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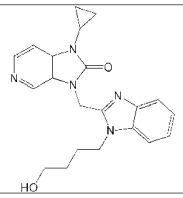
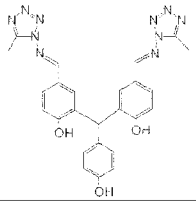
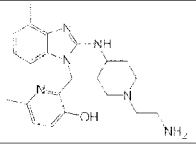
[Continued on next page]

(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''-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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— *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 ALIOS079.txt, created August 19, 2014, 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.

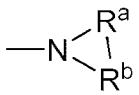
[0012] Symptoms of the measles include fever, cough, runny nose, red eyes and a generalized rash. Some individuals with measles can develop pneumonia, ear infections and bronchitis. Mumps leads to swelling of the salivary glands. Symptoms of mumps include fever, loss of appetite and fatigue. Individuals 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 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 heteroalicyclyl 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 heteroalicyclyl can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-. If no "a" and "b" are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, aryl, heteroaryl or heteroalicyclyl 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 "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 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 multicyclic 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 C_6-C_{14} aryl group, a C_6-C_{10} aryl group, or a C_6 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 multicyclic 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 "heteroalicyclyl(alkyl)" and "heterocyclyl(alkyl)" refer to a heterocyclic or a heteroalicyclylic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a heteroalicyclyl(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 -CH_2- tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), and butylene (-$CH_2CH_2CH_2CH_2$-). 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 –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(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, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(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 aryl-C(=O)-$(CH_2)_n$- and heteroaryl-C(=O)-$(CH_2)_n$-, 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-$(CH_2)_n$- ,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 $H_2N(CH_2)_n$- ,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 "SO_2R" 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 "X_3CSO_2-" group wherein each X is a halogen.

[0044] A "trihalomethanesulfonamido" group refers to an "$X_3CS(O)_2N(R_A)$-" 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 $-NH_2$ 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 $-N_3$ 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 "$-SO_2N(R_AR_B)$" 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 "$RSO_2N(R_A)$-" 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 1 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, "C_1-C_3 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-toluensulfonic, 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, C_1-C_7 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 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.

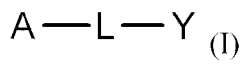
[0076] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates, and hydrates. In some embodiments, 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

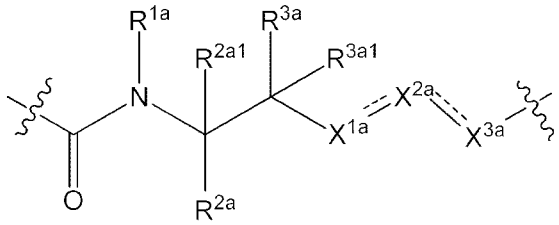
Formula (I)

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

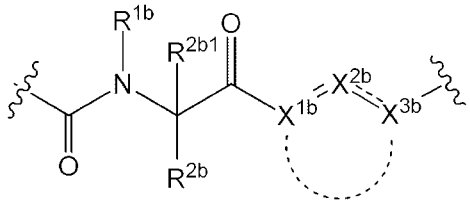


(I)

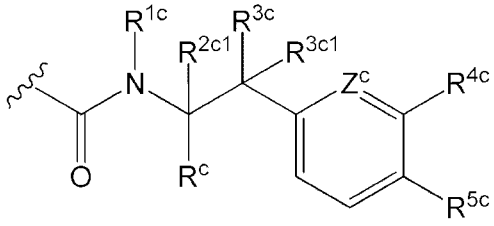
wherein: L can be selected from:



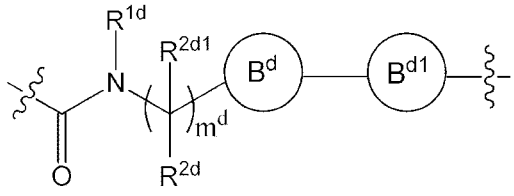
(Ia),



(Ib),

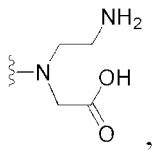


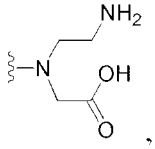
(Ic) and



(Id);

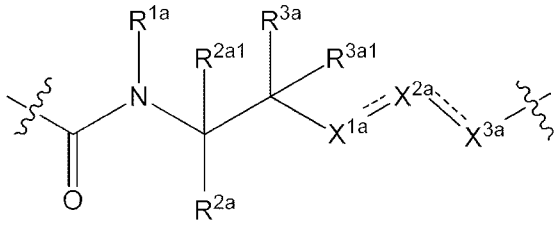
A can be selected from an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-2} alkyl), an optionally substituted heteroaryl and an optionally substituted heterocyclyl; Y can be selected from an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl; R^{1a}, R^{1b}, R^{1c} and R^{1d} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; R^{2a}, R^{2a1}, R^{2b}, R^{2b1}, R^{2c}, R^{2c1}, R^{2d} and R^{2d1} can be each independently selected from hydrogen, an optionally substituted C_{1-4} alkyl, an optionally substituted aryl(C_{1-6} alkyl),

an optionally substituted heterocyclyl(C_{1-6} alkyl), an alkoxyalkyl, an aminoalkyl, a hydroxyalkyl and hydroxy; or R^{2a1} can be hydrogen, and R^{1a} and R^{2a} can be joined together with the atoms to which they are attached to form an optionally substituted 5 membered heterocyclyl or an optionally substituted 6 membered heterocyclyl, R^{2b1} can be hydrogen, and R^{1b} and R^{2b} can be joined together with the atoms to which they are attached to form an optionally substituted 5 membered heterocyclyl or an optionally substituted 6 membered heterocyclyl; -------- between X^{1a} and X^{2a} represents a single or double bond between X^{1a} and X^{2a}; -------- between X^{2a} and X^{3a} represents a single or double bond between X^{2a} and X^{3a}; provided that -------- between X^{1a} and X^{2a} and -------- between X^{2a} and X^{3a} cannot be both double bonds and at least one of -------- is a double bond; when -------- between X^{1a} and X^{2a} represents a double bond and -------- between X^{2a} and X^{3a} is a single bond, then X^{1a} can be N (nitrogen) or CR^{4a1}, X^{2a} can be N (nitrogen) or CR^{5a} and X^{3a} can be NR^{6a1}, C(=O) or $CR^{6a2}R^{6a3}$; and when -------- between X^{1a} and X^{2a} represents a single bond and -------- between X^{2a} and X^{3a} is a double bond, then X^{1a} can be NR^{4a} or $CR^{4a2}R^{4a3}$, X^{2a} can be N (nitrogen) or CR^{5a} and X^{3a} can be N (nitrogen) or CR^{6a}; or X^{1a}, X^{2a} and X^{3a} can be each independently C (carbon), N (nitrogen), O (oxygen) or C(=O), and form a ring or ring system selected from an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl by joining X^{1a} and X^{3a} together; with the proviso that the valencies of X^{1a}, X^{2a} and X^{3a} can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl, and X^{1a}, X^{2a} and X^{3a} are uncharged; R^{3a} and R^{3a1} can be each independently selected from hydrogen, hydroxy, halogen, amino, an optionally substituted C_{1-4} alkyl, an optionally substituted C_{2-4} alkenyl, an optionally substituted C_{2-4} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{1-4} alkoxy, -O-carboxy, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, CHF_2, CF_3 and  , provided that R^{3a} and R^{3a1} cannot be both hydrogen; or R^{3a} and R^{3a1} can together form =N-OR^a; or R^{3a} and R^{3a1} can together with the atom to which they are attached can be joined to form an optionally substituted 3 membered ring, an optionally substituted 4 membered ring, an optionally substituted 5 membered ring or

an optionally substituted 6 membered ring; R^{4a}, R^{4a1}, R^{4a2} and R^{4a3} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; R^{5a} and R^{5a1} can be each independently be hydrogen or an unsubstituted C_{1-4} alkyl; R^{6a} and R^{6a1} can be each independently hydrogen, an optionally substituted C_{1-4} alkyl or an optionally substituted alkoxyalkyl; R^{6a2} and R^{6a3} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; X^{1b}, X^{2b} and X^{3b} can be each independently C (carbon), N (nitrogen), O (oxygen) or C(=O), and form a bi-cyclic ring selected from an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl by joining X^{1b} and X^{3b} together; provided that at least one of X^{1b}, X^{2b} and X^{3b} comprises a nitrogen atom; with the proviso that the valencies of X^{1b}, X^{2b} and X^{3b} can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl, and X^{1b}, X^{2b} and X^{3b} are uncharged; R^{3c} and R^{3c1} can be each independently selected from hydrogen, hydroxy, halogen, amino, an optionally substituted C_{1-4} alkyl, an optionally substituted C_{2-4} alkenyl, an optionally substituted C_{2-4} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{1-4} alkoxy, -O-carboxy, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, CHF_2, CF_3 and  , provided that R^{3c} and R^{3c1} cannot be both hydrogen; or R^{3c} and R^{3c1} can together form =N-OR^c; or R^{3c} and R^{3c1} can together with the atom to which they are attached can be joined to form an optionally substituted 3 membered ring, an optionally substituted 4 membered ring, an optionally substituted 5 membered ring or an optionally substituted 6 membered ring; R^a and R^c can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; R^{4c} and R^{5c} can be taken together to form an unsubstituted aryl, an unsubstituted heteroaryl or an optionally substituted heterocyclyl; Z^c can be N or CH; m^d can be 0 or 1; and ring B^d can be an optionally substituted C_5 cycloalkyl; ring B^{d1} can be an optionally substituted pyridinyl; and provided that when L is Formula (IIc), then Y is absent.

Formula (Ia)

[0079] In some embodiments, L can be Formula (Ia):

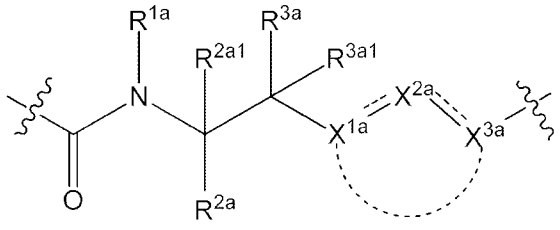


(Ia).

[0080] In some embodiments of Formula (Ia), X^{1a} can be CR^{4a1} or $CR^{4a2}R^{4a3}$, X^{2a} can be N (nitrogen), and X^{3a} can be CR^{6a} or $CR^{6a2}R^{6a3}$. In some embodiments of Formula (Ia), -------- between X^{1a} and X^{2a} can be a single bond, -------- between X^{2a} and X^{3a} can be a double bond, X^{1a} can be $CR^{4a2}R^{4a3}$, X^{2a} can be N (nitrogen), and X^{3b} can be CR^{6a}. In other embodiments of Formula (Ia), -------- between X^{1a} and X^{2a} can be a double bond, -------- between X^{2a} and X^{3a} can be a single bond, X^{1a} can be CR^{4a1}, X^{2b} can be N (nitrogen), and X^{3b} can be $CR^{6a2}R^{6a3}$. In some embodiments, including those of this paragraph, R^{5a} can be hydrogen. In some embodiments including those of this paragraph, R^{5a1} can be hydrogen. In some embodiments, $-X^{1a}$------X^{2a}------X^{3a}- can be $-CH_2-N=CH-$ or $-CH=N-CH_2-$. In other embodiments, $-X^{1a}$------X^{2a}------X^{3a}- can be $-N=N-CH_2-$, $-N=CH-CH_2-$ or -N=CH-NH-. In still other embodiments, $-X^{1a}$------X^{2a}------X^{3a}- can be $-CH_2-CH=N-$, -NH-CH=NH- or -NH-N=CH-. In some embodiments, X^{1a}, X^{2a} and X^{3a} can be each independently C (carbon), N (nitrogen), O (oxygen) or C(=O), and form a ring or ring system selected from an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl by joining X^{1a} and X^{3a} together; with the proviso that the valencies of X^{1a}, X^{2a} and X^{3a} can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl; and X^{1a}, X^{2a} and X^{3a} are uncharged.

Formula (Ia1)

[0081] In some embodiments, L of Formula (Ia) can be Formula (Ia1):

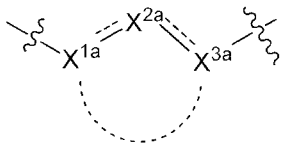
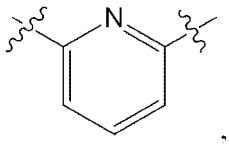
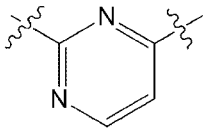
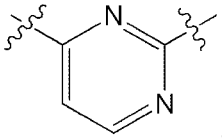
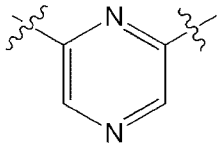
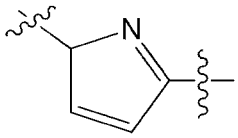
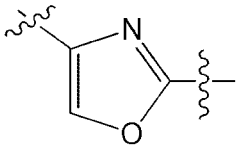
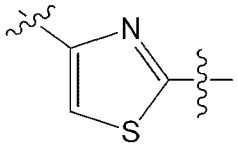
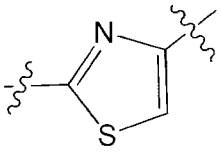
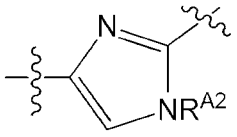
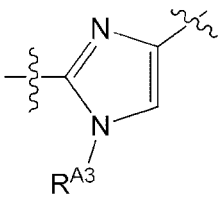
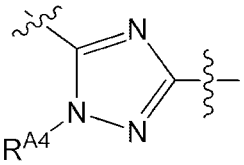
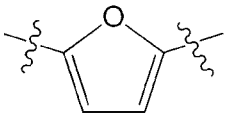


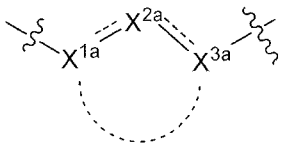
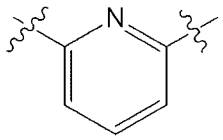
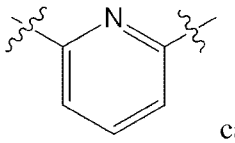
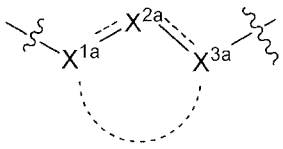
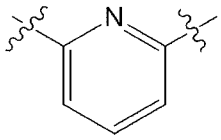
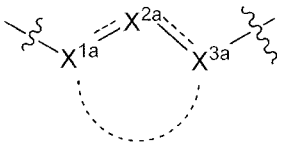
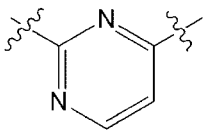
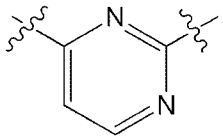
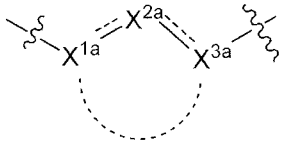
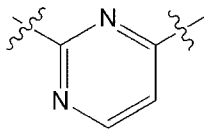
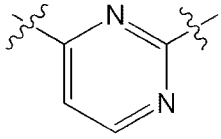
(Ia1)

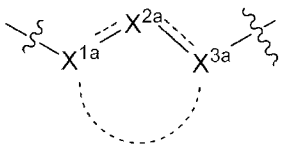
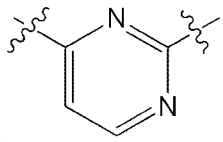
wherein: X^{1a}, X^{2a} and X^{3a} can be each independently C (carbon), N (nitrogen), O (oxygen) or C(=O), and form a ring or ring system selected from an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl by joining X^{1a} and X^{3a} together; with the proviso that the valencies of X^{1a}, X^{2a} and X^{3a} can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl; and X^{1a}, X^{2a} and X^{3a} are uncharged.

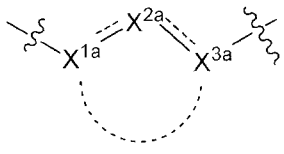
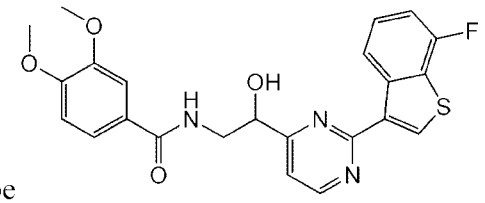
[0082] In some embodiments of Formula (Ia1), X^{1a} can be C, X^{2a} can be N and X^{3a} can be C. In some embodiments of Formula (Ia1), -------- between X^{1a} and X^{2a} can be a single bond, -------- between X^{2a} and X^{3a} can be a double bond, X^{1a} can be C, X^{2a} can be N and X^{3a} can be C. In other embodiments of Formula (Ia1), -------- between X^{1a} and X^{2a} can be a double bond, -------- between X^{2a} and X^{3a} can be a single bond, X^{1a} can be C, X^{2a} can be N and X^{3a} can be C. In still other embodiments of Formula (Ia1), -------- between X^{1a} and X^{2a} can be a single bond, -------- between X^{2a} and X^{3a} can be a single bond, X^{1a} can be C, X^{2a} can be O and X^{3a} can be C. In some embodiments, the valencies of X^{1a}, X^{2a} and X^{3a} can be each independently satisfied with hydrogen or an unsubstituted C_{1-4} alkyl, such as CH_3.

[0083] In some embodiments, the ring or ring system of Formula (Ia1) can be an optionally substituted aryl. In other embodiments, the ring or ring system of Formula (Ia1) can be an optionally substituted mono-cyclic heteroaryl. In still other embodiments, the ring or ring system of Formula (Ia1) can be an optionally substituted bi-cyclic heteroaryl. In some embodiments, the ring or ring system of Formula (Ia1) can be an optionally substituted mono-cyclic heterocyclyl. In some embodiments, the ring or ring system of Formula (Ia1) can be an optionally substituted bi-cyclic heterocyclyl.

[0084] In some embodiments of Formula (Ia1),  can be selected from 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  , an optionally substituted  , an optionally substituted  , and an optionally substituted  ; wherein R^{A1}, R^{A2}, R^{A3} and R^{A4} can be each independently hydrogen or an unsubstituted C_{1-6} alkyl.

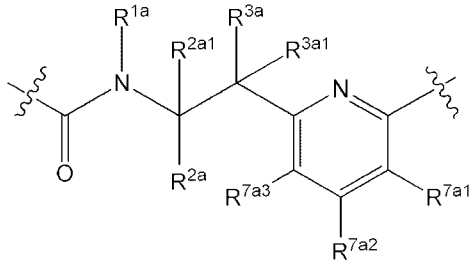
[0085] In some embodiments,  can be an optionally substituted  . In some embodiments,  can be substituted with one or more substituents selected from amino, mono-substituted amino, di-substituted amino, hydroxyalkyl, alkyl and alkoxy. In some embodiments,  can be an unsubstituted  . In other embodiments,  can be a substituted  or a substituted  . In some embodiments,  can be an optionally substituted  or an optionally substituted  , R^{3a} can be hydroxy and R^{3a1} can be selected from amino, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{3-6} cycloalkyl (for example, cyclopropyl), an unsubstituted C_{1-4} alkoxy (such as OCH_3), hydroxy, halogen and an unsubstituted heteroaryl (for example, thiazole).

[0086] In some embodiments, when one of R^{3a} and R^{3a1} is H and the other of R^{3a} and R^{3a1} is OH, then  is not an unsubstituted  . In other embodiments, when one of R^{3a} and R^{3a1} is H, then the other of R^{3a} and R^{3a1} is not OH.

In some embodiments,  is not an optionally substituted pyrimidine. In some embodiments, a compound of Formula (I) cannot be  .

