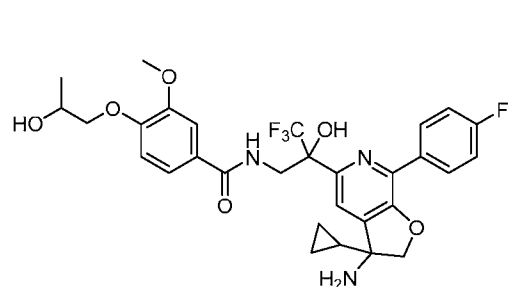
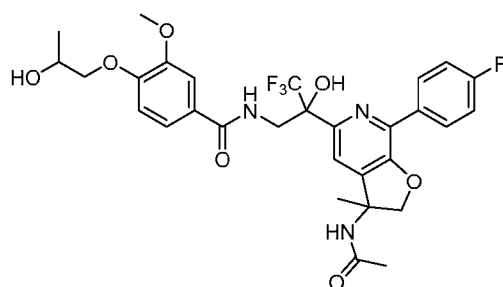
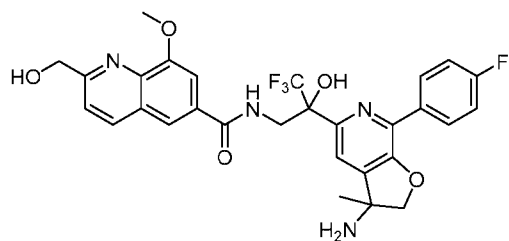
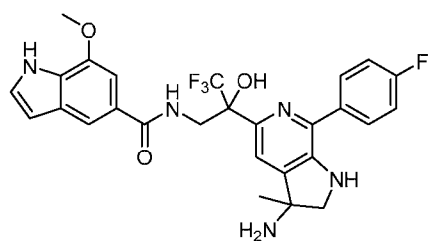
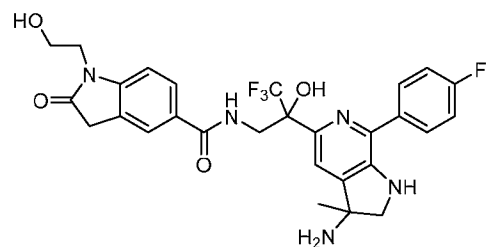
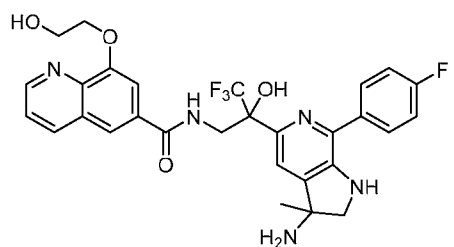
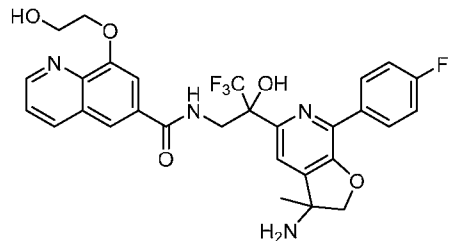
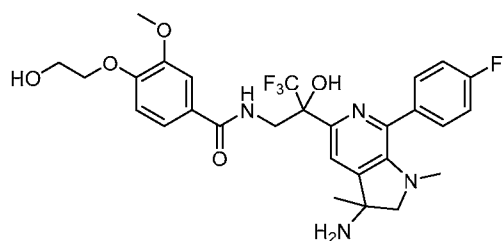