Formula (Ia2)

[0087] In some embodiments, L of Formula (Ia) can be Formula (Ia2):

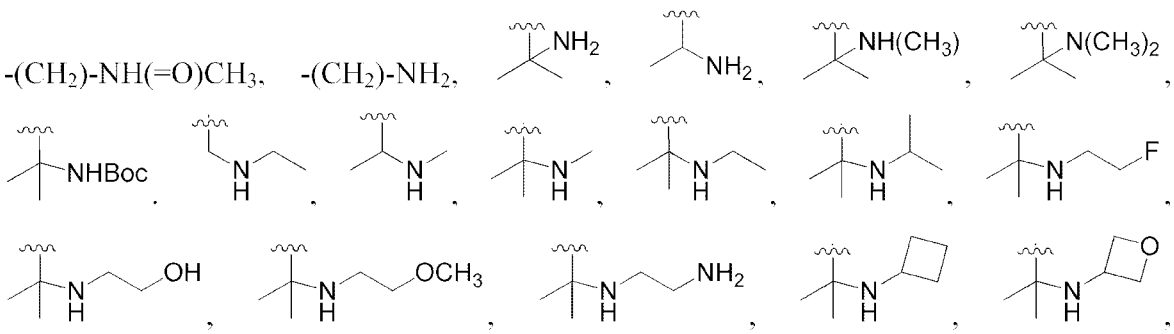


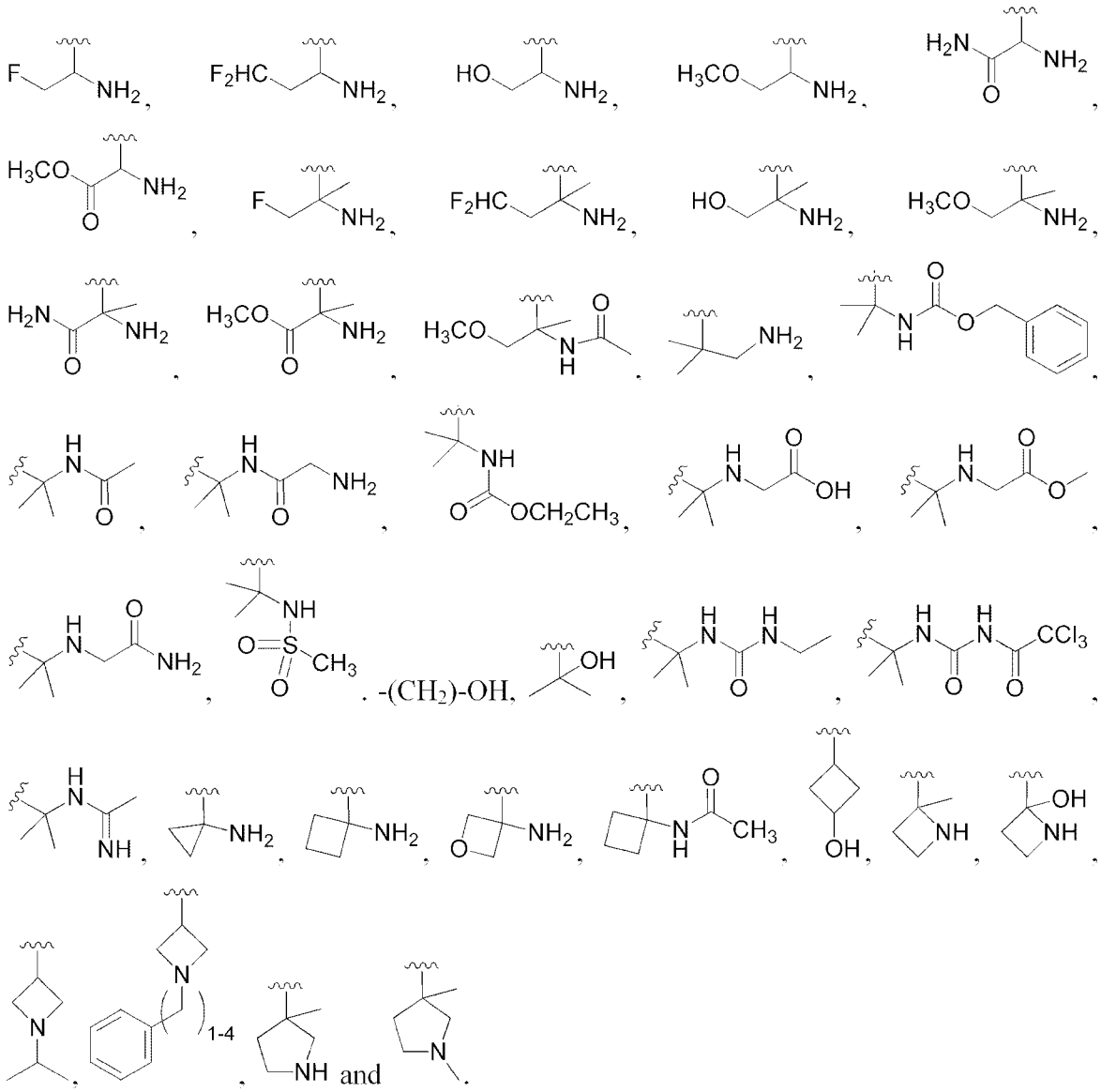
(Ia2)

wherein R^{7a1}, R^{7a2} and R^{7a3} can be each independently selected from hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C_{1-8} alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C_{1-8} alkyl), haloalkyl, an optionally substituted O-amido and an optionally substituted C-carboxy. In some embodiments, R^{7a1}can be an unsubstituted C_{1-4} alkoxy, and R^{7a2} and R^{7a3} can be both hydrogen. In other embodiments, R^{7a1}can be a substituted C_{1-4} alkoxy, and R^{7a2} and R^{7a3} can be both hydrogen. For example, R^{7a1}can be a substituted C_{1-4} alkoxy substituted with an amino, mono-substituted amino or a di-substituted amino. In some embodiments, R^{7a1} can be hydrogen, R^{7a2} can be an optionally substituted C_{1-4} alkyl, and R^{7a3} can be hydrogen. In other embodiments, R^{7a1} can be hydrogen, R^{7a2} can be a substituted C_{3-6} cycloalkyl, and R^{7a3} can be hydrogen. In still other embodiments, R^{7a1} can be hydrogen, R^{7a2} can be a mono-

substituted amino, and R^{7a3} can be hydrogen. In yet still other embodiments, R^{7a1} can be a mono-substituted amino or an optionally substituted O-amido (such as $-C(=O)NH_2$) and R^{7a2} and R^{7a3} can be both hydrogen. For example, the mono-substituted amino of R^{7a1} or R^{7a2} can be $-N(C_{1-4}$ alkyl), such as $-NCH_3$. In some embodiments, R^{7a1} can be a substituted C_{1-8} alkyl (such as an amino substituted C_{1-8} alkyl) and R^{7a2} and R^{7a3} can be both hydrogen. In other embodiments, R^{7a1} and R^{7a2} can be both hydrogen and R^{7a3} can be halogen. In other embodiments, R^{7a1} and R^{7a3} can be both hydrogen and R^{7a2} can be an optionally substituted heterocyclyl, such as an optionally substituted mono-cyclic heterocyclyl. Examples of optionally substituted mono-cyclic heterocyclyl at R^{7a2} include, but are not limited to, an optionally substituted azetidine, an optionally substituted pyrrolidine, an optionally substituted pyrrolidinone, an optionally substituted piperidine and an optionally substituted oxetane.

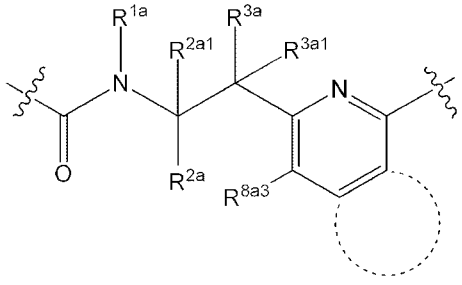
[0088] When R^{7a1}, R^{7a2} and/or R^{7a3} are substituted, possible substituent(s) includes those provided in the list of "substituted" along with urea, amidine and acetylurea. For example, the C_{1-4} alkyl, C_{3-6} cycloalkyl and mono-cyclic heterocyclyl of R^{7a2} can be substituted with various substituent(s), such as, halo, hydroxy, C_{1-4} alkoxy, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted C-carboxy, amino, an optionally substituted mono-substituted amino, an optionally substituted di-substituted amino, an optionally substituted C-amido, an optionally substituted N-amido, an optionally substituted N-carbamyl, an optionally substituted N-sulfonamido, an optionally substituted urea, an optionally substituted amidine and an optionally substituted acetylurea (e.g., halogenated acetylurea). Non-limiting examples of substituted C_{1-4} alkyls and substituted C_{3-6} cycloalkyls of R^{7a2} are as follows:





Formula (Ia3)

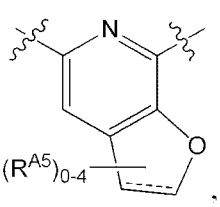
[0089] In some embodiments, L of Formula (Ia) can be Formula (Ia3):

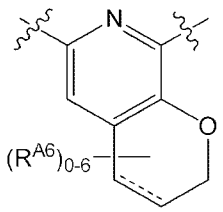


(Ia3)

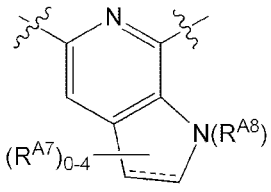
wherein: the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted cycloalkyl an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; and R^{8a3} can be selected from hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C_{1-8} alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C_{1-8} alkyl), haloalkyl and an optionally substituted C-carboxy.

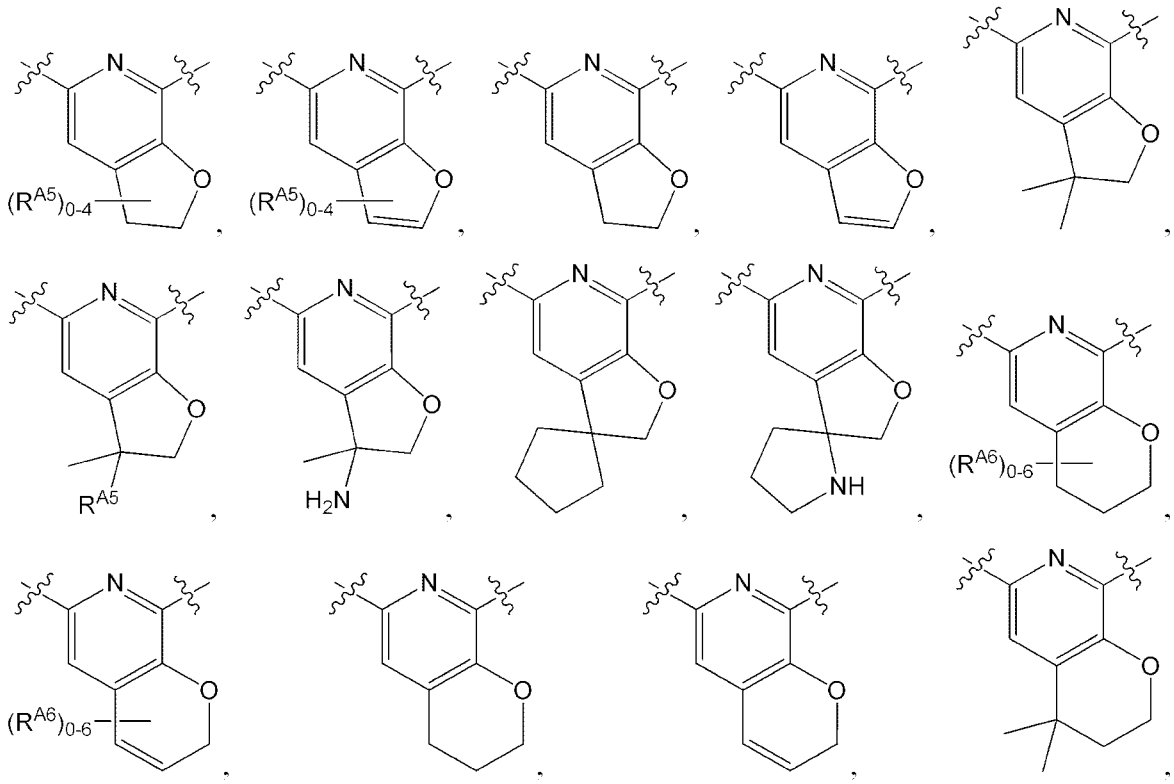
[0090] In some embodiments of Formula (Ia3), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 5-membered cycloalkyl. In other embodiments of Formula (Ia3), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 6-membered cycloalkyl. In still other embodiments of Formula (Ia3), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted aryl (for example, phenyl). In some embodiments of Formula (Ia3), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 5-membered heteroaryl. In other embodiments of Formula (Ia3), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 6-membered heteroaryl. In still other embodiments of Formula (Ia3), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 5-membered heterocyclyl. In yet still other embodiments of Formula (Ia3), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 6-membered heterocyclyl.

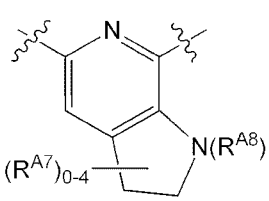
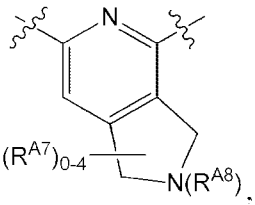
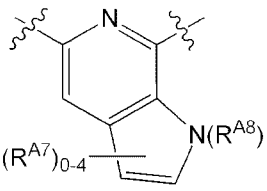
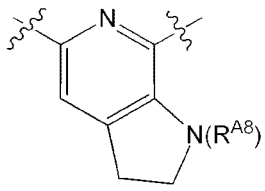
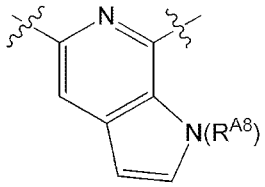
[0091] In some embodiments, the bicyclic ring system can be selected from an optionally substituted 

, an optionally substituted 

and an

optionally substituted  ; wherein each ------ can be independently absent or a bond; each R^{A5}, each R^{A6}, each R^{A7} can be halogen, an unsubstituted C_{1-6} alkyl, hydroxy, amino, an optionally substituted mono-substituted amino, an optionally substituted di-substituted amino, $-(CH_2)_{1-4}OH$, $-(CH_2)_{1-4}NH_2$ or N-sulfinamido (for example, $-NH-S(=O)C_{1-4}$ alkyl), or two R^{A5}, two R^{A6} or two R^{A7} are taken together to form an optionally substituted 5- membered ring to an optionally substituted 6-membered ring (such as an optionally substituted cycloalkyl or an optionally substituted heterocyclyl); and R^{A8} can be hydrogen or an unsubstituted C_{1-6} alkyl. In some embodiments of this paragraph, ------ can be absent. In some embodiments of this paragraph, ------ can be a bond such that a double bond is present between the between carbons. In some embodiments, at least two R^{A5} groups can be an unsubstituted C_{1-6} alkyl (for example, CH_3). In some embodiments, at least two R^{A6} groups can be an unsubstituted C_{1-6} alkyl (for example, CH_3). Examples of these bi-cyclic groups include the following:







and


[0092] In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{1a} can be hydrogen. In other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{1a} can be an unsubstituted C_{1-4} alkyl.

[0093] In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), both R^{2a} and R^{2a1} can be hydrogen. In other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{2a} can be hydrogen and R^{2a1} can be an unsubstituted C_{1-4} alkyl. In still other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{2a} can be hydrogen and R^{2a1} can be a substituted C_{1-4} alkyl. In yet still other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{2a} can be hydrogen and R^{2a1} can be an optionally substituted aryl(C_{1-6} alkyl) or an optionally substituted heterocyclyl(C_{1-6} alkyl). In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{2a} can be hydrogen and R^{2a1} can be an alkoxyalkyl, an aminoalkyl or a hydroxyalkyl. In other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{2a} can be hydrogen and R^{2a1} can be hydroxy. In still other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{2a1} can be hydrogen, and R^{1a} and R^{2a} can be joined together with the atoms to which they are attached to form an optionally substituted 5 membered heterocyclyl (for example, pyrrolidinyl) or an optionally substituted 6 membered heterocyclyl (for example, piperdinyl). In yet still other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{2a} and R^{2a1} both can be an optionally substituted C_{1-4} alkyl.

[0094] In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be hydrogen, and R^{3a1} can be selected from amino, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{3-6} cycloalkyl (for example, cyclopropyl), an unsubstituted C_{1-4} alkoxy (such as OCH_3), an unsubstituted -O-

carboxy (such as –OC(=O)C_{1-4} alkyl), hydroxy, halogen, an unsubstituted heteroaryl (for example, thiazole) and an optionally substituted heterocyclyl (for example, azetidine). In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be hydrogen, and R^{3a1} can be hydroxy. In other embodiments or Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} and R^{3a1} can be both halogen. In still other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be hydrogen, and R^{3a1} can be unsubstituted C_{1-4} alkyl. In yet still other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be hydroxy, and R^{3a1} can be selected from amino, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{3-6} cycloalkyl (for example, cyclopropyl), an unsubstituted C_{1-4} alkoxy (such as OCH_3), hydroxy, halogen, an unsubstituted heteroaryl (for example, thiazole) and an optionally substituted heterocyclyl (for example, azetidine). In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be hydroxy, and R^{3a1} can be an unsubstituted C_{1-4} alkyl. In other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be hydroxy, and R^{3a1} can be an unsubstituted C_{2-4} alkenyl (such as ethenyl or propenyl) or an unsubstituted C_{2-4} alkynyl (such as ethynyl or propynyl). In still other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be hydroxy, and R^{3a1} can be CF_3. In yet still other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be hydroxy, and R^{3a1} can be CHF_2. In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be halogen, and R^{3a1} can be CF_3 or CHF_2. In other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be halogen, and R^{3a1} can be CHF_2. In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be hydroxy, and R^{3a1} can be an unsubstituted C_{3-6} cycloalkyl, for example, an unsubstituted cyclopropyl. In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be halogen, and R^{3a1} can be an unsubstituted C_{3-6} cycloalkyl, for example, an unsubstituted cyclopropyl. In other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} can be an unsubstituted C_{1-4} alkoxy (such as methoxy), and R^{3a1} can be an unsubstituted C_{1-4} alkyl (such as methyl). In still other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} and R^{3a1} can be both an unsubstituted C_{1-4} alkyl, for example, R^{3a} and R^{3a1} can be both methyl. In yet sill other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), one of R^{3a} and R^{3a1} can be an optionally substituted mono-cyclic heteroaryl; and the other of R^{3a} and R^{3a1} can be hydroxy.

In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), one of R^{3a} and R^{3a1} can be an unsubstituted C_{1-4} alkyl (such as methyl) ; and the other of R^{3a} and R^{3a1} can be an unsubstituted -O-carboxy (such as $-OC(=O)C_{1-4}$ alkyl).

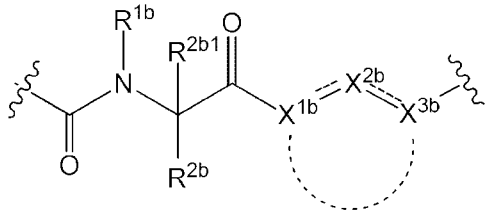
[0095] When one of R^{3a} and R^{3a1} is a substituted C_{1-4} alkyl, the C_{1-4} alkyl can be substituted with various substituents. For example, in some embodiments, one of R^{3a} and R^{3a1} is a substituted C_{1-4} alkyl substituted with substituent selected from halogen, hydroxy, amino, mono-substituted amino (for example, $-NH(C_{1-4}$ alkyl)), di-substituted amino, -N-amido, mono-cyclic heteroaryl and mono-cyclic heterocyclyl. In some embodiments, one of R^{3a} and R^{3a1} can be an optionally substituted mono-cyclic heteroaryl or an optionally substituted mono-cyclic heterocyclyl and the other of R^{3a} and R^{3a1} can be hydroxy. The mono-cyclic heteroaryl substituted on the C_{1-4} alkyl of one of R^{3a} and R^{3a1} can be 5-membered or 6-membered heteroaryl. The mono-cyclic heterocyclyl substituted on the C_{1-4} alkyl of one of R^{3a} and R^{3a1} can be 4-membered, 5-membered or 6-membered heterocyclyl. For example, one of R^{3a} and R^{3a1} can be a substituted C_{1-4} alkyl substituted with substituent selected from an optionally substituted imidazole, an optionally substituted pyrazole, an optionally substituted pyrrolidine, an optionally substituted piperidine, an optionally substituted piperazine, an optionally substituted morpholine, an optionally substituted triazole, an optionally substituted piperazinone and an optionally substituted azetidine.

[0096] In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} and R^{3a1} can together form $N=OR^a$. In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} and R^{3a1} together form N=OH. In other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} and R^{3a1} can together form $N=OCH_3$. In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), R^{3a} and R^{3a1} can join together with the atom to which they are attached to form an optionally substituted 3 to 6 membered ring. In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), the 3 to 6 membered ring can be a C_{3-6} cycloalkyl. In other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), the ring can be a 3 to 6 membered heterocyclyl, for example, an optionally substituted oxetane or an optionally substituted oxazolidinone. In some embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), 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 of Formulae (Ia), (Ia1),

(Ia2) and/or (Ia3), the carbon can have a (R)-configuration. In other embodiments of Formulae (Ia), (Ia1), (Ia2) and/or (Ia3), the carbon to which R^{3a} and R^{3a1} are attached can have a (S)-configuration.

Formula (Ib)

[0097] In some embodiments, L of Formula (I) can be Formula (Ib):



(Ib).

wherein the dotted curved line between X^{1b} and X^{3b} indicates a bi-cyclic ring selected from an optionally substituted bi-cyclic heteroaryl and an optionally substituted bi-cyclic heterocyclyl by joining X^{1b} and X^{3b} together, wherein -------- between X^{1b} and X^{2b} represents a single or double bond between X^{1b} and X^{2b}; -------- between X^{2b} and X^{3b} represents a single or double bond between X^{2b} and X^{3b}; wherein X^{1b}, X^{2b} and X^{3b} can be each independently C (carbon), N (nitrogen), O (oxygen) or C(=O); and provided that at least one of X^{1b}, X^{2b} and X^{3b} comprises a nitrogen atom and both -------- cannot be double bonds; with the proviso that the valencies of X^{1b}, X^{2b} and X^{3b} can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl; and X^{1b}, X^{2b} and X^{3b} are uncharged. In some embodiments, the valencies of X^{1b}, X^{2b} and X^{3b} can be each independently satisfied with a substituent selected from hydrogen and an unsubstituted C_{1-4} alkyl. In some embodiments, the valencies of X^{1b}, X^{2b} and X^{3b} can be each independently satisfied with hydrogen or methyl.

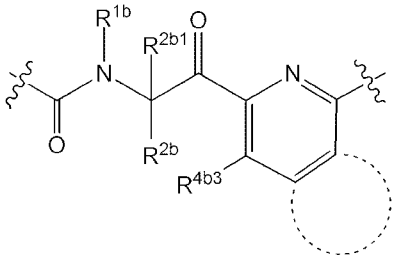
[0098] In some embodiments of Formula (Ib), the bi-cyclic ring can be an optionally substituted 9-membered bi-cyclic heteroaryl. In other embodiments of Formula (Ib), the bi-cyclic ring can be an optionally substituted 9-membered bi-cyclic heterocyclyl. In still other embodiments of Formula (Ib), the bi-cyclic ring can be an optionally substituted 10-membered bi-cyclic heteroaryl. In yet still some embodiments of Formula (Ib), the bi-cyclic ring can be an optionally substituted 10-membered bi-cyclic heterocyclyl.

[0099] In some embodiments of Formula (Ib), X^{1b} can be C, X^{2b} can be N and X^{3b} can be C. In other embodiments of Formula (Ib), X^{1b} can be N, X^{2b} can be N and X^{3b} can be C. In still other embodiments of Formula (Ib), X^{1b} can be N, X^{2b} can be C(=O) and X^{3b} can be N. In yet still other embodiments of Formula (Ib), X^{1b} can be C, X^{2b} can be O and X^{3b} can be C.

[0100] In some embodiments of Formula (Ib), when X^{1b} can be C, X^{2b} can be N and X^{3b} can be C, the bi-cyclic ring can be an optionally substituted bi-cyclic heteroaryl ring. In other embodiments of Formula (Ib), when X^{1b} can be C, X^{2b} can be N and X^{3b} can be C, the bi-cyclic ring can be an optionally substituted bi-cyclic heterocyclyl ring.

Formula (Ib1)

[0101] In some embodiments, L of Formula (Ib) can be Formula (Ib1):

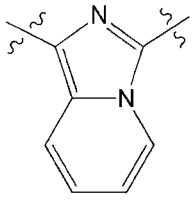
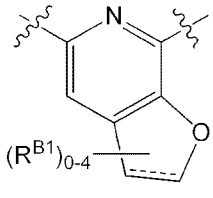
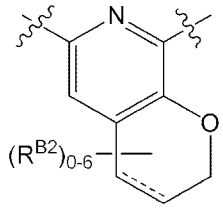
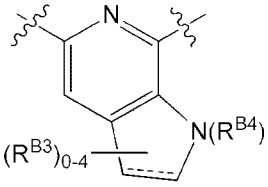


(Ib1)

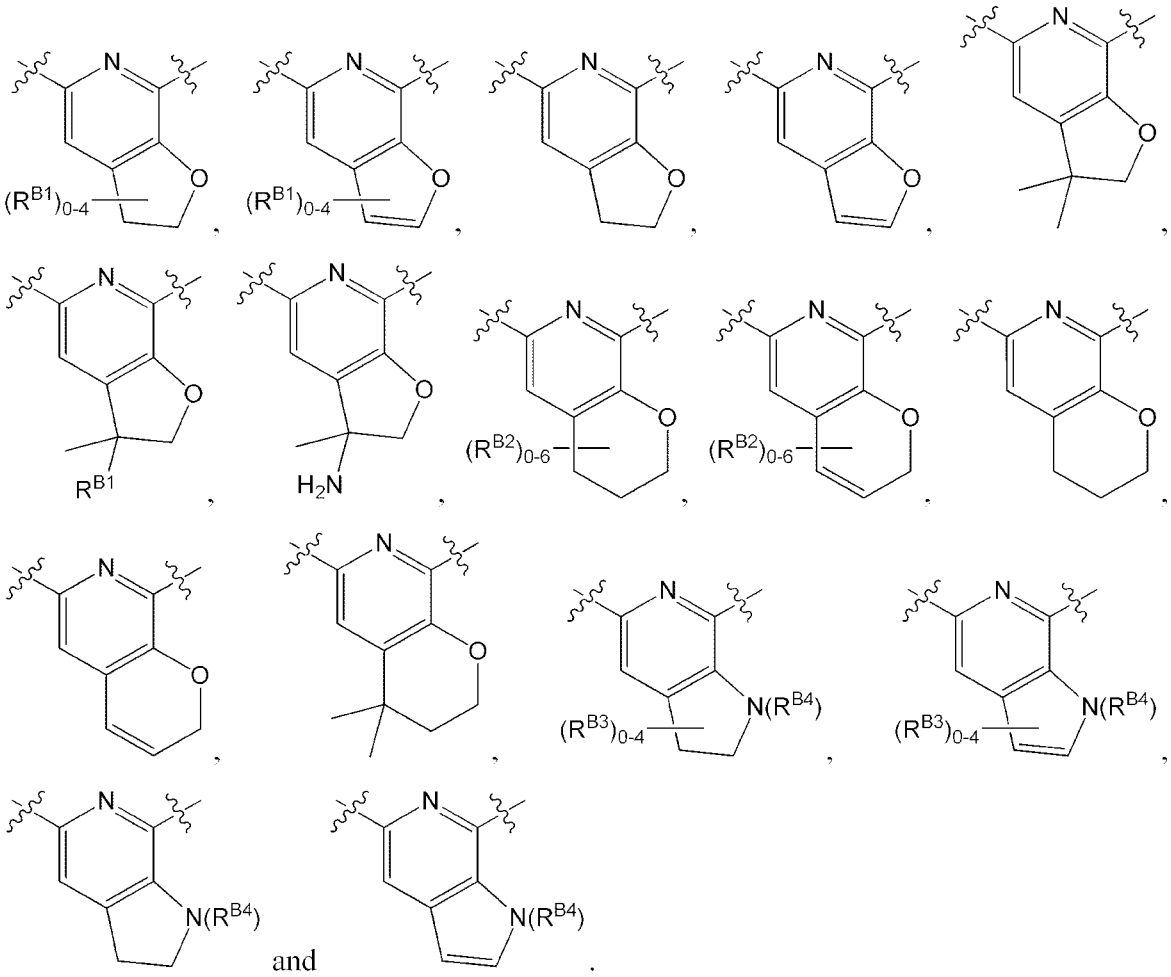
wherein: the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; and R^{4b3} can be selected from hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C_{1-8} alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C_{1-8} alkyl), haloalkyl and an optionally substituted C-carboxy.

[0102] In some embodiments of Formula (Ib1), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 5-membered cycloalkenyl. In other embodiments of Formula (Ib1), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 6-membered

cycloalkenyl. In still other embodiments of Formula (Ib1), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted aryl (for example, phenyl). In some embodiments of Formula (Ib1), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 5-membered heteroaryl. In other embodiments of Formula (Ib1), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 6-membered heteroaryl. In still other embodiments of Formula (Ib1), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 5-membered heterocyclyl. In yet still other embodiments of Formula (Ib1), the dashed semi-circle along with the two carbon atoms to which it is connected can form an optionally substituted 6-membered heterocyclyl.

[0103] In some embodiments, the bi-cyclic ring system can be selected from an optionally substituted  , an optionally substituted  , an optionally substituted an optionally substituted  and an optionally substituted  ; wherein each ----- can be independently absent or a bond; each R^{B1}, each R^{B2} and each R^{B3} can be an unsubstituted C_{1-6} alkyl, halogen, hydroxy, amino, mono-substituted amino, di-substituted amino or –NH-S(=O)C_{1-4} alkyl; and R^{B4} can be hydrogen or an unsubstituted C_{1-6} alkyl,. In some embodiments of this paragraph, ------ can be absent. In some embodiments of this paragraph, ------ can be a bond such that a double bond is present between the between carbons. In some embodiments, at least two R^{B2} groups can be an unsubstituted C_{1-6} alkyl (for example, CH_3). In some embodiments, at least two

R^{B3} groups can be an unsubstituted C_{1-6} alkyl (for example, CH_3). Examples of these bi-cyclic groups include the following:



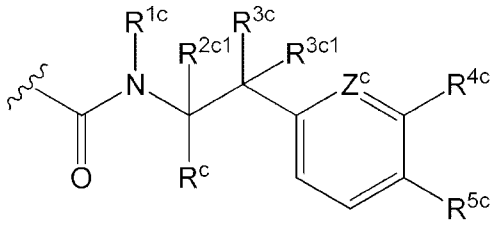
[0104] In some embodiments of Formulae (Ib) and (Ib1), R^{1b} can be hydrogen.

[0105] In some embodiments of Formulae (Ib) and (Ib1), both R^{2b} and R^{2b1} can be hydrogen. In other embodiments of Formulae (Ib) and (Ib1), R^{2b} can be hydrogen and R^{2b1} can be an unsubstituted C_{1-4} alkyl. In still other embodiments of Formulae (Ib) and (Ib1), R^{2b} can be hydrogen and R^{2b1} can be a substituted C_{1-4} alkyl. In yet still other embodiments of Formulae (Ib) and (Ib1), R^{2b} can be hydrogen and R^{2b1} can be an optionally substituted aryl(C_{1-6} alkyl) or an optionally substituted heterocyclyl(C_{1-6} alkyl). In some embodiments of Formulae (Ib) and (Ib1), R^{2b} can be hydrogen and R^{2b1} can be an alkoxyalkyl, an aminoalkyl or a hydroxyalkyl. In other embodiments of Formulae (Ib) and (Ib1), R^{2b} can be hydrogen and R^{2b1} can be hydroxy. In still other embodiments of Formulae (Ib) and (Ib1), R^{2b1} can be

hydrogen, and R^{1b} and R^{2b} can be joined together with the atoms to which they are attached to form an optionally substituted 5 membered heterocyclyl or an optionally substituted 6 membered heterocyclyl.

Formula (Ic)

[0106] In some embodiments, L can be Formula (Ic):



(Ic).

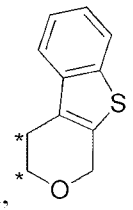
[0107] In some embodiments of Formula (Ic), R^{1c} can be hydrogen. In other embodiments of Formula (Ic), R^{1c} can be an unsubstituted C_{1-4} alkyl.

[0108] In some embodiments of Formula (Ic), both R^{2c} and R^{2c1} can be hydrogen. In other embodiments of Formula (Ic), R^{2c} can be hydrogen and R^{2c1} can be an unsubstituted C_{1-4} alkyl. In still other embodiments of Formula (Ic), R^{2c} can be hydrogen and R^{2c1} can be a substituted C_{1-4} alkyl. In yet still other embodiments of Formula (Ic), R^{2c} can be hydrogen and R^{2c1} can be an optionally substituted aryl(C_{1-6} alkyl) or an optionally substituted heterocyclyl(C_{1-6} alkyl). In some embodiments of Formula (Ic), R^{2c} can be hydrogen and R^{2c1} can be an alkoxyalkyl, an aminoalkyl or a hydroxyalkyl. In other embodiments of Formula (Ic), R^{2c} can be hydrogen and R^{2c1} can be hydroxy. In still other embodiments of Formula (Ic), R^{2c} and R^{2c1} both can be an optionally substituted C_{1-4} alkyl.

[0109] In some embodiments of Formula (Ic), R^{3c} can be hydrogen, and R^{3c1} can be selected from amino, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{3-6} cycloalkyl (for example, cyclopropyl), an unsubstituted C_{1-4} alkoxy (such as OCH_3), hydroxy, halogen and an unsubstituted heteroaryl (for example, thiazole). In some embodiments, R^{3c} can be hydrogen, and R^{3c1} can be hydroxy. In other embodiments, R^{3c} and R^{3c1} can be both halogen. In still other embodiments, R^{3c} can be hydrogen, and R^{3c1} can be unsubstituted C_{1-4} alkyl. In yet still other embodiments of Formula (Ic), R^{3c} can be hydroxy, and R^{3c1} can be selected from amino, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an

unsubstituted C_{3-6} cycloalkyl (for example, cyclopropyl), an unsubstituted C_{1-4} alkoxy (such as OCH_3), hydroxy, halogen and an unsubstituted heteroaryl (for example, thiazole). In some embodiments of Formula (Ic), R^{3c} can be hydroxy, and R^{3c1} can be an unsubstituted C_{1-4} alkyl. In some embodiments of Formula (Ic), R^{3c} and R^{3c1} can together form $N=OR^c$, for example, N=OH or $N=OCH_3$. In some embodiments of Formula (Ic), R^{3c} and R^{3c1} can join together with the atom to which they are attached to form an optionally substituted 3 to 6 membered ring. In some embodiments, the 3 to 6 membered ring can be a C_{3-6} cycloalkyl. In other embodiments, the ring can be a 3 to 6 membered heterocyclyl, for example, an optionally substituted oxetane. In some embodiments, the carbon to which R^{3c} and R^{3c1} are attached can be a chiral center. When the carbon to which R^{3c} and R^{3c1} are attached a chiral center, in some embodiments, the carbon can have a (R)-configuration. In other embodiments, the carbon to which R^{3c} and R^{3c1} are attached can have a (S)-configuration.

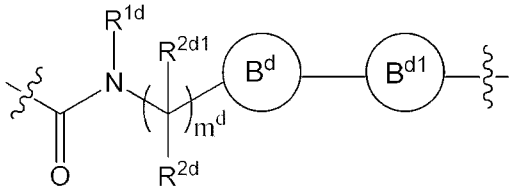
[0110] In some embodiments of Formula (Ic), Z^c can be N. In some embodiments of Formula (Ic), Z^c can be CH.

[0111] In some embodiments of Formula (Ic), R^{4c} and R^{5c} can be taken together to form an unsubstituted aryl (for example, phenyl). In other embodiments of Formula (Ic), R^{4c} and R^{5c} can be taken together to form an unsubstituted heteroaryl, such as piperdinyl. In still other embodiments of Formula (Ic), R^{4c} and R^{5c} can be taken together to form an optionally substituted heterocyclyl. In some embodiments, the optionally substituted heterocyclyl can be an optionally substituted tricyclic heterocyclyl, such as an optionally substituted, 

wherein * each indicate a point of attachment to the 6-membered ring.

Formula (Id)

[0112] In some embodiments, L can be Formula (Id):



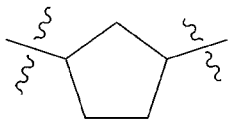
(Id).

[0113] In some embodiments of Formula (Id), R^{1d} can be hydrogen. In other embodiments of Formula (Id), R^{1d} can be an unsubstituted C_{1-4} alkyl.

[0114] In some embodiments of Formula (Id), both R^{2d} and R^{2d1} can be hydrogen. In other embodiments of Formula (Id), R^{2d} can be hydrogen and R^{2d1} can be an unsubstituted C_{1-4} alkyl. In still other embodiments of Formula (Id), R^{2d} can be hydrogen and R^{2d1} can be a substituted C_{1-4} alkyl. In yet still other embodiments of Formula (Id), R^{2d} can be hydrogen and R^{2d1} can be an optionally substituted aryl(C_{1-6} alkyl) or an optionally substituted heterocyclyl(C_{1-6} alkyl). In some embodiments of Formula (Id), R^{2d} can be hydrogen and R^{2d1} can be an alkoxyalkyl, an aminoalkyl or a hydroxyalkyl. In other embodiments of Formula (Id), R^{2d} can be hydrogen and R^{2d1} can be hydroxy. In still other embodiments of Formula (Id), R^{2d} and R^{2d1} both can be an optionally substituted C_{1-4} alkyl.

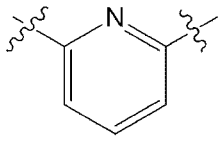
[0115] In some embodiments of Formula (Id), m^d can be 0. In other embodiments of Formula (Id), m^d can be 1.

[0116] In some embodiments of Formula (Id), ring B^d can be an optionally substituted C_5 cycloalkyl. In some embodiments, ring B^d can be an optionally substituted



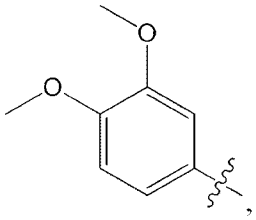
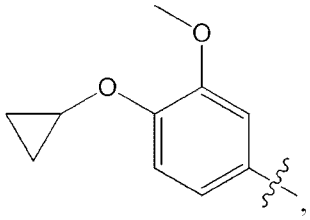
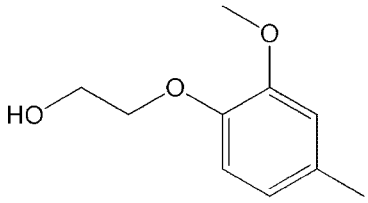
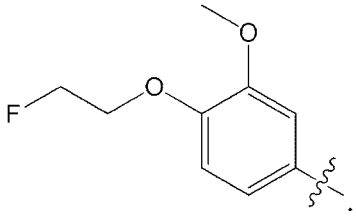
.

[0117] In some embodiments of Formula (Id), ring B^{d1} can be an optionally substituted pyridinyl having the structure



. The C_5 cycloalkyl and/or pyridinyl ring can be unsubstituted or substituted with one or more substituents. Suitable substituents include, but are not limited to, amino, mono-substituted amino, di-substituted amino, hydroxyalkyl, alkyl and alkoxy.

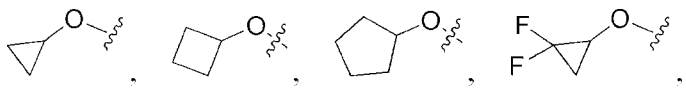
[0118] In some embodiments, A can be substituted. In other embodiments, A can be unsubstituted. When A is substituted, possible substituent(s) includes those provided in the list of "substituted" along with those described herein.

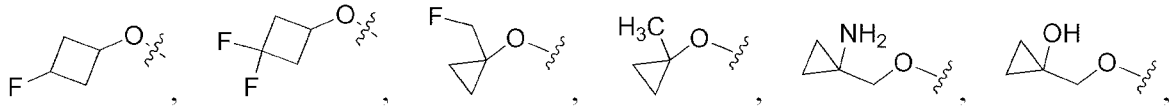
[0119] In some embodiments, A can be an optionally substituted aryl. For example, A can be an optionally substituted phenyl. In some embodiments, A can be a para-substituted phenyl, a meta-substituted phenyl or an ortho-substituted phenyl. In some embodiments, A can be a di-substituted phenyl. For example, A can be a 3,4-substituted phenyl, such as  ,  ,  , and  . 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.

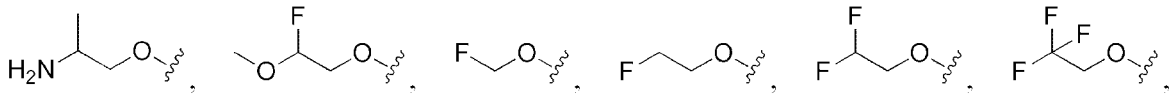
[0120] In some embodiments and without limitation, A can be a phenyl substituted with one or more substituents selected from an unsubstituted C_{1-4} alkyl, an optionally substituted C_{1-4} alkyl, cycloalkyl, hydroxy, an optionally substituted C_{1-4} alkoxy, C_{1-4} alkoxy, halogen, haloalkyl, an optionally substituted haloalkoxy, nitro, amino, mono-substituted amino, di-substituted amino, -O-amido, sulfenyl, alkyoxyalkyl, an optionally substituted aryl (for example, an optionally substituted phenyl), an optionally substituted monocyclic heteroaryl, an optionally substituted monocyclic heterocyclyl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted monocyclic heteroaryl(C_{1-4} alkyl), an optionally substituted monocyclic heterocyclyl(C_{1-4} alkyl), hydroxyalkyl 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, amino, mono-alkyl amine, di-alkyl amine and an amino acid. In some embodiments, the optionally substituted haloalkoxy can be further substituted, for example,

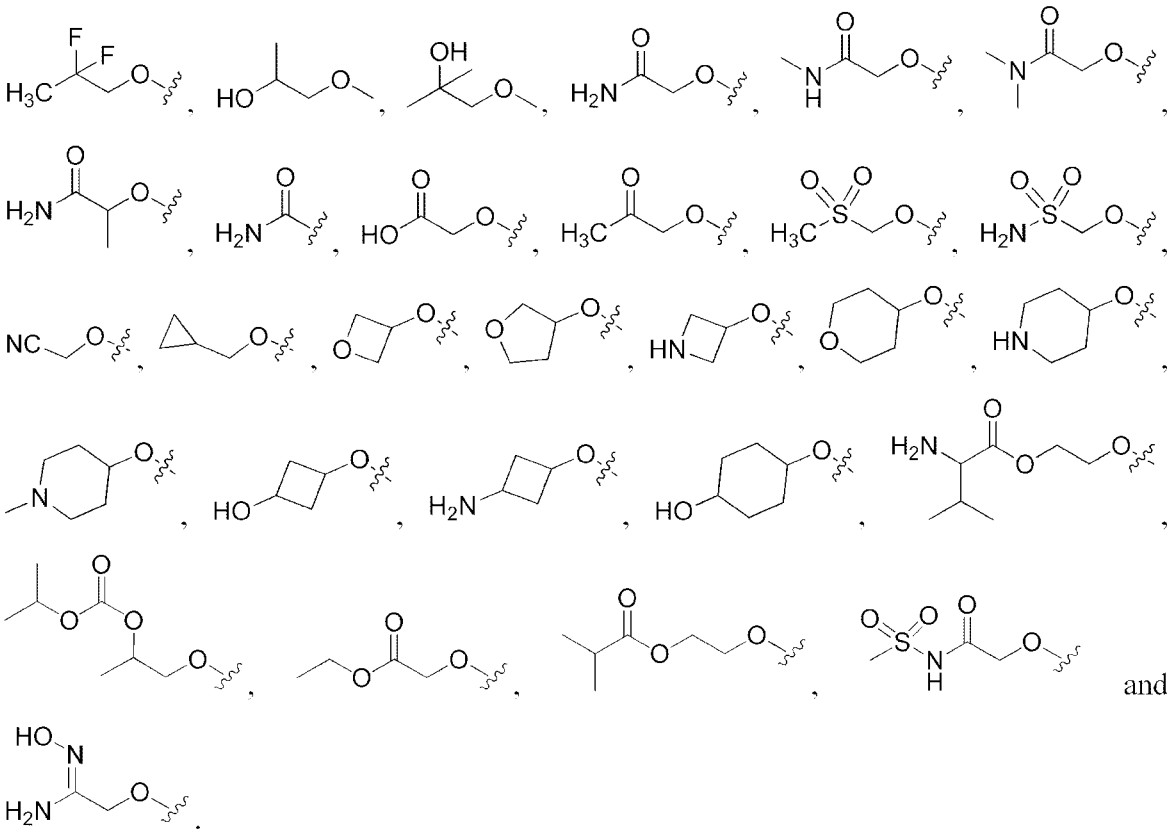
further substituted with an C_{1-4} alkoxy. In some embodiments, the optionally substituted heteroaryl can be further substituted, for example, further substituted with an C_{1-4} alkyl.