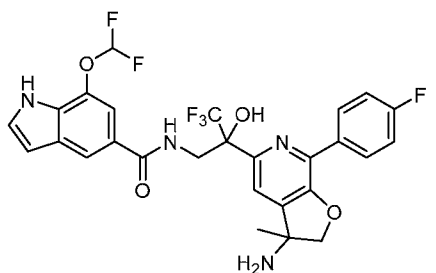




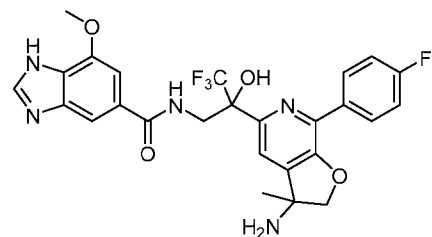




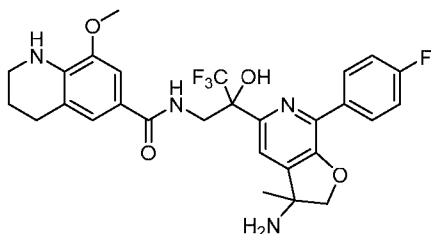




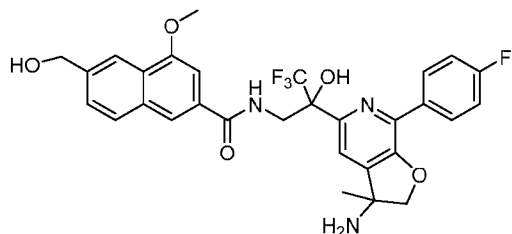
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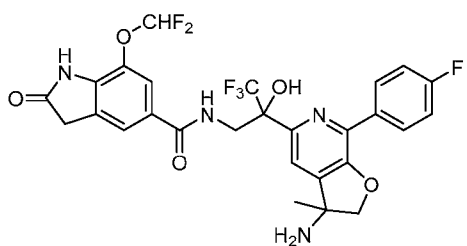
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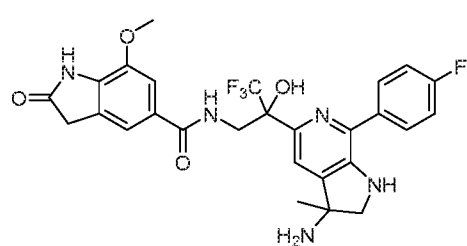
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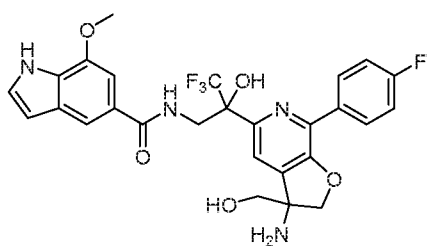
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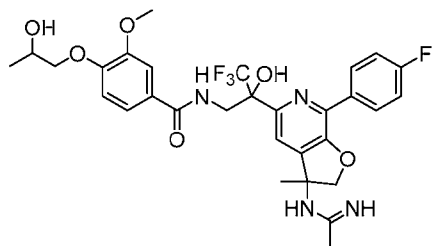
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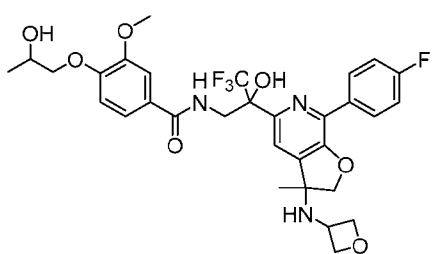
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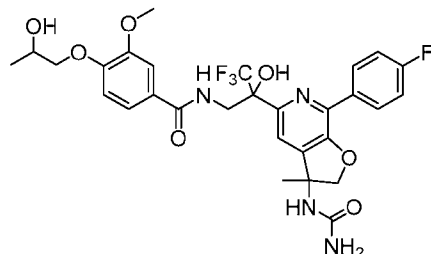
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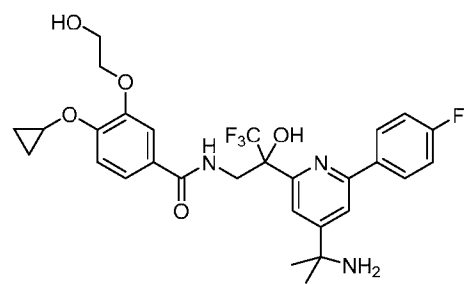