[0121] Examples of suitable substituents include, but are not limited to, methyl, ethyl, propyl (n-propyl and iso-propyl), butyl (n-butyl, iso-butyl and t-butyl), hydroxy, methoxy, ethoxy, propoxy (n-propoxy and iso-propoxy), butoxy (n-butoxy, iso-butoxy and 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 (for example, -NH-C(=O)C_{1-4} alkyl), alkylthio (such as CH_3CH_2S-), N-sulfonamido (for example, -NH-S(O)$_2C_{1-4}$ alkyl), 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,

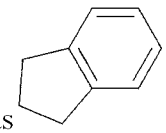








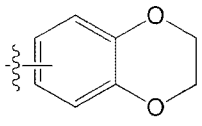
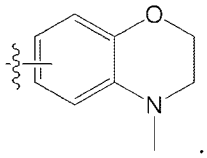
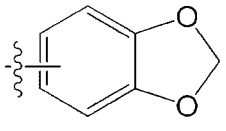
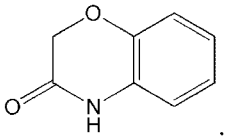
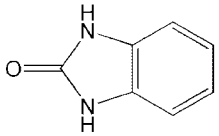
and

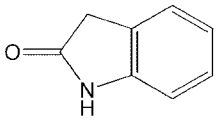
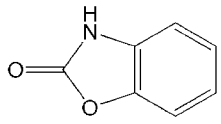
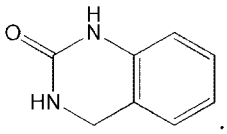
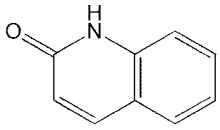
[0122] In some embodiments, A can be an optionally substituted cycloalkyl. Suitable examples of optionally substituted cycloalkyls include, but are not limited to, an optionally substituted cyclohexyl and an optionally substituted cycloheptyl. In other embodiments, A can be an optionally substituted cycloalkenyl, for example, an optionally substituted cyclohexenyl. In some embodiments, A can be an optionally substituted bi-cyclic cycloalkenyl, such as  .

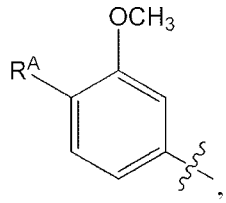
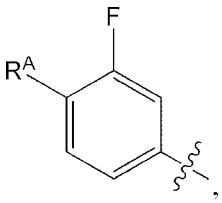
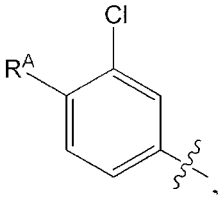
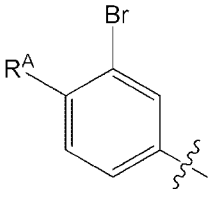
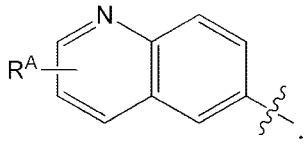
[0123] In some embodiments, A can be an optionally substituted aryl(C_{1-2} alkyl). In some embodiments, A can be an optionally substituted benzyl.

[0124] 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.

[0125] In some embodiments, the optionally substituted heteroaryl can be selected from an optionally substituted imidazole, 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 quinoline, an optionally substituted imidazole, an optionally substituted oxazole, an optionally substituted isoxazole, an optionally substituted benzoimidazole, an optionally substituted benzooxazole, 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 benzooxazole or an optionally substituted benzothiazole.

[0126] 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

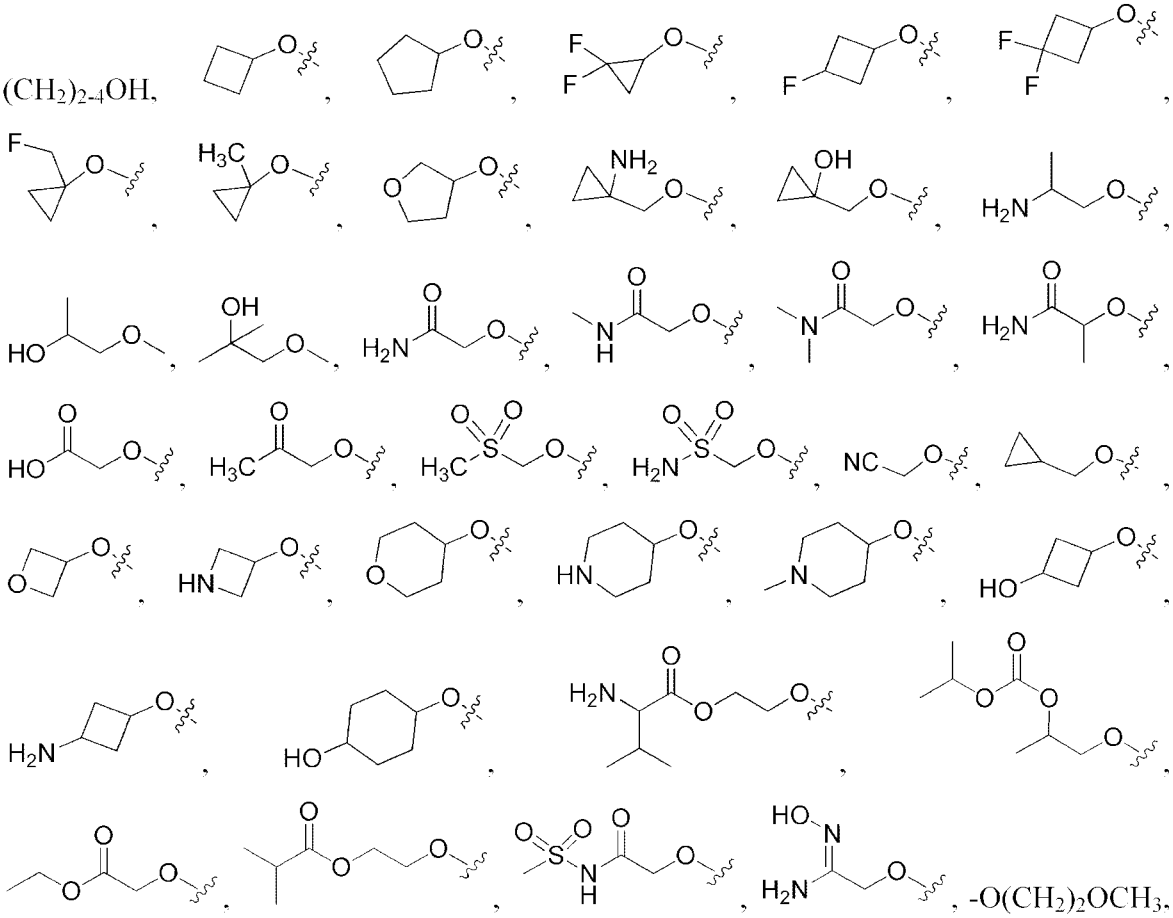
can be an optionally substituted  . In still other embodiments, A can be an optionally substituted  . In yet still other embodiments, A can be an optionally substituted  . In some embodiments, A can be an optionally substituted  .

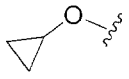
[0127] In some embodiments, A can be substituted with one or more R^A's. In some embodiments, one R^A can be present. In some embodiments, two R^A's can be present. In some embodiments, three R^A's can be present. In some embodiments, four or more R^A's can be present. When two or more R^A's are present, 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:  ,  ,  ,  or  .

[0128] 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, alkyoxyalkyl, aryl, monocyclic heteroaryl, monocyclic heterocyclyl and aminoalkyl. In some

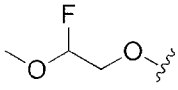
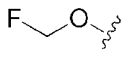
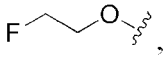
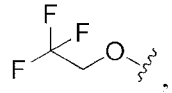
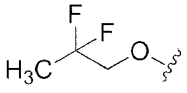
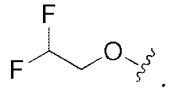
embodiments, the optionally substituted C_{1-4} alkoxy can be further substituted, for example, further substituted with a substituent selected from C_{1-4} alkyl, halo, hydroxy, C-carboxy, C-amido, N-amido, amino, mono-alkyl amine, di-alkyl amine and an amino acid. In some embodiments, the optionally 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.

[0129] 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).

[0130] 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, $-O(CH_2)_2-NH_2$, $-O(CH_2)_2-NH(CH_3)$, $-O(CH_2)_2-N(CH_3)_2$, $-O-(CH_2)_{2-4}OH$,  , $-O(CH_2)_2OCH_3$, 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 $-O(CH_2)_{0-2}$-

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(CH_2)$_{0-2}$-tetrazolone and/or  . In some embodiments, R^A can be substituted C_{1-6} alkoxy substituted by one or more of the following: halo, hydroxy, C_{1-4} 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.

[0131] In some embodiments, each R^A can be haloalkyl, for example, trifluoromethyl.

[0132] In some embodiments, each R^A can be an optionally substituted haloalkoxy, for example, difluoromethoxy, trifluoromethoxy,  ,  ,  ,  ,  and/or  .

[0133] In some embodiments, each R^A can be halogen, for example, chloro, bromo and/or fluoro.

[0134] 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 and/or amino.

[0135] In some embodiments, each R^A can be hydroxy.

[0136] In some embodiments, each R^A can be alkylthio, for example ethylthio.

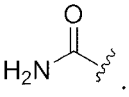
[0137] In some embodiments, each R^A can be aminoalkyl, such as -(CH_2)$_{1-2}$-NH(CH_3).

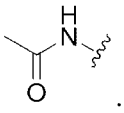
[0138] In some embodiments, each R^A can be alkoxyalkyl, for example, -CH_2-O-CH_3.

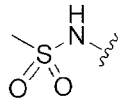
[0139] In some embodiments, each R^A can be an optionally substituted aryl(C_{1-4} alkyl). In some embodiments, each R^A can be an optionally substituted monocyclic heteroaryl(C_{1-4} alkyl). In some embodiments, each R^A can be an optionally substituted

monocyclic heterocyclyl(C_{1-4} alkyl). Non-limiting examples include an optionally substituted -$(CH_2)_{1-2}$-imidazole, an optionally substituted -$(CH_2)_{1-2}$-pyrrolidinone, an optionally substituted -$(CH_2)_{1-2}$-imidazolidinone.

[0140] In some embodiments, each R^A can be hydroxyalkyl, for example, -$(CH_2)_{1-4}$-OH.

[0141] In some embodiments, each R^A can be –O-amido, for example,  .

[0142] In some embodiments, each R^A can be –N-amido, for example,  .

[0143] In some embodiments, each R^A can be -N-sulfonamido, for example,  .

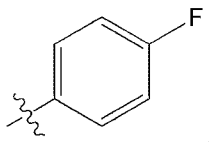
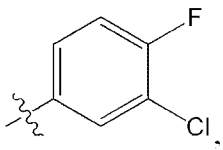
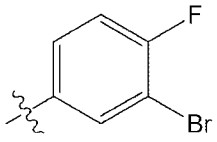
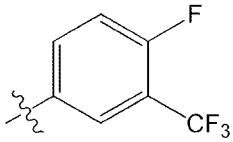
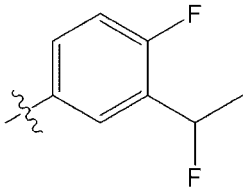
[0144] In some embodiments, each R^A can be aminoalkyl, for example, -CH_2-NH_2 and/or –CH_2-N(CH_3)H.

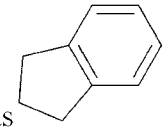
[0145] In some embodiments, each R^A can be an optionally substituted aryl, for example, an optionally substituted phenyl.

[0146] 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.

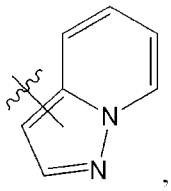
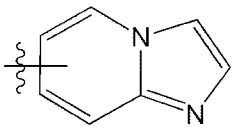
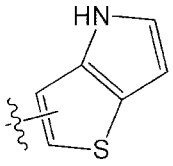
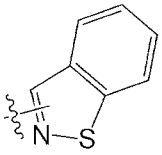
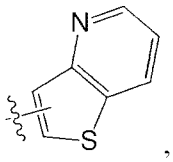
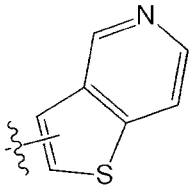
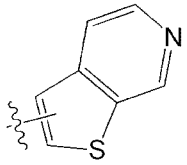
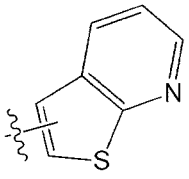
[0147] In some embodiments, each R^A can be an optionally substituted monocyclic heterocyclyl, for example, an optionally substituted pyrrolidinyl, an optionally substituted piperidinyl, an optionally substituted morpholinyl and/or an optionally substituted pyrrolidinone.

[0148] 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-

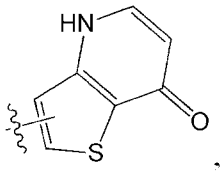
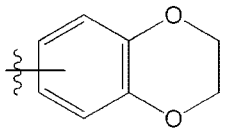
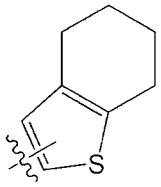
halo substituted phenyls include, but are not limited to,  ,  ,  and  . In some embodiments, Y can be di-substituted phenyl of the structure  . In some embodiments, Y can be a substituted phenyl that is substituted with 3 more substituents. In other embodiments, Y can be unsubstituted phenyl. In some embodiments, Y can be a substituted naphthyl. In other embodiments, Y can be an unsubstituted naphthyl.

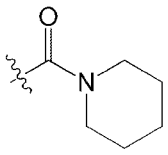
[0149] In some embodiments, Y can be an optionally substituted cycloalkyl (e.g., an optionally substituted cyclohexyl and an optionally substituted cycloheptyl). In other embodiments, Y can be an optionally substituted cycloalkenyl, for example, an optionally substituted cyclohexenyl. In some embodiments, Y can be an optionally substituted bi-cyclic cycloalkenyl, such as  .

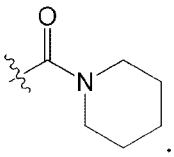
[0150] In some embodiments, Y can be an optionally substituted mono-cyclic heteroaryl. In some embodiments, Y can be selected from an optionally substituted imidazole, an optionally substituted furan, an optionally substituted thiophene, an optionally substituted pyrrole, an optionally substituted pyrimidine, 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.

[0151] 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 benzooxazole, 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  , an optionally substituted  , an optionally substituted  , an optionally substituted  , an optionally substituted  , an optionally substituted  and an optionally substituted  . In some embodiments, Y can 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.

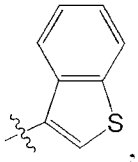
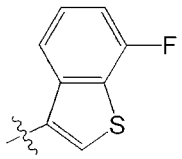
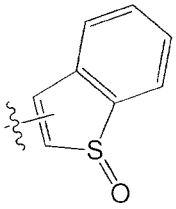
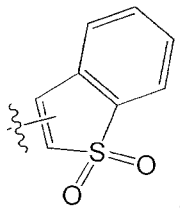
[0152] In some embodiments, Y can be an optionally substituted heterocyclyl. In some embodiments, Y can be an optionally substituted mono-cyclic heterocyclyl, such as an optionally substituted pyridinone. In other embodiment, Y can be an optionally substituted

bi-cyclic heterocyclyl. For example, Y can be an optionally substituted  , an optionally substituted  or an optionally substituted  .

[0153] 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 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  .

[0154] 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.

[0155] 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 optionally substituted  , an optionally substituted  and an optionally substituted  .

[0156] In some embodiments, Y can be an optionally substituted benzofuran.

[0157] 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), C_{1-4} alkyl and/or halo. In other embodiments, Y can be an unsubstituted indole.

[0158] In some embodiments, Y can be substituted with one or more halogen. In some embodiments, Y can be substituted with one or more unsubstituted C_{1-4} alkyl. In some embodiments, Y can be substituted with more 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.

[0159] In some embodiments, a compound of Formula (I) can be selected from the following compounds: 1, 13-1, 100, 101, 102, 103, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 116a, 116b, 117, 117a, 117b, 118, 118a, 118b, 119, 120, 120a, 120b, 121, 122, 122a, 122b, 123, 124, 125, 126, 127, 128, 129, 131, 132, 133, 134, 138, 139, 142, 143, 144, 145, 146, 147, 148, 151, 152, 153, 154, 155, 158, 159, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 218, 219, 221, 223, 224, 225, 226, 227, 228, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 306, 307, 308, 309, 310, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498a, 498b, 498c, 498d, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517,

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Pharmaceutical Compositions

[0160] 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.

[0161] 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.

[0162] 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.

[0163] 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.

[0164] 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.

[0165] 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.

[0166] 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.

[0167] 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.

[0168] 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.

[0169] 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.

[0170] 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

[0171] 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).

[0172] 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).

[0173] 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).

[0174] In some embodiments, the paramyxovirus infection is a human respiratory syncytial virus infection.

[0175] 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.

[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 treat and/or ameliorate 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 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 hendravirus 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 hendravirus polymerase complex and/or nipahvirus polymerase complex.

[0177] 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.

[0178] 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.

[0179] 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.

[0180] 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.

[0181] 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.

[0182] 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.

[0183] 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).

[0184] 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).

[0185] 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.

[0186] 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.

[0187] 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.

[0188] 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]-[0159].

[0189] 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.

[0190] 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).

[0191] 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 undesireable.

[0192] 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.

[0193] 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.

[0194] 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).

[0195] 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.

[0196] 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.

[0197] 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.

[0198] 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-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 (e.g., ALX-0171 (a trivalent nanobody, Ablynx) a peptide fusion inhibitor (such as a peptide having the sequence DEFDASISQVNEKINQSLAFIRKSDELL (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) AZ27
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') CUUGACUUUGCUAAGAGCCdTdT (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.

[0199] 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 2014/031784, published February 27, 2014, all of which are hereby incorporated by reference.

[0200] 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.

[0201] 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.

[0202] 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.

[0203] 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 [0198]-[0199] (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 [0198]-[0199] (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 [0198]-[0199] (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 [0198]-[0199] (including the table), including a pharmaceutically acceptable salt and prodrug thereof, can be less compared to the amount of the compound described in paragraphs [0198]-[0199] (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 [0198]-[0199] (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.

[0204] 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 [0198]-[0199] (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 [0198]-[0199] (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 [0198]-[0199] (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 [0198]-[0199] (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 [0198]-[0199] (including the table), including pharmaceutically acceptable salts and prodrugs thereof).

[0205] 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.

[0206] 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.

[0207] 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 ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0208] 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.

[0209] 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.

[0210] 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 administrated 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.

[0211] 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

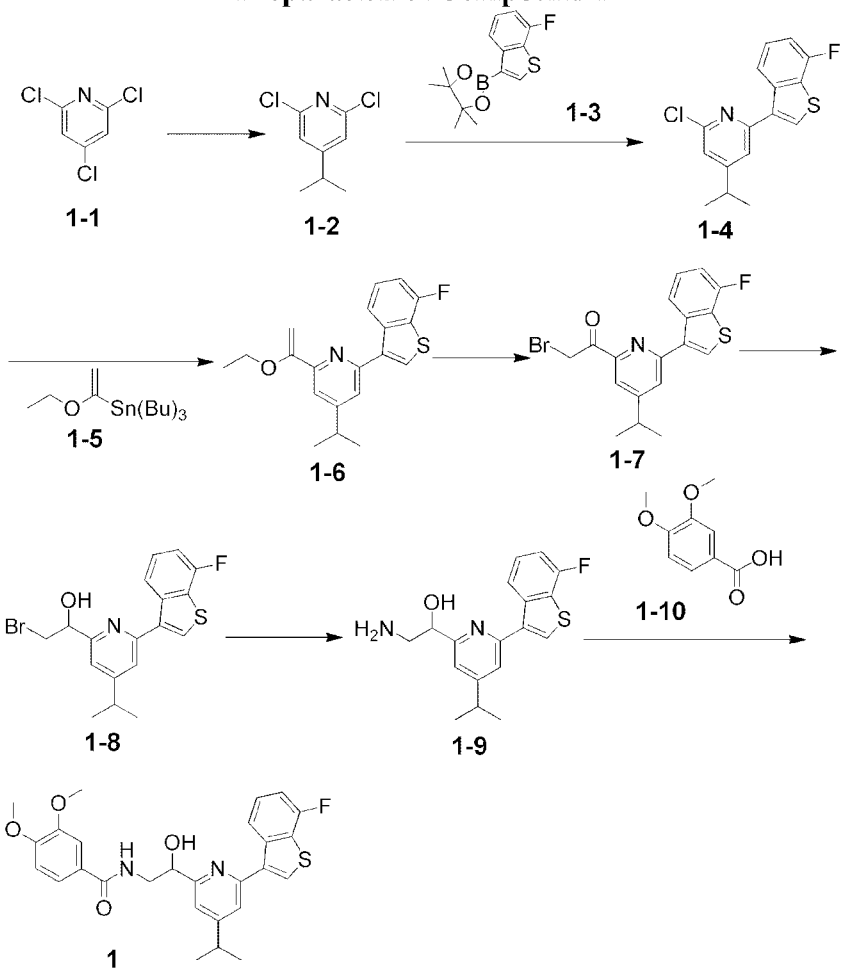
[0212] Compounds of Formula (I), and those described herein may be prepared in various ways. Some compounds of Formula (I) can be obtained commercially and/or prepared utilizing known synthetic procedures. General synthetic routes to the compounds of Formula (I), and some examples of starting materials 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

[0213] 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 1



[0214] To a mixture of **1-1** (3.65 g, 20 mmol) in NMP:THF (2 mL/20 mL), $Fe(acac)_3$ (622 mg, 2 mmol) was added. The solution was cooled to 0°C and i-PrMgCl (20 mL, 2N) was added slowly at 0°C. The solution was stirred for 2 h at 0°C. The solution was extracted with EA, and washed with brine. The organic phase was concentrated to give crude **1-2** as a colorless solid (2.4 g, 63.5%). +ESI-MS: m/z 190.1 $[M+H]^+$.

[0215] To a mixture of **1-2** (1 g, 5.29 mmol) and **1-3** (1.03 g, 5.29 mmol) in DMF (30 mL) were added $Pd(dppf)Cl_2$ (420 mg, 0.529 mmol) and a freshly prepared KF solution (2.57 g in 10 mL of water). The system was degassed and then charged with nitrogen 3 times. The mixture was stirred under nitrogen at 70°C using an oil bath for 8 h. The reaction solution was cooled to r.t., diluted with EA and separated from the water layer. The EA solution was washed with brine, dried over Na_2SO_4 and concentrated. The residue was

purified on a silica gel column to give **1-4** as a colorless solid (0.5 g, 31%). +ESI-MS: m/z 306.0 $[M+H]^+$.

[0216] To a mixture of **1-4** (900 mg, 2.95 mmol), **1-5** (1.07 g, 2.95 mmol) and KF (0.684 g, 11.8 mmol) in DMF (10 mL) was added $Pd(dppf)Cl_2$ (228 mg, 0.295 mmol). The system was degassed and then charged with nitrogen 3 times. The mixture was stirred under nitrogen at 70°C using an oil bath for 8 h. The reaction solution was cooled to r.t., diluted with EA and H_2O. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated to give crude **1-6** (1 g). +ESI-MS: m/z 342.1 $[M+H]^+$.

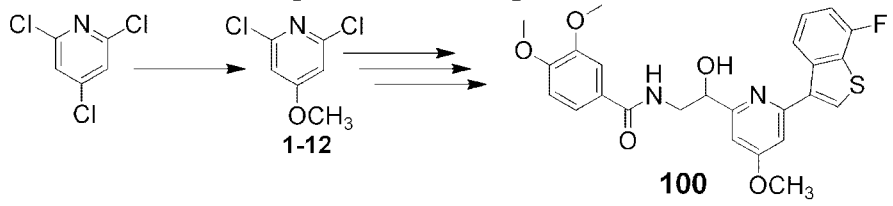
[0217] A mixture of **1-6** (1 g, 2.9 mmol) and NBS (516 mg, 2.9 mmol) in a mixture of THF (10 mL) and H_2O (1 mL) was stirred at r.t. for 30 mins. The solution was diluted with water and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with a sat. $Na_2S_2O_3$ solution, followed by brine. The solution was dried over Na_2SO_4 and evaporated to give crude **1-7** (1 g). +ESI-MS: m/z 392.0 $[M+H]^+$.

[0218] To a solution of **1-7** (1 g, 2.55 mmol) in a mixture of THF (5 mL) and MeOH (0.5 mL) was added $NaBH_4$ (193 mg, 5.1mmol) at 0°C. The mixture was stirred at 0°C for 30 mins with TLC monitoring. The reaction was quenched by the addition of H_2O and extracted with EA. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column to give **1-8** (200 mg, 20%). +ESI-MS: m/z 394.0 $[M+H]^+$.

[0219] A mixture of **1-8** (200 mg, 0.50 mmol) and sat. NH_4OH/EtOH (1 mL/5 mL) in a sealed tube was heated to 70°C for 6 h. The solution was removed under reduced pressure to give crude **1-9** (160 mg, 90.0%), which was used for next step directly without purification. +ESI-MS: m/z 331.1 $[M+H]^+$.

[0220] To a solution of **1-9** (65 mg, 0.363 mmol), HATU (172 mg, 0.45 mmol) and DIPEA (117 mg, 0.909 mmol) in anhydrous DMF (1 mL) was added **1-10** (100 mg 0.303 mmol) at 25°C. The solution was stirred for 10 h at r.t. The solution was diluted with 1.0 N aqueous $NaHCO_3$ solution (2 x 40 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified on a silica gel column to give **1** (100 mg, 67.1%). +ESI-MS: m/z 495.1 $[M+H]^+$.

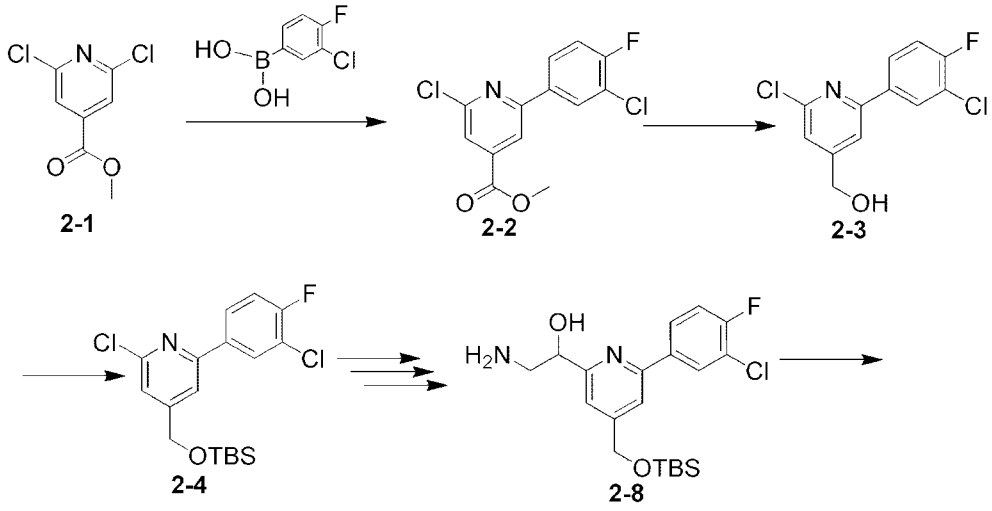
EXAMPLE 2
Preparation of Compound 100

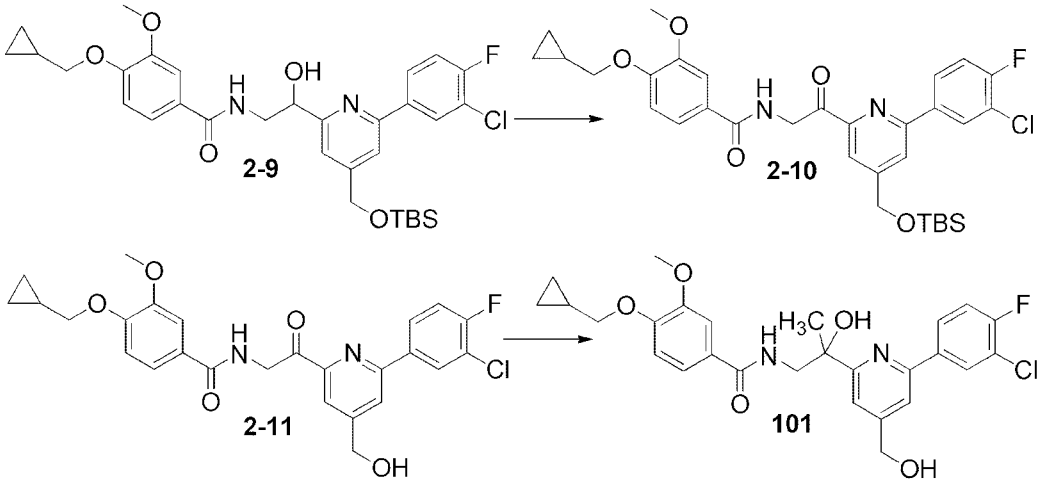


[0221] A solution of 2,4,6-trichloropyridine (6.5 g, 36 mmol) in anhydrous methanol (20 mL) was added MeONa (2.9 g, 54 mmol) at 0°C. The reacton mixture was stirred at r.t. for 12 h. The reaction was quenched with dry ice, and the mixture was filtered. The solution was concentrated under reduced pressure, and the residue was dissolved in EA. The mixture was washed with water, and the organic layers were dried over $NaSO_4$. The solvent was concentrated to give **1-12** (4.2 g, 67%).

[0222] Compound **100** was prepared using **1-12** and 4-(cyclopropylmethoxy)-3-methoxybenzoic acid, and by following a synthetic route, which closely follows that described for the preparation of **1**. **100**: +ESI-MS: m/z 483. 1 [M+H]+.

EXAMPLE 3
Preparation of Compound 101





[0223] To a solution of **2-1** (3 g, 14 mmol) and the boronic acid (2.5 g, 14 mmol) in dioxane/H_2O (30 mL/5 mL) was added $Pd(dppf)Cl_2$ (1.02 g,1.4 mmol) and Cs_2CO_3 (6.8 g, 21 mmol). The system was degassed and then charged with nitrogen for 3 times. The mixture was stirred under nitrogen at 80°C in an oil bath for 2 h. The solution was cooled to r.t., diluted with EA and separated from the water layer. The EA solution was washed by brine, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column to give **2-2** (2 g, 47.9%).

[0224] To a solution of **2-2** (2 g, 6.7 mmol) in MeOH/DCM (20 mL/20 mL) was added $NaBH_4$ (510 mg, 13.4 mmol) slowly at 0°C. The solution was stirred for 10 mins and heated to 50°C and stirred for 2 h. The solution was quenched with H_2O and extracted with EA. The solution was concentrated to give crude **2-3** (1.81 g, 100 %).

[0225] To a solution of **2-3** (1.81 g, 6.7 mmol) in DMF was added imidazole (1.36 g, 1.34 mmol) at r.t. TBSCl (201 mg, 1.34 mmol) was added. The solution was stirred for 18 h. The solution was washed with water and extracted with EA. The organic phase was concentrated to give **2-4** (1.8 g, 70.0%). ESI-LCMS: m/z 385.9 $[M+H]^+$.

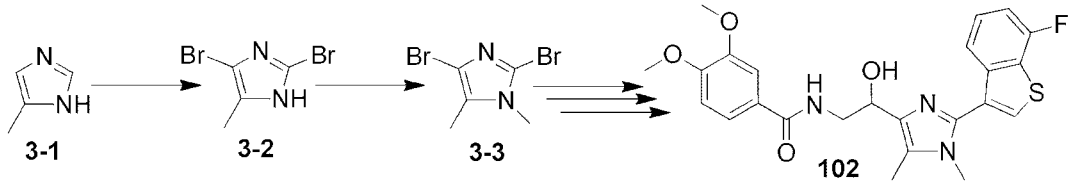
[0226] Compound **2-10** was prepared using **2-4** and 4-(cyclopropylmethoxy)-3-methoxybenzoic acid, and by following a synthetic route, which closely follows that described for the preparation of **1**. ^{1}H-NMR (400 MHz, $CDCl_3$), δ = 8.00 (d, *J*=5.51 Hz, 1 H) 7.87 (br. s., 1 H) 7.78 (s, 1 H) 7.81 (s, 1 H) 7.34 (s, 1 H) 7.26 (d, *J*=8.38 Hz, 1 H) 7.14 (t, *J*=8.71 Hz, 1 H) 6.92 (br, 1 H) 6.74 (d, *J*=8.38 Hz, 1 H) 5.13 (d, *J*=4.41 Hz, 2 H) 4.72 (s, 2

H) 3.71-3.85 (m, 5 H) 1.09 (br, 1 H), 0.83 (s, 10 H) 0.46-0.56 (m, 2 H), 0.19-0.30 (m, 2 H), 0.00 (s, 7 H).

[0227] To a solution of **2-10** (100 mg, 0.163 mmol) in dioxane (2 mL) was added concentrated HCl (2 mL) at r.t. and the mixture was stirred for 30 mins. The solution was quenched by aqueous $NaHCO_3$ solution and extracted by EA. The combined organic layers were washed by brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC(FA) to give **2-11** (30 mg, 37.0%) as a white solid. +ESI-MS: m/z 498.9 $[M+H]^+$.

[0228] The solution of **2-11** (100 mg, 0.20 mmol) in THF (2 mL) was added MeMgBr (1 mL, 3 mmol) at r.t. and the mixture was stirred for 2 h. The solution was quenched with H_2O and extracted with EA. The combined organic layers were washed by brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE:EA=1:1) to give **101** (20 mg, 19.4%) as a white solid. +ESI-MS: m/z 514.9 $[M+H]^+$.

EXAMPLE 4
Preparation of Compound 102

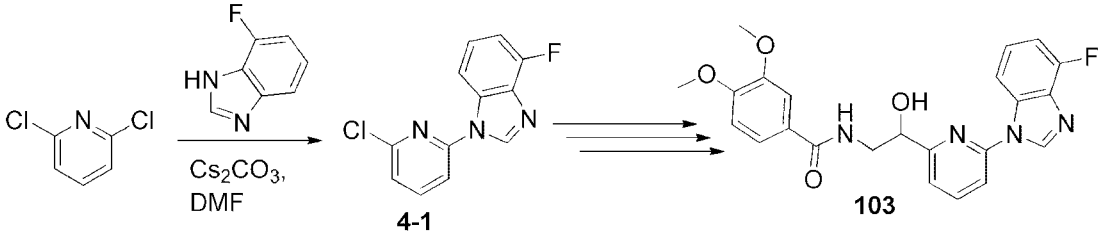


[0229] To a solution of **3-1** (3.4 g, 40 mmol) in THF (50 mL) at r.t. was added NBS (14 g, 80 mmol). The mixture was stirred for 1 h. The solvent were removed under reduced pressure. Purification by column chromatography on silica gel (PE:EA=2:1) provided **3-2** as white solid (9.6 g, 99%). +ESI-MS: m/z 239.0 [M+H]+

[0230] To a solution of **3-2** (9.6 g, 40 mmol) and K_2CO_3 (5.4 g, 40 mmol) in DMF (50 mL) at 40°C was added CH_3I (6 g, 40 mmol). The mixture was stirred for 2 h at r.t. The solution was poured into water and extracted with EtOAc. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA=20:1) to provide **3-3** (3 g, 30%). +ESI-MS: m/z 253.0 [M+H]+.

[0231] Compound **102** was obtained by closely following the procedure for obtaining **1** using **3-3** and 3,4-dimethoxybenzoic acid. Compound **102** was obtained as a white solid. +ESI-MS: m/z 470.1 $[M+H]^+$.

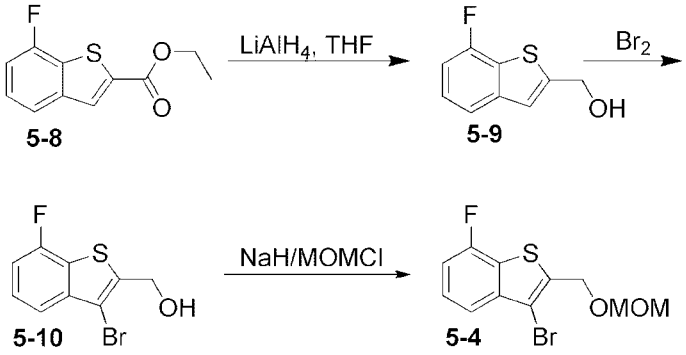
EXAMPLE 5
Preparation of Compound 103

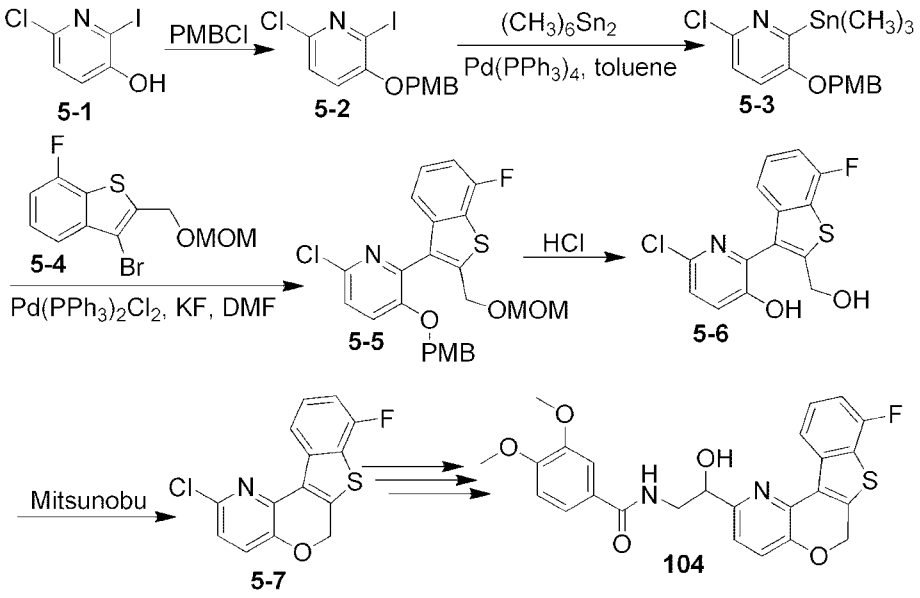


[0232] To a stirring mixture of 2,6-dichloropyridine (270 mg, 1.82 mmol) and 7-fluoro-1H-benzo[d]imidazole (248 mg, 1.82 mmol) in DMF (3 mL) was added Cs_2CO_3 (709 mg, 2. 2 mmol). The mixture was reacted at 120°C for 2 h and then cooled to r.t. The mixture was diluted with EtOAc and washed with a sat. NaCl solution. The layers were separated. The aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue afforded **4-1** (300 mg) as a white solid. LCMS: m/z 248.1 $[M+H]^+$.

[0233] Compound **103** was obtained as a yellow oil (100 mg) by closely following the procedure for obtaining **1** using **4-1** and 3,4-dimethoxybenzoic acid. LCMS: m/z 437.25 $[M+H]^+$.

EXAMPLE 6
Preparation of Compound 104





[0234] To a solution of **5-1** (10 g, 44.0 mmol) in DMF (150 mL) was added NaH (7.0 g, 0.177 mol), and the mixture was stirred at 0°C for 30 mins. The solution was treated with PMBCl (11.67 g, 0.0748 mol), and stirred at r.t. overnight. After complete conversion, the reaction was quenched with MeOH and H_2O, and extracted with EA. The organic phase was concentrated to give **5-2** (11 g, 87.2%). +ESI-MS: m/z 375.9 $[M+H]^+$.

[0235] To a solution of **5-2** (36 g, 96 mmol) in toluene (400 mL) was added $(CH_3)_6Sn_2$ (47.0 g, 144.0 mmol). The mixture was bubbled with nitrogen gas and stirred at 100°C for 3 h. The mixture was concentrated in vacuum to give the crude product, which was purified by column chromatography to give **5-3** (22 g). +ESI-MS: m/z 414.0 $[M+H]^+$.

[0236] To a solution of **5-8** (30 g, 134 mmol) in anhydrous THF (500 mL) was added $LiAlH_4$ (7.6 g, 200 mmol) in portions at 0°C, and the mixture was stirred at r.t. for 2 h (monitored by TLC). The reaction was quenched with a sat. NH_4Cl solution, and extracted with EA to give the crude product, which was purified by column chromatography to give **5-9** (22 g). +ESI-MS: m/z 183.0 $[M+H]^+$.

[0237] To a solution of **5-9** (22 g, 121 mmol) in THF (400 mL) was added NBS (25.7 g, 145 mmol), and the mixture was stirred at r.t. overnight (monitored by TLC). The reaction was quenched with a sat. $Na_2S_2O_3$ solution, and extracted with EA to give the crude product , which was purified by column chromatography to give **5-10** (23 g). +ESI-MS: m/z 460.9 $[M+H]^+$.

[0238] To a solution of **5-10** (22 g, 84.6 mmol) in anhydrous THF (200 mL) was added NaI (8.12 g, 33.85 mmol) in portions at 0^0C, and the mixture was stirred at 0^0C for 30 mins. MOMCl (27.08 g, 338.5 mmol) was added, and the mixture was stirred at r.t. for 4 h. The reaction was quenched with water and extracted with EA. The organic layer was dried over sodium sulfate, and concentrated in vacuum to give the crude product, which was purified by column chromatography to give **5-4** (21 g). +ESI-MS: m/z 304.9 $[M+H]^+$.

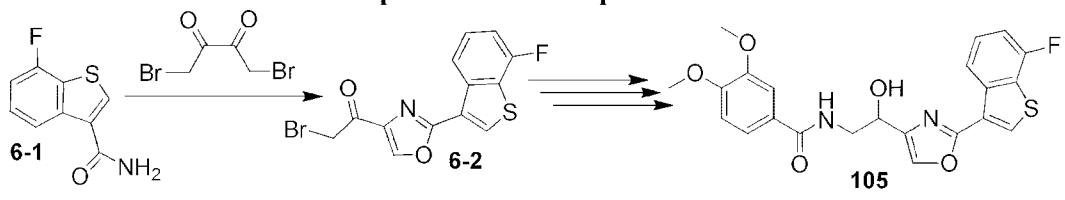
[0239] To a solution of **5-3** (6.36 g, 15.4 mmol) in DMF (50 mL) were added **5-4** (4.7 g, 15.4 mmol), KF (3.7 g, 61.6 mmol) and $Pd(PPh_3)_2Cl_2$ (324 mg, 0.46 mmol). The mixture was bubbled with nitrogen gas and stirred at 100^0C overnight. The mixture was diluted with water and extracted with EA. The organic layer was dried over sodium sulfate, and concentrated in vacuum to give the crude product, which was purified by column chromatography to give **5-5** (3.8 g). +ESI-MS: m/z 474.1 $[M+H]^+$.