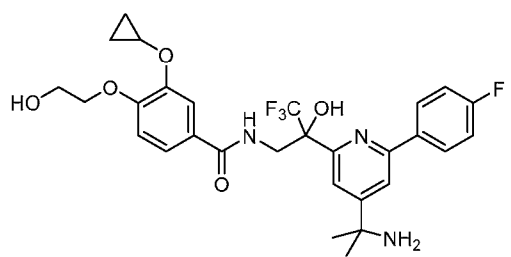
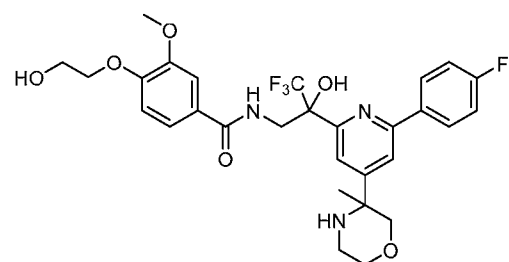
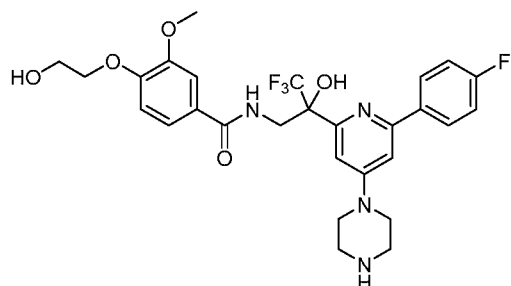
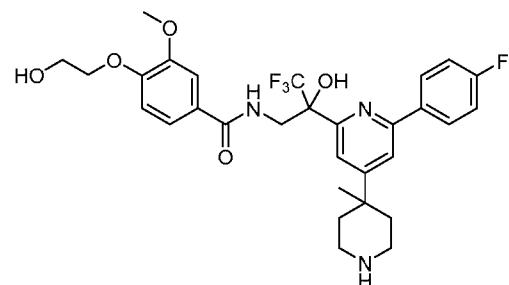
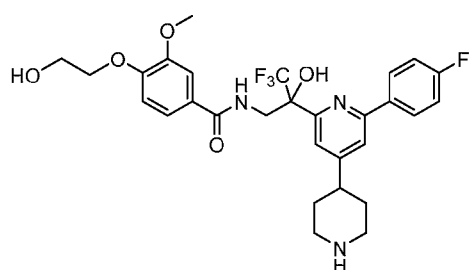
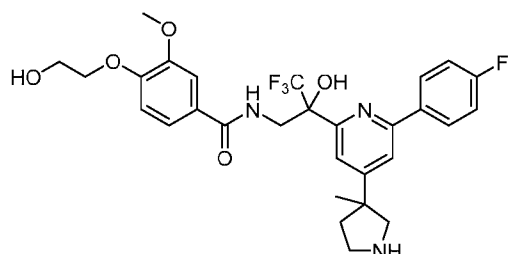
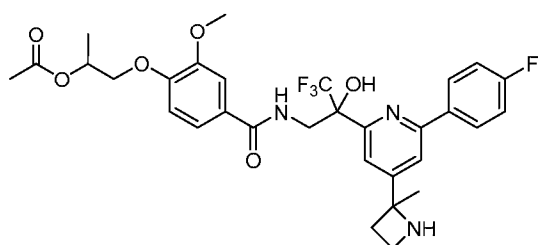
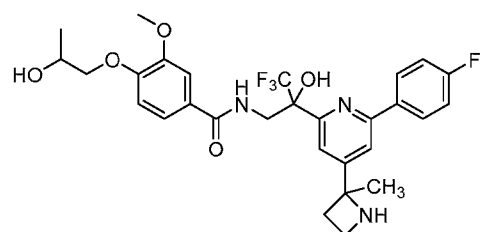
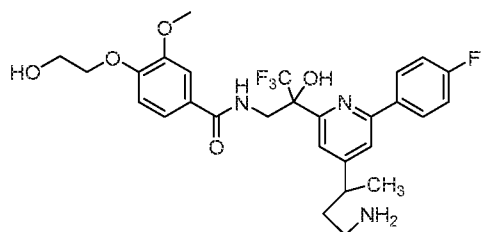
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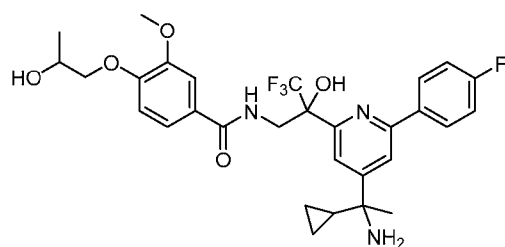
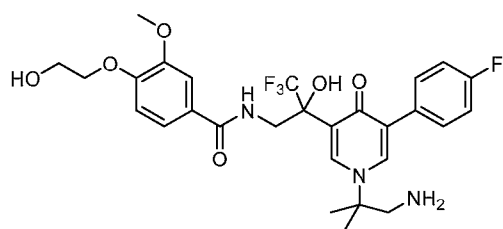
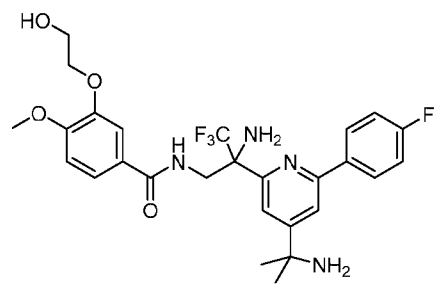
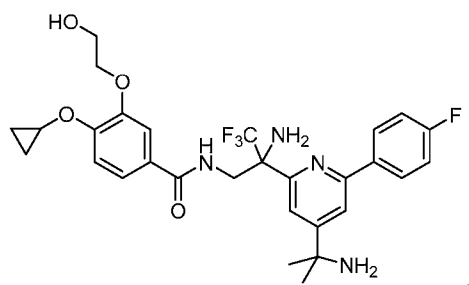
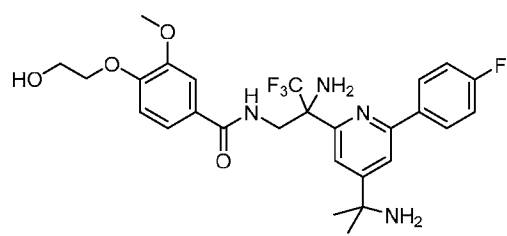
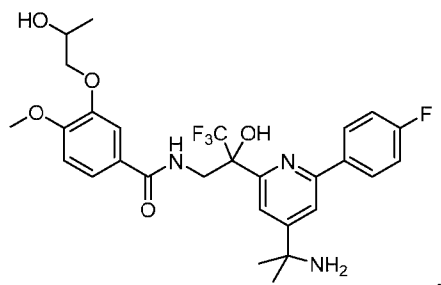
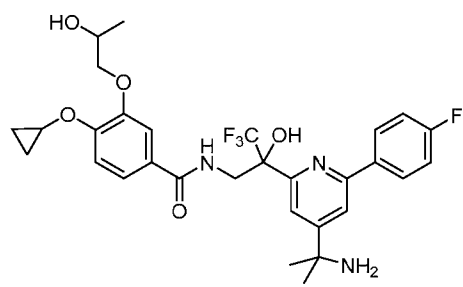
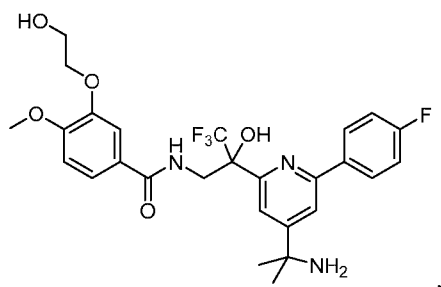