[0240] To a solution of **5-5** (4.5 g, 9.51 mmol) in THF (30 mL) was added 10% HCl (30 mL), and stirred 110^0C overnight. The mixture was cooled to r.t., and the pH was adjusted to 7.0 by adding a sat. $NaHCO_3$ solution. The mixture was extracted with EA. The organic layer was dried over sodium sulfate, and concentrated in vacuum to give **5-6** (2.0 g), which was used in the next step without purification. +ESI-MS: m/z 310.0 $[M+H]^+$.

[0241] To a solution of **5-6** (1.3 g, 4.2 mmol) in THF (100 mL) was added PPh_3 (1.32 g, 5.05 mmol), and the mixture was stirred at r.t. for 10 mins. DIAD (1.01 g, 5.05 mmol) was added in portions, and the mixture stirred at refluxed for 4 h. The mixture was concentrated in vacuum to give the crude product, which was purified by column chromatography to give **5-7** (0.7 g). +ESI-MS: m/z 292.0 $[M+H]^+$.

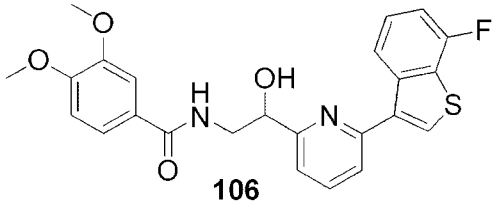
[0242] Compound **104** was obtained as a white solid (50 mg) by closely following the procedure for obtaining **1** by using **5-7** and 3,4-dimethoxybenzoic acid. +ESI-MS: m/z 481.1 $[M+H]^+$.

EXAMPLE 7
Preparation of Compound 105



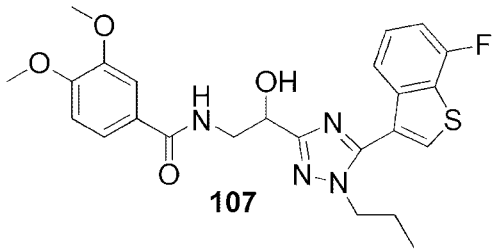
[0243] To a solution of **6-1** (196 mg, 1.0 mmol), 1,4-dibromobutane-2,3-dione (241mg, 1.0 mmol) in DCM (3 mL) was added AgOTf (255mg, 1.0 mmol). The reaction was carried out at 80°C under microwave irradiation for 15 mins. The mixture was concentrated at low pressure. The residue was purified by silica gel column (PE/EA) to **6-2** (270 mg, 80%). +ESI-MS: m/z 339. 9 $[M+H]^+$.

[0244] Compound **105** was obtained (100 mg, 48 %) by closely following the procedure for obtaining **1** using **6-2** and 3,4-dimethoxybenzoic acid. +ESI-MS: m/z 442. 9 $[M+H]^+$.



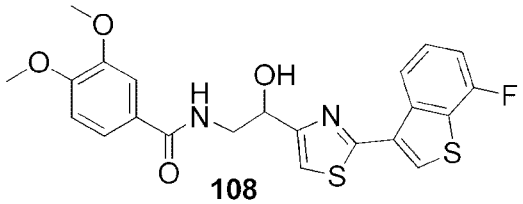
106

[0245] Compound **106** was prepared using 2,6-dibromopyridine, 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 3,4-dimethoxybenzoic acid, and by closely following a synthetic route, which closely follows that described for the preparation of **1**. +ESI-MS: m/z 452.9 $[M+H]^+$.



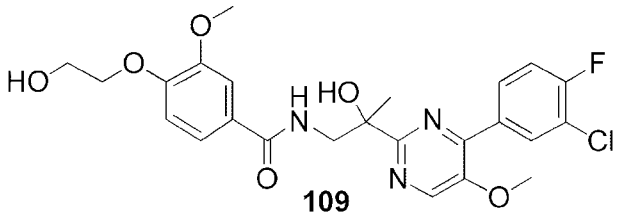
107

[0246] Compound **107** was prepared using 3,4-dimethoxybenzoic acid and 3-bromo-5-(7-fluorobenzo[b]thiophen-3-yl)-1-propyl-1H-1,2,4-triazole, and by closely following a synthetic route, which closely follows that described for the preparation of **1**. +ESI-MS: m/z 485.0 $[M+H]^+$.



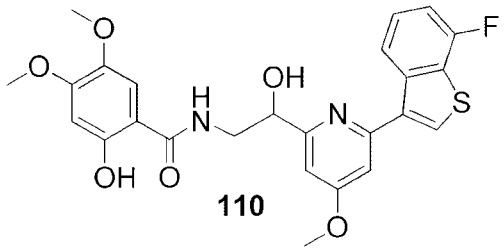
108

[0247] Compound **108** was prepared using 2,4-dibromothiazole, 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 3,4-dimethoxybenzoic acid, and by closely following a synthetic route, which closely follows that described for the preparation of **1**. +ESI-LCMS: m/z 459.0 [M+H]+.



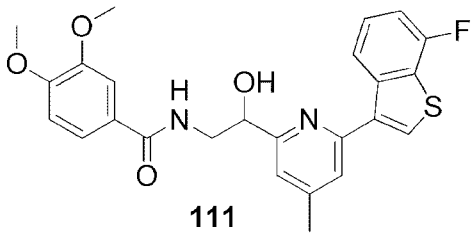
109

[0248] Compound **109** was prepared using 2,4-dichloro-5-methoxypyrimidine, (3-chloro-4-fluorophenyl) boronic acid and 4-(2-hydroxyethoxy)-3-methoxybenzoic acid, and by closely following a synthetic route, which closely follows that described for preparation of **1**. +ESI-MS:m/z 506.1 $[M+H]^+$.



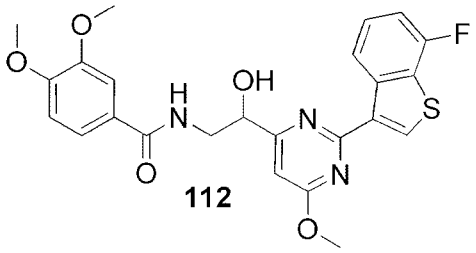
110

[0249] Compound **110** was prepared using 2-hydroxy-4,5-dimethoxybenzoic acid and 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)-4-methoxypyridin-2-yl) ethanol, and by following a synthetic route, which closely follows that described for preparation of **1**. Compound **110** was obtained as a white solid. +ESI-MS:m/z 498.9$[M+H]^+$.



111

[0250] Compound **111** was obtained by closely following the procedure for obtaining **1** by using 2,4-dibromothiazole, 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 3,4-dimethoxybenzoic acid. Compound **111** was obtained as a white solid. +ESI-LCMS: m/z 466.9 $[M+H]^+$.

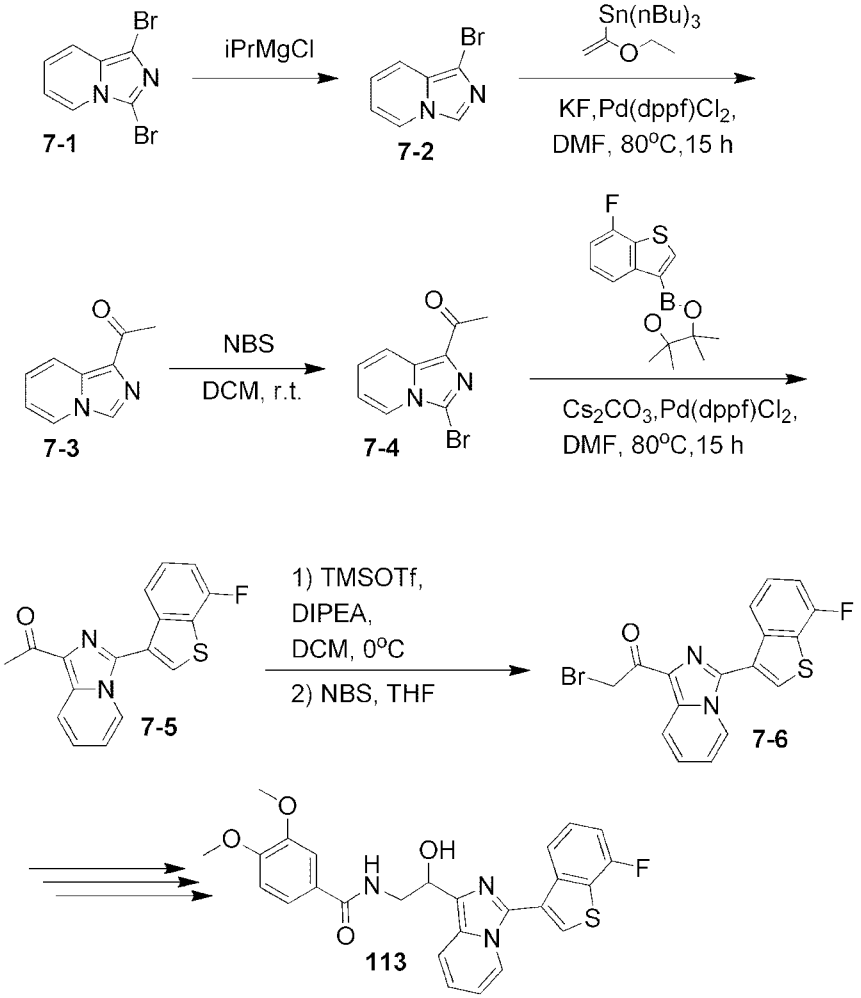


112

[0251] Compound **112** was prepared using 4-chloro-2-iodo-6-methoxypyrimidine, 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 3,4-dimethoxybenzoic acid, and by following a synthetic route, which closely follows that described for preparation of **1**. +ESI-MS: m/z 484.1 $[M+H]^+$.

EXAMPLE 8

Preparation of Compound 113



7-1 7-2 7-3 7-4 7-5 7-6

113

[0252] To a solution of **7-1** (7.5 g, 27.17 mmol) in THF (100 mL) was added slowly i-PrMgCl (25 mL, 2M in THF) at r.t., and the mixture stirred for 10 mins. The

solution was quenched with MeOH and diluted with DCM (20 mL). The solution was washed by brine, dried over Na_2SO_4 and concentrated to give crude **7-2** (5 g, 94.3 %).

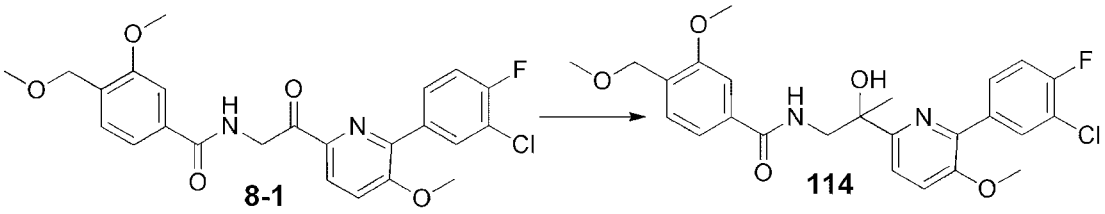
[0253] To a solution of **7-2** (1 g, 5.1 mmol), the tin reagent (3.71 g, 10.2 mmol) and KF (1.18 g, 20.4 mmol) in DMF (10 mL) was added Pd(dppf)Cl_2 (372 mg, 0.51mmol). The system was degassed and then charged with nitrogen for 3 times. The mixture was stirred under nitrogen at 80°C in an oil bath for 15 h. The solution was cooled to r.t. The mixture was diluted with EA. The EA solution was washed by brine, dried over Na_2SO_4 and concentrated to give crude **7-3** (360 mg, 44.2%)

[0254] To a solution of **7-3** (360 mg, 2.25 mmol) in DCM (5 mL) was added NBS (480 mg, 2.7 mmol). The mixture was stirred at r.t. for 30 mins with TLC monitoring. The solution was quenched by aqueous $Na_2S_2O_3$ solution and extracted by EA. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC(FA) to give **7-4** (250 mg, 46.2%) .

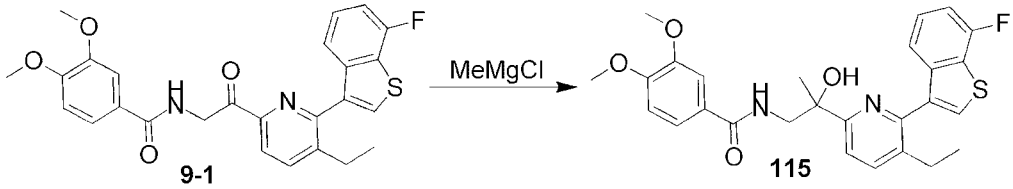
[0255] To a solution of **7-4** (480 mg, 2 mmol) and the dioxaborolane reagent (558 mg, 2 mmol) in dioxane/H_2O (10 mL/2 mL) were added Pd(dppf)Cl_2 (146 mg, 0.2 mmol) and Cs_2CO_3 (975 mg, 3 mmol). The system was degassed and then charged with nitrogen for 3 times. The mixture was stirred under nitrogen at 80°C in an oil bath for 15 h. The solution was cooled to r.t., diluted with EA and separated from the water layer. The EA solution was washed by brine, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column to give **7-5** (400 mg, 64.5%).

[0256] To a solution of **7-5** (550 mg, 1.77 mmol) in DCM (5 mL) was added DIPEA (685 mg, 5.31 mmol) and TMSOTf (589 mg, 2.65 mmol) at 0°C. The solution was stirred for 2 h at r.t. The solution was concentrated and the residue was dissolved in THF (10 mL) and H_2O (1 mL). NBS (471 mg, 2.65 mmol) was added at r.t., and stirred for 1.5 h. The solution was evaporated at low pressure. The residue was purified by chromatography (PE:EA=3:1) to give **7-6** (600 mg, 86.9%).

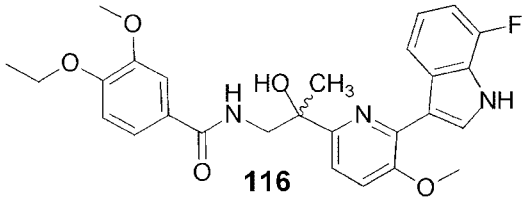
[0257] Compound **113** was prepared from **7-6** and 3,4-dimethoxybenzoic acid by following a synthetic route, which closely follows that described for the preparation of **1**. Compound **113** was obtained as white solids. +ESI-MS: m/z 492.0 $[M+H]^+$.



[0258] To a solution of **8-1** (90 mg, 0.19 mmol) in THF (5 mL) was added CH_3MgBr (3 M, 0.64 M) at 0°C, and stirred at r.t. overnight. The reaction was quenched with NH_4Cl solution and extracted with EA. The organic layer was dried over sodium sulfate, then concentrated in vacuum to give the crude product , which was purified by prep-HPLC to give **114** (18 mg) as a white solid. +ESI-MS: m/z 498.1 $[M+H]^+$.

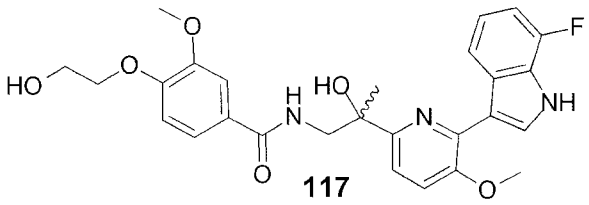


[0259] Compound **115** (57 mg, 60%) was obtained by closely following the procedure for obtaining **114** by using **9-1** (120 mg, 0.2 mmol). Compound **115** was obtained as a white solid. +ESI-MS:m/z 494.9 $[M+H]^+$.



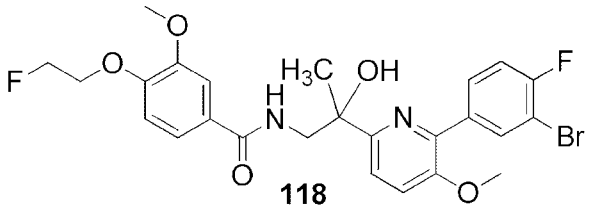
[0260] Compound **116** was obtained by closely following the procedures for obtaining **100** and **114** using 7-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole and 4-ethoxy-3-methoxybenzoic acid. Compound **116** was obtained as a white solid. +ESI-MS: m/z 494.2 $[M+H]^+$.

[0261] Individual enantiomers of **116** (**116a** and **116b**) were obtained by SFC separation of a racemic mixture of **116**. +ESI-MS: m/z 494.2 $[M+H]^+$.



[0262] Compound **117** was obtained by closely following the procedures for obtaining **100** and **114** using 7-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole and 4-(2-hydroxyethoxy)-3-methoxybenzoic acid. Compound **117** was obtained as a white solid. +ESI-MS: m/z 510.2 $[M+H]^+$.

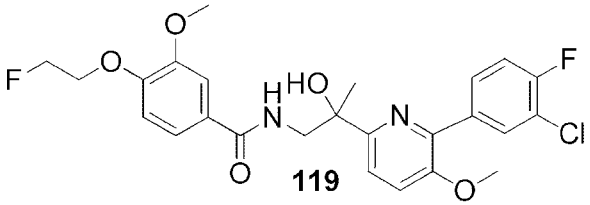
[0263] Individual enantiomers of **117** (**117a** and **117b**) were obtained by SFC separation of a racemic mixture of **117**. +ESI-MS: m/z 510.1 $[M+H]^+$.



118

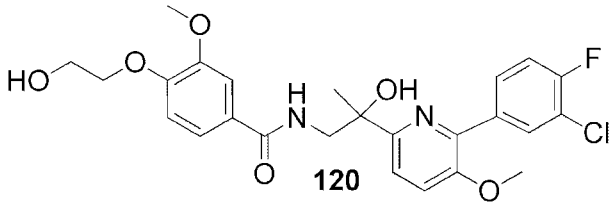
[0264] Compound **118** was prepared using 1-amino-2-(6-(3-bromo-4-fluorophenyl)-5-methoxypyridin-2-yl)propan-2-ol and 4-(2-fluoroethoxy)-3-methoxybenzoic acid and 4-(2-fluoroethoxy)-3-methoxybenzoic acid, and by following a synthetic route, which closely follows that described for preparation of **100** and **114**. +ESI-MS: m/z 551.9 $[M+H]^+$.

[0265] Individual enantiomers of **118** (**118a** and **118b**) were obtained by SFC separation of a racemic mixture of **118.** +ESI-MS: m/z 551.9 $[M+H]^+$.



119

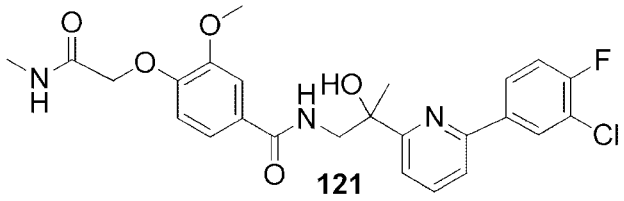
[0266] To a stirring mixture of N-(2-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl)-2-oxoethyl)-4-(2-fluoroethoxy)-3-methoxybenzamide (50 mg, 0.1 mmol) in THF at r.t. under argon was added a solution of MeMgCl in THF (0.5 mL, 1.0 mmol). The mixture was reacted at r.t. for 2 h. The mixture was diluted with EtOAc and slowly quenched with a sat. NH_4Cl solution. The mixture was stirred at r.t. for 10 mins and then the layers were separated. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude mixture was purified via silica gel column and further purified via prep-HPLC to afford **119** as a white solid. LCMS: m/z 507.1 $[M+H]^+$.



120

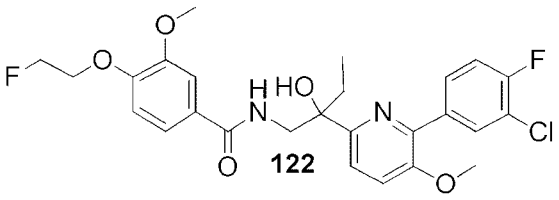
[0267] Compound **120** was prepared using N-(2-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl)-2-oxoethyl)-4-(2-hydroxyethoxy)-3-methoxybenzamide with MeMgBr in THF, and by closely following a synthetic route, which closely follows that described for preparation of **119**. LCMS: m/z 505.15 $[M+H]^+$.

[0268] Individual enantiomers of **120**(**120a** and **120b**) were obtained by SFC separation of a racemic mixture of **120**. +ESI-MS: :m/z 505.1 $[M+H]^+$.

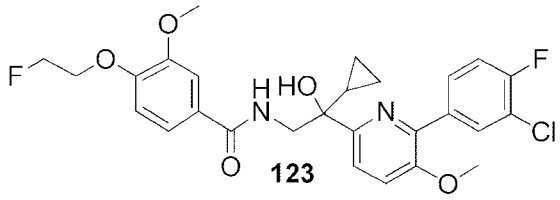


121

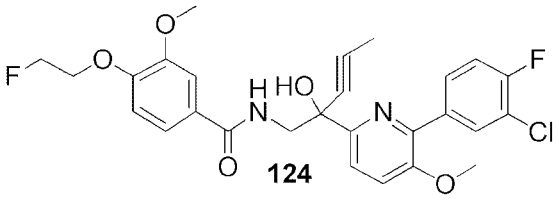
[0269] Compound **121** was prepared using N-(2-(6-(3-chloro-4-fluorophenyl)pyridin-2-yl)-2-oxoethyl)-3-methoxy-4-(2-(methylamino)-2-oxoethoxy)benzamide with MeMgBr in THF, and by following a synthetic route, which closely follows that described for preparation of **119**. LCMS: m/z 502.05 $[M+H]^+$.