, or a

pharmaceutically acceptable salt of the foregoing.

117. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of:



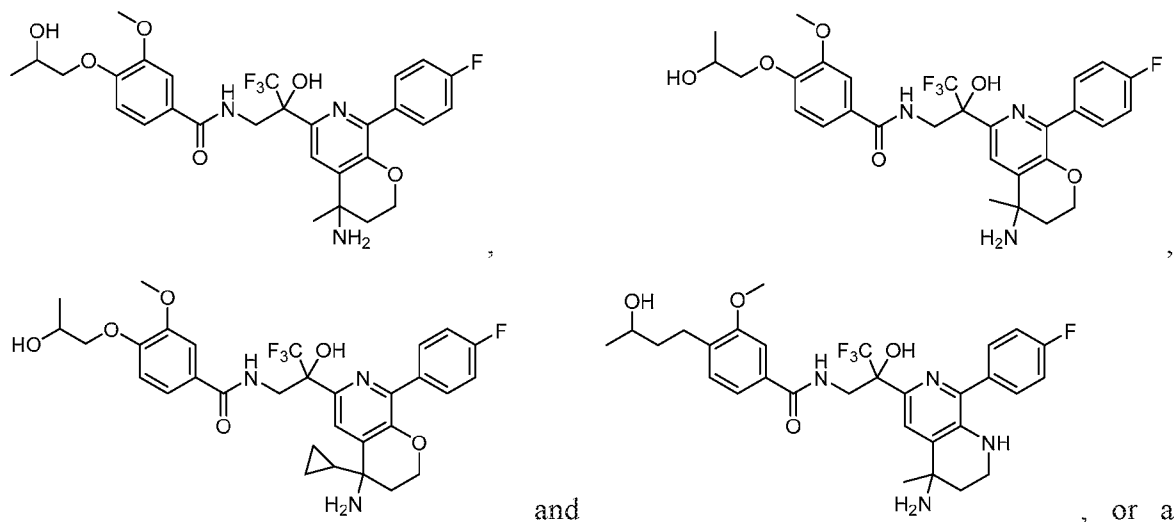


and

, or a

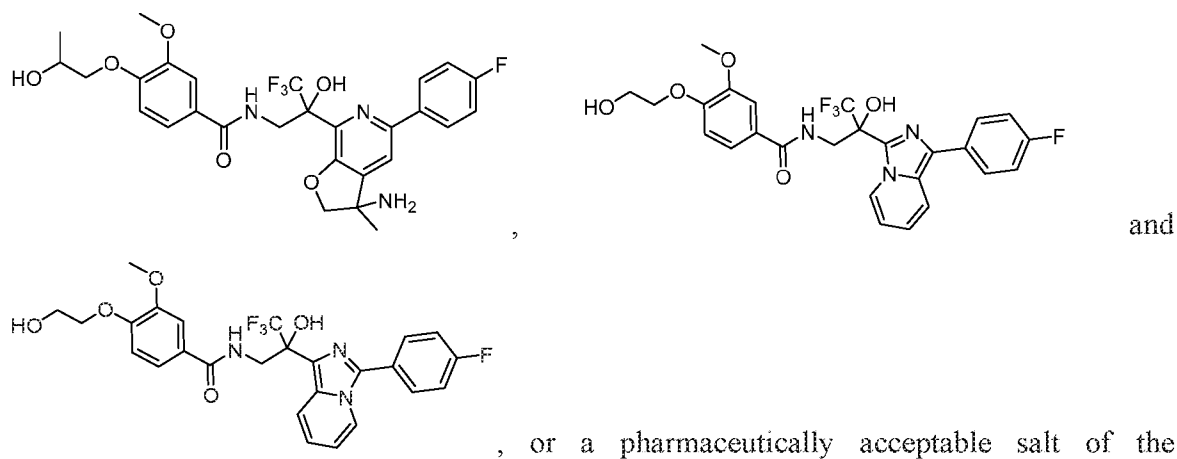
pharmaceutically acceptable salt of the foregoing.

118. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of:



pharmaceutically acceptable salt of the foregoing.

119. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of:



120. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-119, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient, or combination thereof.

121. Use of an effective amount of a compound of any one of Claims 1-119, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 120 in the preparation of a medicament for ameliorating or treating a paramyxovirus infection.

122. Use of an effective amount of a compound of any one of Claims 1-119, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 120 in the preparation of a medicament for inhibiting replication of a paramyxovirus.

123. Use of an effective amount of a compound of any one of Claims 1-116, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 117 in the preparation of a medicament for contacting a cell infected with a paramyxovirus.

124. The use of any one of Claims 121-123, wherein the paramyxovirus infection is a human respiratory syncytial virus infection.

125. The use of any one of Claims 121-124, further comprising the use of one or more additional anti-viral agents.

126. The use of Claim 125, wherein the viral infection is a human respiratory syncytial virus infection; and wherein the one or more agents is an anti-RSV agent selected from the group consisting of an anti-RSV antibody, a fusion protein inhibitor, an N-protein inhibitor, a RSV polymerase inhibitor, an IMPDH inhibitor, an interferon and an other compound that inhibits the RSV virus, or a pharmaceutically acceptable salt of any of the foregoing.

127. The use of Claim 126, wherein the one or more agents is selected from the group consist of RSV-IGIV, palivizumab, motavizumab, 1-cyclopropyl-3-[[1-(4-hydroxybutyl)benzimidazol-2-yl]methyl]imidazo[4,5-c]pyridin-2-one (BMS-433771), 4,4'-bis-{4,6-bis-[3-(bis-carbamoylmethyl-sulfamoyl)-phenylamino]-(1,3,5)triazin-2-ylamino}-biphenyl-2,2"-disulfonic-acid (RFI-641), 4,4'-Bis[4,6-di[3-aminophenyl-N,N-bis(2-carbamoyl-ethyl)-sulfonilimino]-1,3,5-triazine-2-ylamino]-biphenyl-2,2'-disulfonic acid, disodium salt (CL387626), 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-4-methyl-1H-benzimidazol-1-yl]-6-methyl-3-pyridinol (JNJ-2408068), 2-[[6-[[[2-(3-Hydroxypropyl)-5-methylphenyl]amino]methyl]-2-[[3-(morpholin-4-yl)propyl]amino]benzimidazol-1-yl]methyl]-6-methylpyridin-3-ol (TMC-353121), 5,5'-bis[1-(((5-amino-1H-tetrazolyl)imino)methyl)]2,2',4''-methylidynetrisphenol (VP-14637, MDT-637), N-(2-hydroxyethyl)-4-methoxy-N-methyl-3-(6-methyl-[1,2,4]triazolo[3,4-a]phthalazin-3-yl)benzenesulfonamide (P13), 2-((2-((1-(2-aminoethyl)piperidin-4-yl)amino)-4-methyl-1H-benzo[d]imidazol-1-yl)methyl)-6-methylpyridin-3-ol (R170591), 1,4-bis(3-methylpyridin-4-yl)-1,4-diazepane (C15), (R)-9b-(4-chlorophenyl)-1-(4-fluorobenzoyl)-2,3-dihydro-1H-