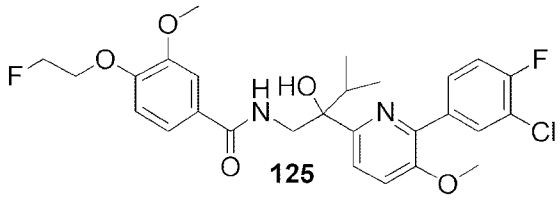
122



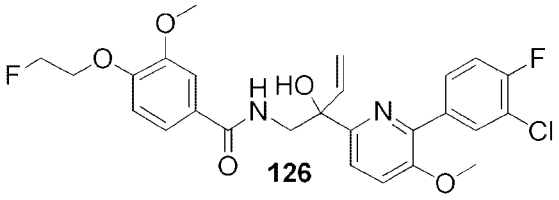
123



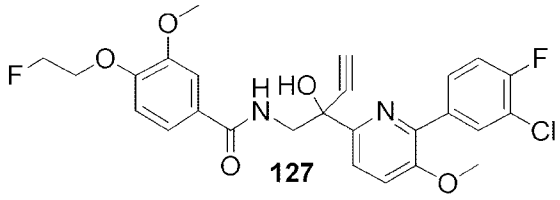
124



125



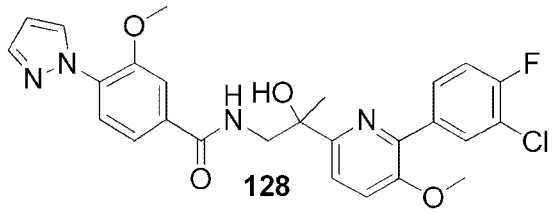
126



127

[0270] Compounds **122**, **123**, **124**, **125**, **126** and **127** were prepared using N-(2-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl)-2-oxoethyl)-4-(2-fluoroethoxy)-3-methoxybenzamide with different Grignard reagents in THF, and by following a synthetic route, which closely follows that described for preparation of **119**. **122**: LCMS: m/z 521.15 $[M+H]^+$. **123**: LCMS: m/z 533.15 $[M+H]^+$. **124**: LCMS: m/z 531.10 $[M+H]^+$. **125**: LCMS: m/z 535.15 $[M+H]^+$. **126**: LCMS: m/z 519.15 $[M+H]^+$. **127**: LCMS: m/z 517.05 $[M+H]^+$.

[0271] Individual enantiomers of **122** (**122a** and **122b**) were obtained by SFC separation of a racemic mixture of **122**.

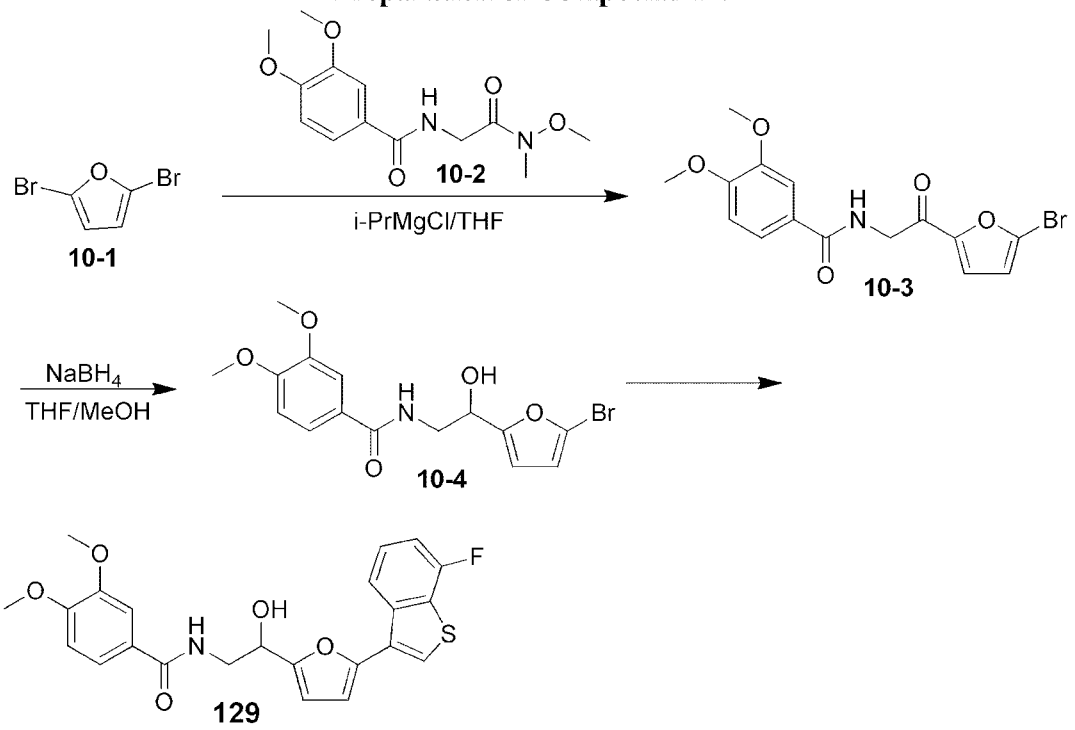


128

[0272] Compound **128** was prepared using N-(2-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl)-2-oxoethyl)-3-methoxy-4-(1H-pyrazol-1-yl)benzamide with MeMgBr in THF, and by following a synthetic route, which closely follows that described for preparation of **119**. LCMS: m/z 511.10 $[M+H]^+$.

EXAMPLE 9

Preparation of Compound 129

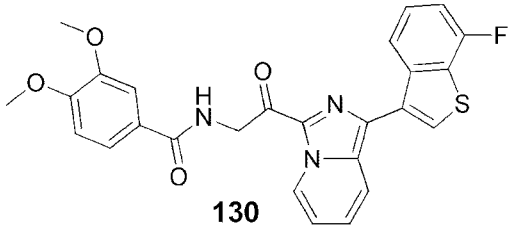


[0273] A 50 mL flask with a magnetic stirring bar was charged with **10-1** (223 mg, 1.0 mmol), Weinreb amide (**10-2**, 282 mg, 1.0 mmol), and THF (10 mL) under N_2 atmosphere. The solution was treated with i-PrMgCl (1.3 M, 2.0 eq.) dropwise at r.t. The mixture was stirred for 1 h at r.t. Water (50 mL) and EA (50 mL) were added. The organic layer was separated and the aqueous phase extracted with EA. The combined organic layers were dried with $MgSO_4$ and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (PE) to provide **10-3** as a solid (332 mg, 90%). +ESI-MS: m/z 367.0, 369.0 $[M+H]^+$.

[0274] To a stirred solution of **10-3** (368 mg, 1.0 mmol) in MeOH/THF (5 mL/5 mL) was added $NaBH_4$ (380 mg, 10 mmol) in portions until the starting materials was consumed. The volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (PE: EtOAc=2:1) to give **10-4** as a colorless oil (370 mg, 100%). +ESI-MS: m/z 369.0, 371.0 $[M+H]^+$.

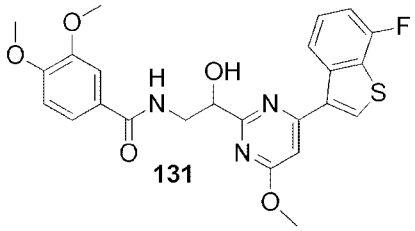
[0275] A 50 mL flask with a magnetic stirring bar was charged with **10-4** (165 mg, 0.5 mmol), 2-(7-fluorobenzo[b]thiophen-3-yl)-dioxaborolane (278 mg, 1.0 mmol),

$Pd(dppf)Cl_2$ (8 mg, 1 mol%), KF (180 mg, 3.0 mmol), and dioxane/H_2O(20 mL/5 mL) under N_2 atmosphere. The mixture was stirred for 10 h at 100°C. Water (50 mL) and EA (50 mL) were added. The organic layer was separated and the aqueous phase extracted with EA. The combined organic phases were dried with $MgSO_4$ and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel to provide **129** as a white solid (176 mg, 80%). +ESI-MS: m/z 463.9 $[M+Na]^+$.



130

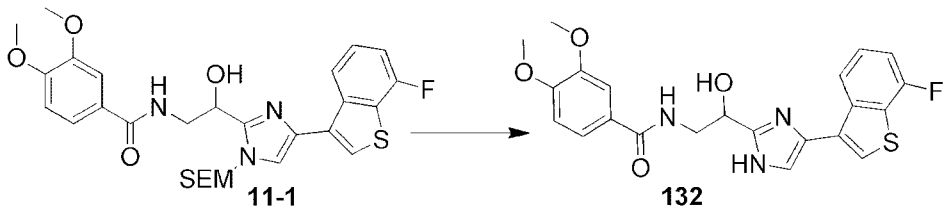
[0276] Compound **130** was obtained following the procedure for obtaining **129** by using **10-2**, 1,3-dibromoimidazo[1,5-a]pyridine and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting materials, and then the oxidizing reagent DMP. Compound **130** was obtained as a white solid. +ESI-MS: m/z 489.8 $[M+H]^+$.



131

[0277] Compound **131** (176 mg, 80%) was obtained following the procedure for obtaining **129** by using **10-2**, 4-chloro-2-iodo-6-methoxypyrimidine and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. +ESI-MS: m/z 483.9 $[M+H]^+$.

EXAMPLE 10
Preparation of Compound 132

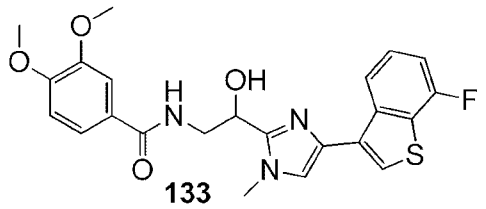


11-1 **132**

[0278] Compound **11-1** was prepared using **10-2**, 2,4,5-tribromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and 3,4-dimethoxy-N-(2-

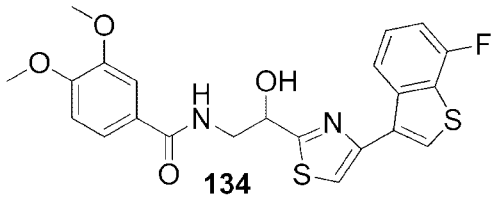
(methoxy(methyl)amino)-2-oxoethyl)benzamide, and by following a synthetic route, which closely follows that described for preparation of **129**.

[0279] Compound **11-1** (402 mg, 0.62 mmol) was dissolved in TFA/DCM (1/1, 6 mL), and stirred at r.t. for 3 h. The solvent was removed and the residue was purified by column (DCM /MeOH= 50:1 to 20:1) on silica gel to give **132** (149 mg, 72.4%). +ESI-MS:m/z 442.1$[M+H]^+$.



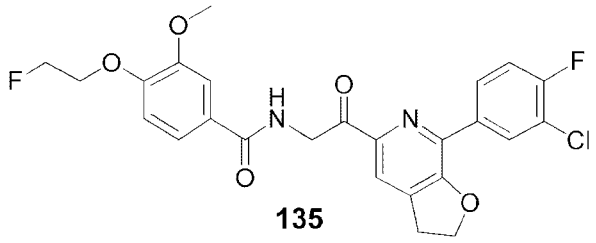
133

[0280] Compound **133** was prepared using 2,4,5-tribromo-1-methyl-1H-imidazole and 3,4-dimethoxy-N-(2-(methoxy(methyl)amino)-2-oxoethyl)benzamide, and by following a synthetic route, which closely follows that described for preparation of **129**. +ESI-MS:m/z 455.9$[M+H]^+$.



134

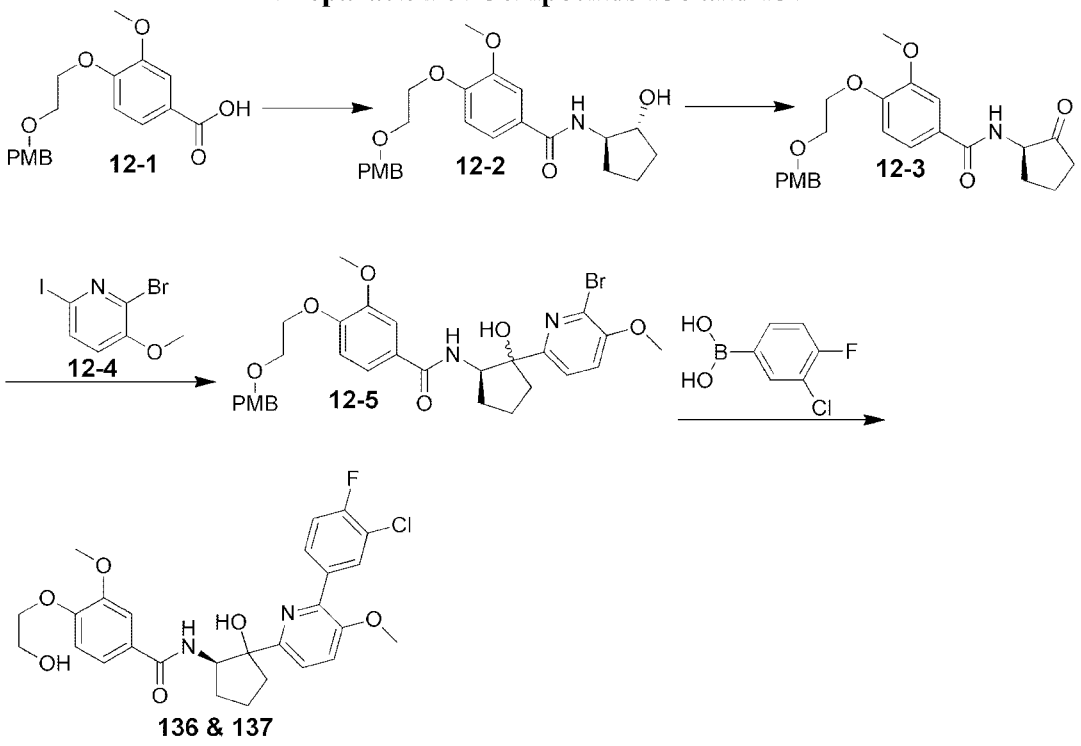
[0281] Compound **134** was prepared using 2,4-dibromothiazole and 3,4-dimethoxy-N-(2-(methoxy(methyl)amino)-2-oxoethyl)benzamide, and by following a synthetic route, which closely follows that described for preparation of **129**. +ESI-MS: m/z 459.0 $[M+H]^+$.



135

[0282] +ESI-MS: m/z 502.9 $[M+H]^+$.

EXAMPLE 11
Preparation of Compounds 136 and 137



[0283] A mixture of **12-1** (3.26 g, 9.80 mmol), (1R,2R)-2-aminocyclopentan-1-ol hydrochloride (1.04 g, 7.55 mmol), EDC (2.17 g, 11.3 mmol), HOBT (1.53 g, 11.3 mmol) and TEA (2.60 mL, 18.9 mmol) in DCM (50 mL) was stirred at r.t. for 18 h. The mixture was washed twice with 1M aq. HCl solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded **12-2** as a white solid (2.98 g, 95%). UPLC/MS(ES^+): m/z 416.29 $[M+H]^+$.

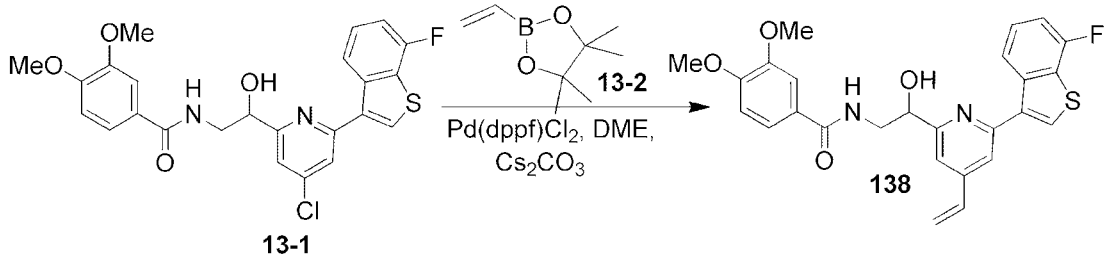
[0284] Dess-Martin periodinane (4.55 g, 10.7 mmol) was added to a solution of **12-2** (2.98 g, 7.16 mmol) in DCM (50 mL). The mixture was stirred at r.t. for 1.5 h. A 1:1 mixture of 10% aq. $Na_2S_2O_3$ solution and sat. aq. $NaHCO_3$ solution was added, and the mixture was stirred for 40 mins. The layers were separated and the organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded **12-3** as a white solid (2.86 g, 96%). UPLC/MS(ES^+): m/z 413.18 $[M+H]^+$.

[0285] *n*-Butyllithium (1.6M solution in hexane, 1.50 mL, 2.42 mmol) was added dropwise to a stirred solution of **12-4** (760 mg, 2.42 mmol) in toluene (15 mL), which had

been pre-cooled to –78°C. After 20 mins, a solution of **12-3** (500 mg, 1.21 mmol) in THF (10 mL) was added. The mixture was stirred at –78°C for 30 mins. The mixture was allowed to warm to r.t. and then quenched with MeOH. The volatiles were removed under reduced pressure. The residue was partitioned between EtOAc and water. The layers were separated and the organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromathography (water:CH_3CN 100:0 to 95:5) to afford **12-5** as a 2:1 diastereomeric mixture (470 mg, 65%). UPLC/MS(ES^+): m/z 601.22 $[M+H]^+$.

[0286] A mixture of (3-chloro-4-fluorophenyl)boronic acid (50.5 mg, 0.290 mmol), **12-5** (70 mg, 0.116 mmol), Pd(dppf)Cl_2 (4.3 mg, 0.006 mmol) and aq. Na_2CO3 (2M solution, 174 uL, 0.348 mmol) in DCE (2 mL) was degassed and heated to 85°C. After 1 h, water was added and the aqueous phase was extracted with DCM. The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in a 10:1 DCM-TFA solution (3 mL) and the mixture was stirred at r.t. for 30 mins. A 1M aq. NaOH solution was added and the mixture was stirred for further 30 mins. The phases were separated and the organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (DCM-MeOH, 98:2) afforded compounds **136** and **137**. **136**: UPLC/MS(ES^+): m/z 531.26 $[M+H]^+$. **137**: UPLC/MS(ES^+): m/z 531.26 $[M+H]^+$.

EXAMPLE 12
Preparation of Compound 138

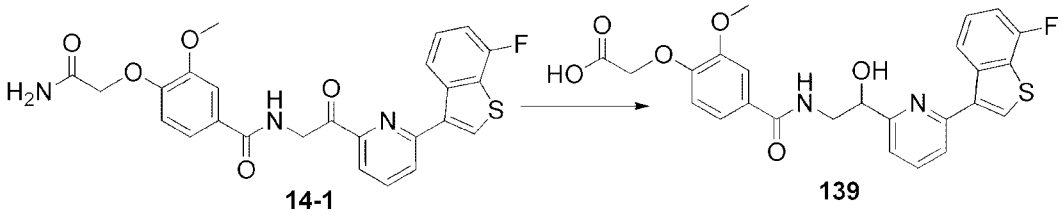


[0287] Compound **13-1** was obtained following the procedure for obtaining **1** by using 2,4,6-trichloropyridine, 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 3,4-dimethoxybenzoic acid.

[0288] To a solution of **13-1** (972 mg, 2 mmol) in DME (15 mL) was added **13-2** (616 mg, 4 mmol), Pd(dppf)Cl_2(146 mg, 0.2 mmol) and Cs_2CO_3(1.3 g, 4 mmol). The

mixture was stirred for 16 h at 120°C under N_2. The reaction solution was filtered and to give a clear solution. The solution was extracted with EtOAc (80 mL) and washed with brine (3 x 20 mL). Compound **138** was purification by silica column chromatography using EA:PE =1:1 as the elute (900 mg, 94%). ESI-MS: m/z 478.9 $[M+H]^+$.