imidazo[1',2':1,2]pyrrolo[3,4-c]pyridin-5(9bH)-one (BTA9981), [2,2-bis(docosyloxy-oxy-methyl)propyl-5-acetaoamido-3,5-dideoxy-4,7,8,9-tetra-O-(sodium-oxysulfonyl)-D-glycero-D-galacto-2-nonulopyranosid]onate (MBX-300), BTA-C286, N-(2-((S)-2-(5-((S)-3-aminopyrrolidin-1-yl)-6-methylpyrazolo[1,5-a]pyrimidin-2-yl)piperidine-1-carbonyl)-4-chlorophenyl)methanesulfonamide (GS-5806), an anti-RSV nanobody, a peptide fusion inhibitor (such as a peptide having the sequence DEFDASISQVNEKINQSLAFIRKSDELL (T-67), a peptide having the sequence FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST (T-118), (S)-1-(2-fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)urea (RSV-604), STP-92, iKT-041, 6-{4-[(biphenyl-2-ylcarbonyl) amino]benzoyl}-N-cyclopropyl-5,6-dihydro-4H-thieno[3,2-d][1]benzazepine-2-carboxamide (YM-53403). N-cyclopropyl-5-(4-(2-(pyrrolidin-1-yl)benzamido)benzoyl)-5,6,7,10-tetrahydrobenzo[b]cyclopenta[d]azepine-9-carboxamide, 6-(4-(2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)nicotinamido)benzoyl)-N-cyclopropyl-5,6-dihydro-4H-benzo[b]thieno[2,3-d]azepine-2-carboxamide, 4-amino-8-(3-{[2-(3,4-dimethoxyphenyl)ethyl]amino} propyl)-6,6-dimethyl-2-(4-methyl-3-nitrophenyl)-1H-imidazo[4,5-h]-isoquinoline-7,9(6H,8H)-dione, AZ27, ribavirin, 5-ethynyl-1-beta-D-ribofuranosylimidazole-4-carboxamide (EICAR), 4-hydroxy-3-beta-D-ribofuranosylpyrazole-5-carboxamide (pyrazofurin), 1-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1H-1,2,4-triazole-3-carboximidamide (Taribavirin, viramidine), (2R,3R,4R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(chloromethyl)-4-fluoro-2-((isobutyryloxy)methyl)tetrahydrofuran-3-yl isobutyrate, (2R,3R,4R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(chloromethyl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl isobutyrate, ((2R,3R,4R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(chloromethyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methyl triphosphate, 4-amino-1-((2R,3R,4R,5R)-5-(chloromethyl)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one, 1,3,4-thiadiazol-2-ylcyanamide (LY253963), tetrahydrofuran-3-yl-3-(3-(3-methoxy-4-(oxazol-5-yl)phenyl)ureido)benzylcarbamate (VX-497), (4E)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-2-benzofuran-5-yl)-4-methylhex-4-enoic acid (Mycophenolic acid), 2-morpholin-4-ylethyl-(E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1H-2-benzofuran-5-yl)-4-methylhex-4-enoate (Mycophenolate Mofetil), a Type 1 interferon, a Type 2 interferon, a

Type 3 interferon, a double stranded RNA oligonucleotide, 5-methyl-N-[4-(trifluoromethyl)phenyl]-isoxazole-4-carboxamide (leflumomide), N-(2-chloro-4-methylphenyl)-2-((1-(4-methoxyphenyl)-1H-benzo[d]imidazol-2-yl)thio)propanamide (JMN3-003), an intratracheal formulation of recombinant human CC10 (CG-100), high titer, human immunoglobulin (RI-001), a non-neutralizing mAb against the G protein (mAb 131-2G), ALN-RSV01, ALN-RSV02, Medi-559, Medi-534 and Medi-557, or a pharmaceutically acceptable salt of the foregoing.

Figure 1

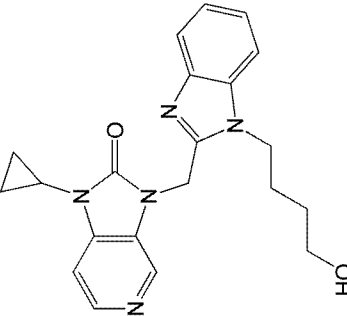
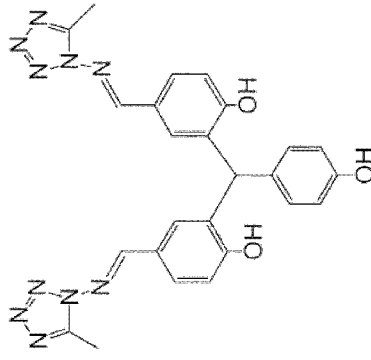
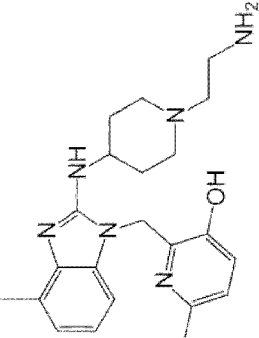
Name or CAS No.	IUPAC Name	Structure
BMS-433771	1-cyclopropyl-3-[[1-(4-hydroxybutyl)benzimidazol-2-yl]methyl]imidazo[4,5-c]pyridin-2-one	
VP-14637 (MDT-637)	5,5'-bis[1-(((5-amino-1H-tetrazolyl)imino)methyl)]2,2',4''-methylidynetrisphenol	
JNJ-2408068	2-[[2-[1-(2-aminoethyl)-4-piperidinylamino]-4-methyl-1H-benzimidazol-1-yl]-6-methyl-3-pyridinol	

Figure 1 (cont.)

Name or CAS No.	IUPAC Name	Structure
TMC-353121	2-[[6-[[[2-(3-Hydroxypropyl)-5-methylphenyl]amino]methyl]-2-[[3-(morpholin-4-yl)propyl]amino]benzimidazol-1-yl]methyl]-6-methylpyridin-3-ol	
P13	N-(2-hydroxyethyl)-4-methoxy-N-methyl-3-(6-methyl-[1,2,4]triazolo[3,4-a]phthalazin-3-yl)benzenesulfonamide	
C15	1,4-bis(3-methylpyridin-4-yl)-1,4-diazepane	

Figure 1 (cont.)

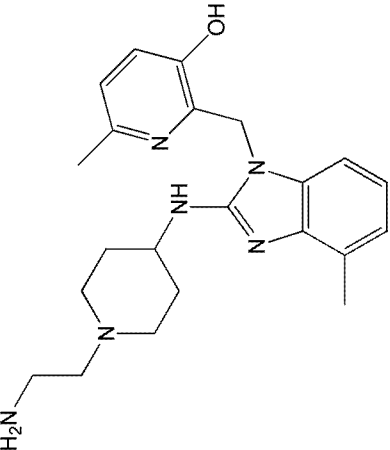
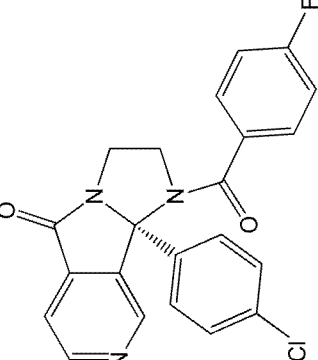
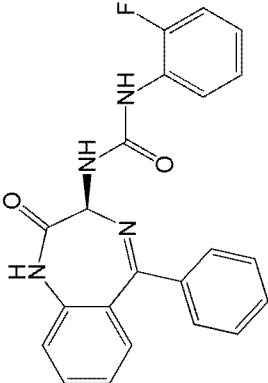
Name or CAS No.	IUPAC Name	Structure
R170591	2-((2-((1-(2-aminoethyl)piperidin-4-yl)amino)-4-methyl-1H-benzod[imidazol-1-yl)methyl)-6-methylpyridin-3-yl	
BTA9981	(R)-9b-(4-chlorophenyl)-1-(4-fluorobenzoyl)-2,3-dihydro-1H-imidazo[1',2':1,2]pyrrolo[3,4-c]pyridin-5(9bH)-one (BTA9981)	
RSV-604	(S)-1-(2-fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzof[e][1,4]diazepin-3-yl)urea	

Figure 1 (cont.)

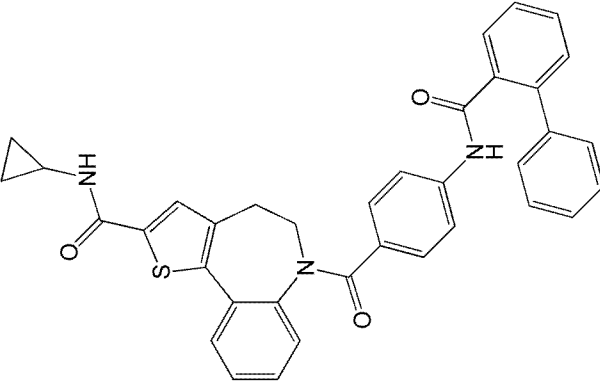
Name or CAS No.	IUPAC Name	Structure
YM-53403	6-{4-[[[(biphenyl-2-ylcarbonyl) amino]benzoyl]-N-cyclopropyl-5,6-dihydro-4H-thieno[3,2-d][1]benzazepine-2-carboxamide	 The chemical structure of YM-53403 is a complex molecule. It features a central benzazepine system, which is a bicyclic structure consisting of a benzene ring fused to a seven-membered ring containing a nitrogen atom. This central system is substituted at the 6-position with a 4-[[[(biphenyl-2-ylcarbonyl) amino]benzoyl]-N-cyclopropyl-5,6-dihydro-4H-thieno[3,2-d][1]benzazepine-2-carboxamide group. This group includes a thienobenzazepine moiety linked via an amide bond to a biphenyl-2-ylcarbonyl group, which is further substituted with an N-cyclopropyl group.

Figure 1 (cont.)

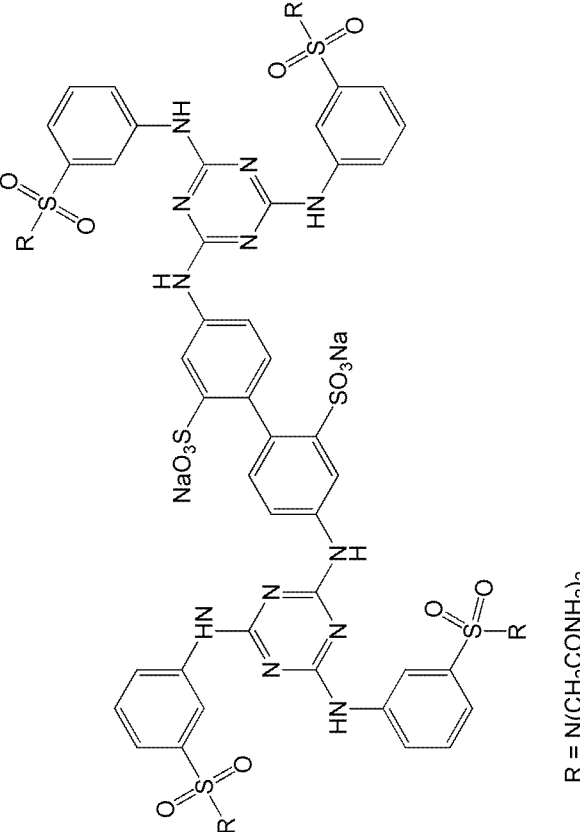
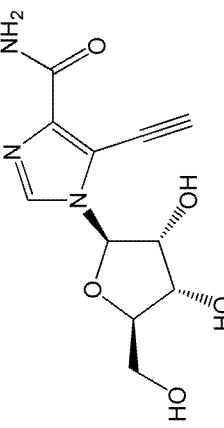
Name or CAS No.	IUPAC Name	Structure
RFI-641	4,4''-bis-{4,6-bis-[3-(bis-carbamoylmethyl-sulfamoyl)-phenylamino]-(1,3,5)triazin-2-ylamino}-biphenyl-2,2''-disulfonic-acid	 $R = N(CH_2CONH_2)_2$
EICAR	5-ethynyl-1-beta-D-ribofuranosylimidazole-4-carboxamide	

Figure 1 (cont.)

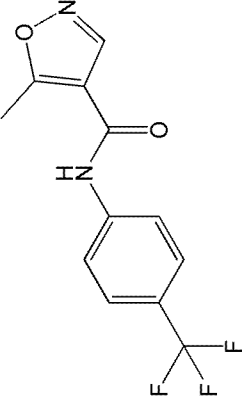
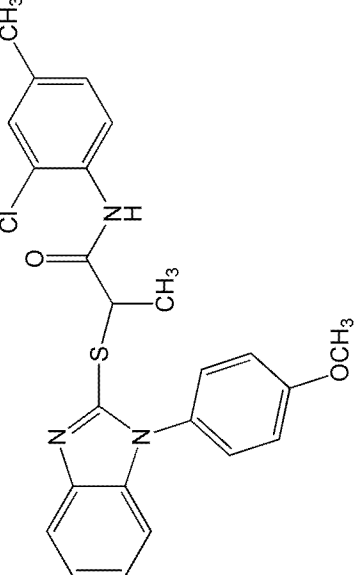
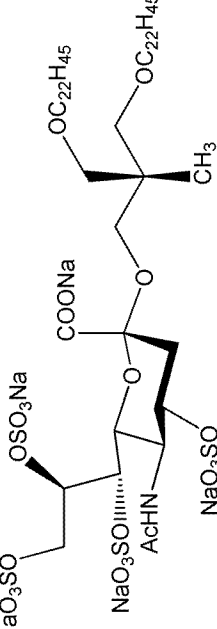
Name or CAS No.	IUPAC Name	Structure
leflumomide	5-methyl-N-[4-(trifluoromethyl) phenyl]-isoxazole-4-carboxamide	
JMN3-003	N-(2-chloro-4-methylphenyl)-2-((1-(4-methoxyphenyl)-1H-benzot[imidazol-2-yl]thio)propanamide	
MBX300	[2,2-bis(docosyloxy-oxymethyl)propyl-5-acetatoamido-3,5-dideoxy-4,7,8,9-tetra-O-(sodium-oxysulfonyl)-D-glycero-D-galacto-2-nonulopyranosid]onate	

Figure 1 (cont.)

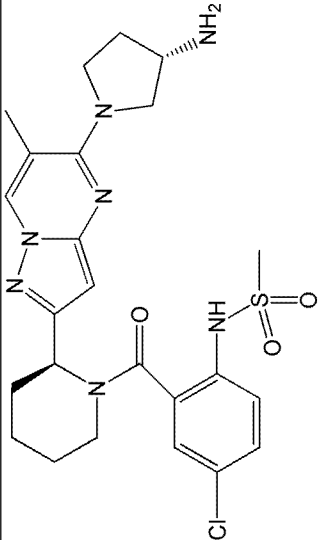
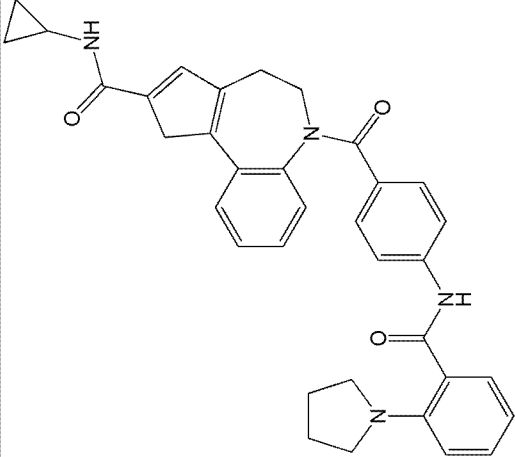
Name or CAS No.	IUPAC Name	Structure
GS-5806	N-(2-((S)-2-(5-((S)-3-aminopyrrolidin-1-yl)-6-methylpyrazolo[1,5-a]pyrimidin-2-yl)piperidine-1-carbonyl)-4-chlorophenyl)methanesulfonamide	
	N-cyclopropyl-5-(4-(2-(pyrrolidin-1-yl)benzamido)benzoyl)-5,6,7,10-tetrahydrobenzo[b]cyclopenta[d]azepine-9-carboxamide	

Figure 1 (cont.)

Name or CAS No.	IUPAC Name	Structure
851658-10-1	4-amino-8-(3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl)-6,6-dimethyl-2-(4-methyl-3-nitrophenyl)-1H-imidazo[4,5-h]-isoquinoline-7,9(6H,8H)-dione	

Figure 1 (cont.)

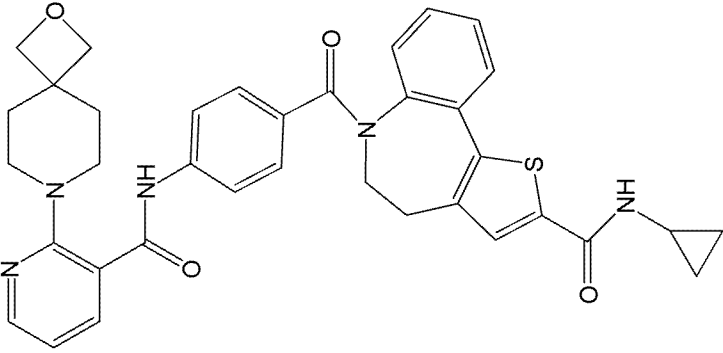
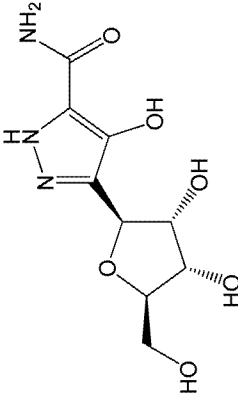
Name or CAS No.	IUPAC Name	Structure
AZ27	6-(4-(2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)nicotinamido)benzoyl)-N-cyclopropyl-5,6-dihydro-4H-benzo[b]thieno[2,3-d]azepine-2-carboxamide	
pyrazofurin	4-hydroxy-3-beta-D-ribofuranosylpyrazole-5-carboxamide	

Figure 1 (cont.)

Name or CAS No.	IUPAC Name	Structure
Taribavirin (viramidine)	1-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1H-1,2,4-triazole-3-carboximidamide	
ribavirin	1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1H-1,2,4-triazole-3-carboxamide	
LY253963	1,3,4-thiadiazol-2-ylcyanamide	
VX-497	tetrahydrofuran-3-yl 3-(3-methoxy-4-(oxazol-5-yl)phenyl)ureido)benzylcarbamate	
Mycophenolic acid	(4E)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-2-benzofuran-5-yl)-4-methylhex-4-enoic acid	

Figure 1 (cont.)

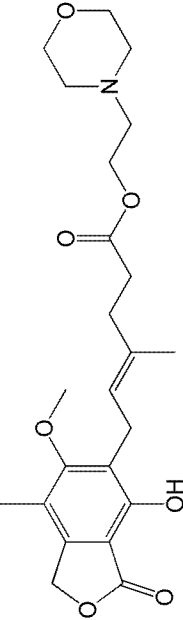
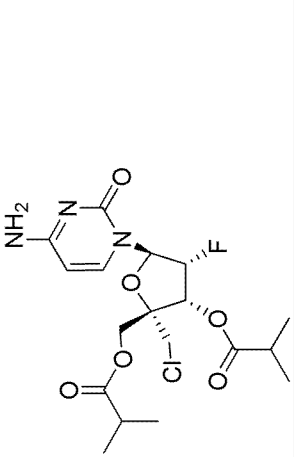
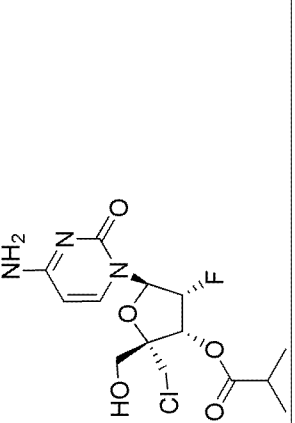
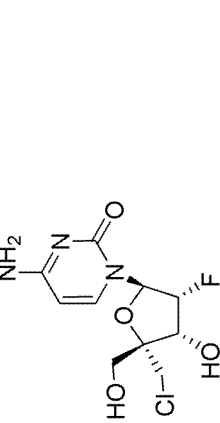
Name or CAS No.	IUPAC Name	Structure
Mycophenolate Mofetil	2-morpholin-4-ylethyl (E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1H-2-benzofuran-5-yl)-4-methylhex-4-enoate	
	(2R,3R,4R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(chloromethyl)-4-fluoro-2-((isobutyryloxy)methyl)tetrahydrofuran-3-yl isobutyrate	
	(2R,3R,4R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(chloromethyl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl isobutyrate	
	4-amino-1-((2R,3R,4R,5R)-5-(chloromethyl)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one	

Figure 1 (cont.)

Name or CAS No.	IUPAC Name	Structure
	((2R,3R,4R,5R)-5-(4-amino-2-oxypyrimidin-1(2H)-yl)-2-(chloromethyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methyl triphosphate	

A. CLASSIFICATION OF SUBJECT MATTER**[See Supplemental Sheet]**

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)

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)

STN (Registry, CAplus): Substructure search based upon formula (I) of claim 1**Espace:** Applicant/Inventor search

Applicant / Inventors names were also searched in internal databases provided by IP Australia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 27 April 2016	Date of mailing of the international search report 27 April 2016
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustalia.gov.au	Authorised officer Gavin Bartell AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262223647

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/US2016/019393
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/026792 A1 (ALIOS BIOPHARMA, INC.) 26 February 2015 The whole document, in particular compounds 499, 504, 506, 507, 652-2 and 652	1-4, 7, 9-11, 16, 21-22, 24, 26, 32, 84, 94, 96-99, 102- 105, 110-112, 115, 120-127
A	WO 2014/031784 A1 (ALIOS BIOPHARMA, INC.) 27 February 2014 The whole document	1-127
P,X	WO 2015/026792 A1 (ALIOS BIOPHARMA, INC.) 26 February 2015 Compounds 543, 647-4 and 651-4	1-4, 7, 10-11, 14, 22, 24, 26, 32, 102-105, 110-111, 113, 115 and 120-127

INTERNATIONAL SEARCH REPORT	International application No. PCT/US2016/019393
Supplemental Box – IPC Marks	
<i>C07D 491/048 (2006.01)</i> <i>C07D 498/04 (2006.01)</i> <i>C07D 491/20 (2006.01)</i> <i>C07D 471/04 (2006.01)</i> <i>C07D 221/04 (2006.01)</i> <i>C07D 213/36 (2006.01)</i> <i>C07D 401/04 (2006.01)</i> <i>C07D 413/04 (2006.01)</i> <i>C07D 213/68 (2006.01)</i> <i>C07D 491/052 (2006.01)</i> <i>A61K 31/4709 (2006.01)</i> <i>A61K 31/4355 (2006.01)</i> <i>A61K 31/4704 (2006.01)</i> <i>A61K 31/536 (2006.01)</i> <i>A61K 31/517 (2006.01)</i> <i>A61K 31/538 (2006.01)</i> <i>A61K 31/437 (2006.01)</i> <i>A61K 31/435 (2006.01)</i> <i>A61K 31/47 (2006.01)</i> <i>A61K 31/44 (2006.01)</i> <i>A61K 31/444 (2006.01)</i> <i>A61K 31/4427 (2006.01)</i> <i>A61K 31/436 (2006.01)</i> <i>A61K 31/4375 (2006.01)</i> <i>A61P 31/14 (2006.01)</i>	

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2016/019393	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2015/026792 A1	26 February 2015	WO 2015026792 A1	26 Feb 2015
		AU 2014308991 A1	24 Mar 2016
		CA 2921294 A1	26 Feb 2015
		SG 11201600977X A	30 Mar 2016
		US 2015065504 A1	05 Mar 2015
WO 2014/031784 A1	27 February 2014	WO 2014031784 A1	27 Feb 2014
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		AU 2013305759 A2	26 Mar 2015
		CA 2882088 A1	27 Feb 2014
		CN 104736530 A	24 Jun 2015
		EA 201590197 A1	30 Jul 2015
		EP 2888240 A1	01 Jul 2015
		JP 2015531769 A	05 Nov 2015
		KR 20150046259 A	29 Apr 2015
		MX 2015002231 A	17 Jul 2015
		PH 12015500355 A1	20 Apr 2015
		SG 11201501036R A	30 Mar 2015
		US 2015238498 A1	27 Aug 2015
		WO 2015/026792 A1	26 February 2015
AU 2014308991 A1	24 Mar 2016		
CA 2921294 A1	26 Feb 2015		
SG 11201600977X A	30 Mar 2016		
US 2015065504 A1	05 Mar 2015		
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			