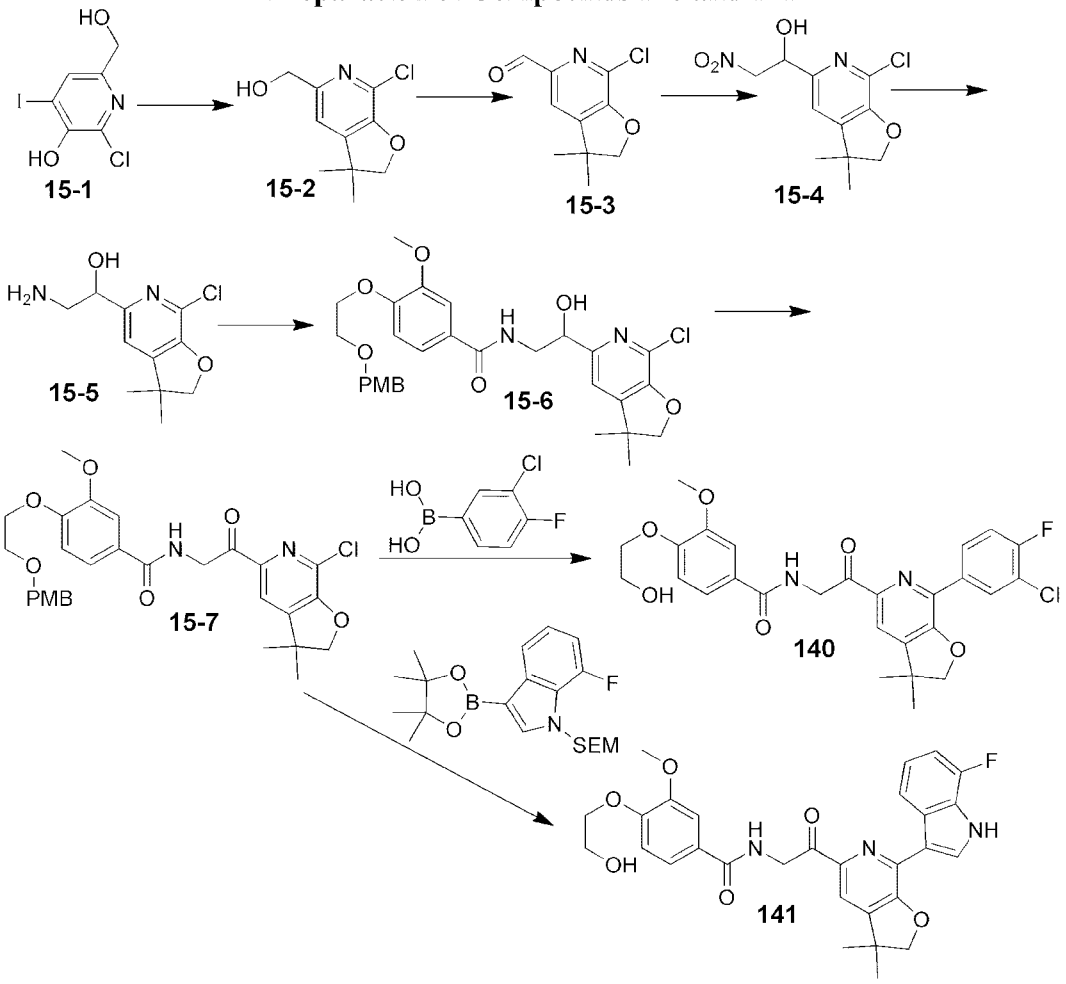
EXAMPLE 13
Preparation of Compound 139



[0289] To a solution of **14-1** (495 mg, 1.0 mmol) in MeOH (10 mL) was added aqueous NaOH (10 mL, 1M). The mixture was stirred for 4 h at 60°C. The solution was cooled to r.t., acidified to pH=3 using 1N HCl solution and extracted with EtOAc. The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to provide **139** (490 mg, 99 %). +ESI-MS: m/z 497.1 $[M+H]^+$.

EXAMPLE 14

Preparation of Compounds 140 and 141



[0290] Compound **15-2** was prepared starting from 2-chloro-6-(hydroxymethyl)-4-iodopyridin-3-ol (**15-1**) according to procedures provided in PCT Publication No. WO 2004/039366, published May 13, 2004, which is hereby incorporated by reference for the limited purpose of its disclosure of the preparation of **15-2**.

[0291] Dess-Martin periodinane (2.00 g, 4.21 mmol) was added to a stirred solution of **15-2** (835 mg) in dry DCM (5 mL). The mixture was stirred at r.t. for 40 mins. and quenched with a 1:1 mixture of 2M aq. $Na_2S_2O_3$ solution-sat. aq. $NaHCO_3$ sol (10 mL). After 30 mins., the layers were separated. The organic portion was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 60:40) afforded **15-3** as a white solid (250 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.44 (s, 6 H), 4.53 (s, 2 H), 7.79 (s, 1 H), 9.92 (s, 1 H).

[0292] Nitromethane (191 uL, 3.54 mmol) and K_2CO_3 (32.5 mg, 0.236 mmol) were added to a solution of **15-3** (250 mg, 1.18 mmol) in dry THF (5 mL). The mixture was stirred at r.t. for 30 h and EtOAc was added. The organic portion was washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford crude **15-4** (343 mg), which was used in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.36 -1.49 (m, 6 H), 4.45 (s, 2 H), 4.68 (dd, *J*=13.6, 8.5 Hz, 1 H), 4.85 (dd, *J*=13.4, 3.4 Hz, 1 H), 5.43 (dd, *J*=8.5, 3.3 Hz, 1 H), 7.26 (s, 1 H).

[0293] $NaBH_4$ (21.0 mg, 0.550 mmol) was added to a solution of $NiCl_2$-$6H_2O$ (43.0 mg, 0.183 mmol) in MeOH (3 mL). After 30 mins, **15-4** (100 mg, 0.367 mmol) dissolved in MeOH (2 mL) was added, followed by additional solid $NaBH_4$ (28.0 mg, 0.730 mmol). The reaction was monitored by UPLC. When complete, the mixture was filtered through a pad of celite and the organic portion was concentrated under reduced pressure. The residue was eluted through a SCX-cartridge using MeOH and 2M NH_3-MeOH solution to afford **15-5**. UPLC/MS(ES$^+$): m/z 243.10 $[M+H]^+$.

[0294] A mixture of **15-5**, 3-methoxy-4-{2-[(4-methoxyphenyl)methoxy]ethoxy}benzoic acid (146 mg, 0.440 mmol), EDC (106 mg, 0.550 mmol), HOBT (74 mg, 0.550 mmol) and TEA (101 uL, 0.730 mmol) in DCM (4 mL) was stirred at r.t. for 18 h. The mixture was washed twice with 1M aq. HCl solution. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 80:20 to 0:100) afforded **15-6** as a pale yellow wax (90 mg, 44% over two steps). UPLC/MS(ES$^+$): m/z 557.30 $[M+H]^+$.

[0295] Dess-Martin periodinane (172 mg, 0.404 mmol) was added to a solution of **15-6** (90 mg, 0.162 mmol) in DCM (4 mL). The mixture was stirred at r.t. for 1 h. A 1:1 sat. aq. $NaHCO_3$ solution-sat. aq. $Na_2S_2O_3$ solution was added. The mixture was stirred at r.t. for 30 mins and the layers were separated. The organic portion was washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 50:50 to 10:90) afforded **15-7** as a pale yellow wax (70 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.45 (s, 6 H), 3.83 (s, 3 H), 3.86 -3.92 (m, 2 H), 3.96 (s, 3 H), 4.27 (t, *J*=5.0 Hz, 2 H), 4.52 (s, 2 H), 4.60 (s, 2 H), 5.11 (d, *J*=4.5 Hz, 2 H), 6.91 (d,

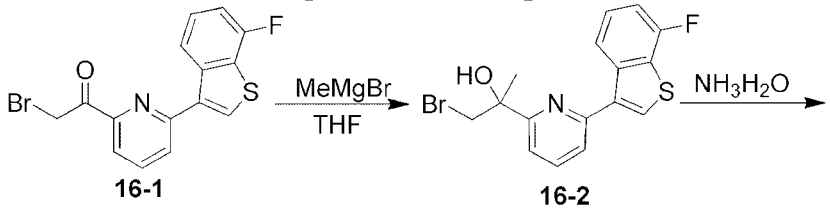
J=8.5 Hz, 2 H), 6.95 (d, *J*=8.5 Hz, 1 H), 7.02 (s, 1 H), 7.32 (d, *J*=8.5 Hz, 2 H), 7.41 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.51 (d, *J*=1.8 Hz, 1 H), 7.90 (s, 1 H).

[0296] A mixture of **15-7** (90.0 mg, 0.126 mmol), (3-chloro-4-fluorophenyl)boronic acid (55.0 mg, 0.316 mmol), $Pd(dppf)Cl_2$ (6.0 mg, 0.008 mmol) and aq. Na_2CO_3 (2M solution, 190 uL, 0.378 mmol) in DCE (3 mL) was degassed and heated to 85°C. After 20 h, the volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 80:20 to 0:100) afforded the PMB-ether (51 mg). The PMB-ether was dissolved in DCM (1.5 mL) and treated with TFA (200 uL). The mixture was stirred at r.t. for 30 mins and quenched with 2M aq. NaOH solution. The layers were separated and the aqueous portion was extracted with DCM. The combined organic portions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 80:20 to 0:100) afforded **140** as a white solid (20 mg, 30% over two steps). ^1H NMR (400 MHz, $CDCl_3$) δ ppm UPLC/MS(ES^+): m/z 529.15 $[M+H]^+$.

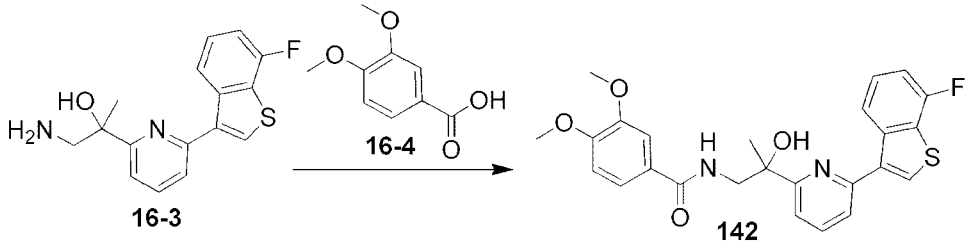
[0297] Coupling of **15-7** with 7-fluoro-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]-methyl}-1H-indole followed removal of all protecting groups (TFA-DCM) afforded **141** as an off-white solid (9% over two steps). UPLC/MS(ES^+): m/z 534.33 $[M+H]^+$.

EXAMPLE 15

Preparation of Compound 142



16-1 16-2



16-3 142

[0298] MeMgBr (0.7 mL, 2 mmol) was added dropwise to a stirred solution of **16-1** (700 mg, 0.3 mmol) in THF (5 mL) at -78°C. After 1 h, the mixture was allowed to warm to r.t. (approx. 2 h). The reaction was quenched with 1N HCl and extracted with

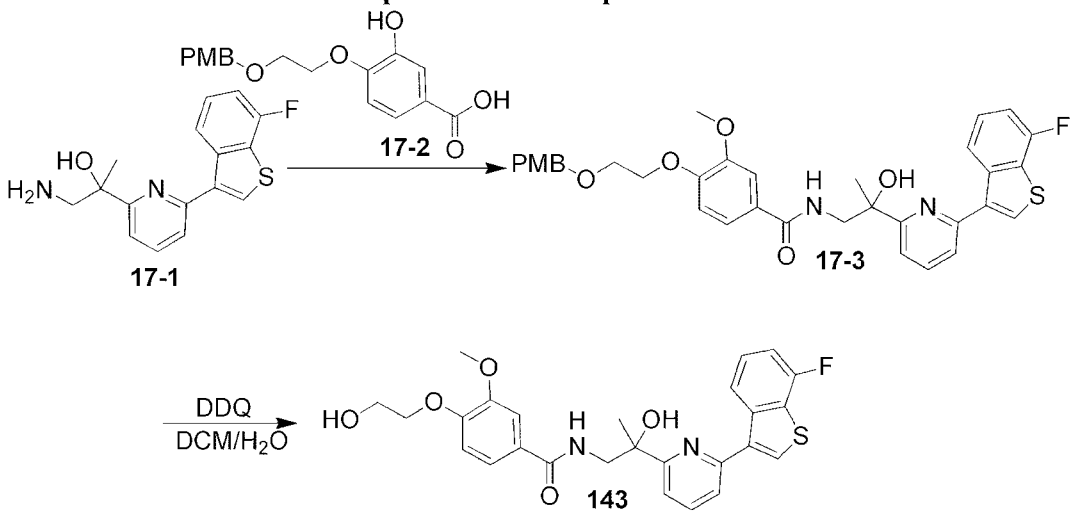
EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column on silica gel (PE:EA=10:1) to give **16-2** (350 mg, 41%).

[0299] A solution of **16-2** (350 mg, 0.96 mmol) in ammonia (6 mL) and EtOH (3 mL) was stirred at 90°C for 10 h. The solvent was removed and the crude product was used in next step without purification.

[0300] To a solution of **16-4** (73 mg, 0.4 mmol) in DIPEA (0.2 mL) and DMF (1 mL) was added HATU (152 mg, 0.4 mmol), and stirred at 40°C for 30 mins. Compound **16-3** (100 mg, 0.33 mmol) was added. The mixture was stirred at 40°C for 10 h. The mixture was diluted with water and extracted with EtOAc. The organic layers was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by prep-HPLC to give **142** (60 mg, 39%). +ESI-MS:m/z 488.9 $[M+Na]^+$.

EXAMPLE 16

Preparation of Compound 143

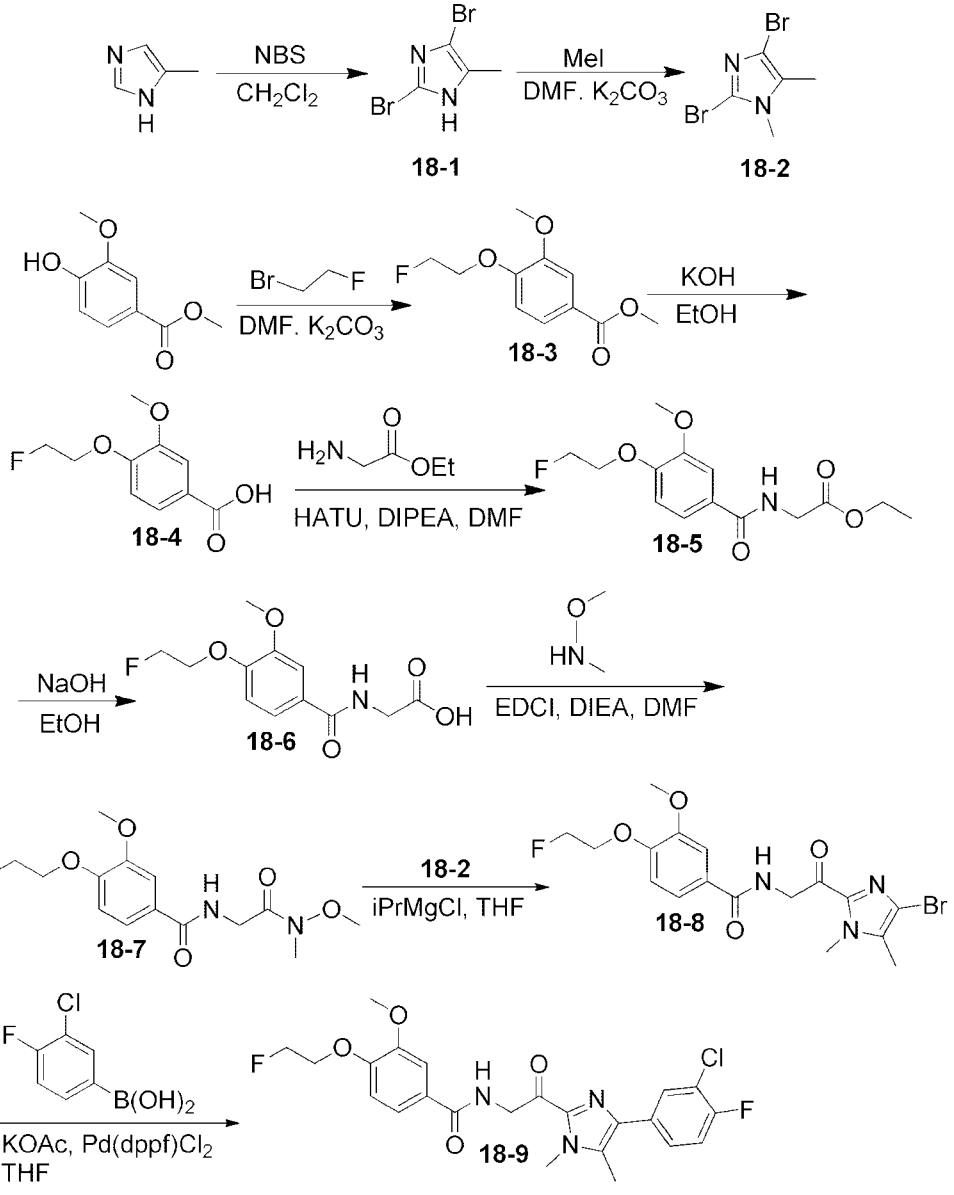


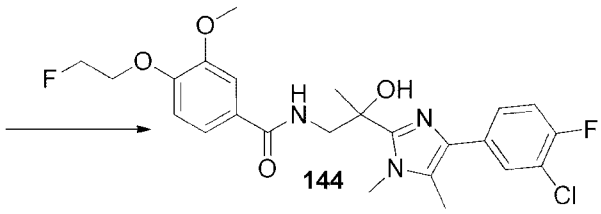
[0301] To a solution of **17-2** (132 mg, 0.4 mmol) in DIPEA (0.2 mL) and DMF (1 mL) was added HATU (152 mg, 0.4 mmol), and the mixture stirred at 40°C for 30 mins. Compound **17-1** (100 mg, 0.33 mmol) was added. The mixture was stirred at 40°C for 10 h. The mixture was diluted with water and extracted with EtOAc. The organic layers was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column on silica gel (PE:EA=1:1) to give **17-3** (60 mg, 32%).

[0302] To a solution of **17-3** (60 mg, 0.1 mmol) in DCM (2 mL) and H_2O (0.2 mL) was added DDQ (45 mg, 0.2 mmol). The mixture was stirred for 2 h. at r.t. The mixture was dissolved in DCM (30 mL). The solution was washed with sat. $NaHCO_3$, dried over Na2SO4, and concentrated. The residue was purified by prep-HPLC to give **143** (30 mg, 60%). +ESI-MS:m/z 496.9 $[M+H]^+$.

EXAMPLE 17

Preparation of Compound 144





[0303] To a solution of 4(5)-methylimidazole (2 g, 24 mmol) in CH_2Cl_2 (150 mL) was added bromine (2.5 mL, 48 mmol) at 0°C. The solution was stirred for 1 H at r.t. The product was filtered and partitioned between EA and sat. $NaHCO_3$. The product was precipitated from MeOH/CH_2Cl_2 to provide **18-1** (4.31 g, 75 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.06 (s, 3H).

[0304] To a solution of **18-1** (3.6 g, 15 mmol) and K_2CO_3 (4.1 g, 30 mmol) in DMF (18 mL) was added iodomethane (1.4 mL, 23 mmol) at 25°C. The solution was stirred for 15 h. The mixture was poured into water and extracted with EA The combined organic phase was dried over anhydrous Na_2SO_4, and the residue was purified by chromatography on silica gel (EA/hexane) to give **18-2** (1.6 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.52 (s, 3H), 2.21 (s, 3H).

[0305] To a solution of methyl vanillate (7.06 g, 39 mmol) and K_2CO_3 (10.7 g, 78 mmol) in DMF (25 mL) was added 1-bromo-2-fluoroethane (4.3 mL, 58 mmol) at 25°C. The solution was stirred for 2 days. The mixture was poured into water and extracted with EA. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **18-3** (8.92 g, 103 %).). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (dd, J=2.15, 8.41, 1H), 7.55 (d, J=8.41, 1H), 4.72-4.86 (m, 2H), 4.27-4.35 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H).

[0306] To a solution of **18-3** (8.92 g, 39 mmol) in MeOH (150 mL) was added 2 N NaOH (40 mL, 78 mmol). The solution was stirred for 2 h at 70°C. The mixture was concentrated, acidified with 2N HCl and extracted with EA to provide **18-4.** (5.0 g, 30 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47 (dd, J=1.96, 8.41, 1H), 7.38 (d, J=1.96, 1H), 6.99 (d, J=8.41, 1H), 4.61-4.76 (m, 2H), 4.17-4.27 (m, 2H).

[0307] To a solution of **18-4** (3.07 g, 14.3 mmol), glycine methyl ester HCl salt (3.6 g, 29 mmol), HATU (6.5 g, 17 mmol) in DMF (15 mL) was added DIEA (10 mL, 57 mmol). The solution was stirred for 18 h at r.t. The mixture was diluted with EA. The

organic phase was washed with water, 1N HCl, $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **18-5** (2.02 g, 51%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J=2.15, 1H), 7.30 (dd, J=2.15, 8.42), 6.90 (d, J-8.42, 1H), 6.57 (br. t, 1H), 4.72-4.85 (m, 2H), 4.22-4.35 (m, 2H), 4.25 (d, J= 5.08, 2H) 3.85 (s, 3H), 3.79 (s, 3H).

[0308] To a solution of **18-5** (2.02 g, 7.1 mmol) in MeOH (50 mL) was added 2 N NaOH (10 mL, 20 mmol). The solution was stirred for 2 h at r.t. The mixture was concentrated, acidified with 2N HCl and extracted with EA to provide **18-6.** (1.38 g, 72 %). ^1H NMR (400 MHz, CD_3OD): δ 7.49 (m, 2H), 7.04 (d, J=8.42, 1H), 4.62-4.85 (m, 2H), 4.25-4.34 (m, 2H), 4.08 (s, 2H), 3.90 (s, 3H).

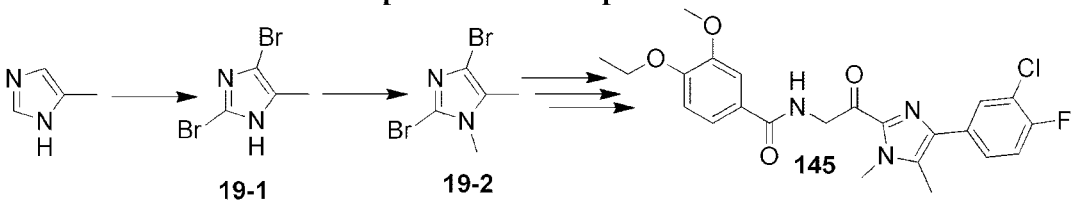
[0309] To a solution of **18-6** (0.52 g, 1.9 mmol), N,O-dimethylhydroxylamine hydrochloride (0.23g, 3.8 mmol), EDCI (0.38g, 2.3 mmol) in DMF (3 mL) was DIEA (1.0 mL, 5.8 mmol). The solution was stirred for 2 h at r.t. The mixture was diluted with EA. The organic phase was washed with water, 1N HCl, $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **18-7** (0.28 g, 47%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J=1.96, 1H), 7.33 (dd, J=1.96, 8.22, 1H), 6.90 (d, J=8.22, 1H), 4.71-4.84 (m, 2H), 4.26-4.36 (m, 4H), 3.91 (3, 3H), 3.76 (s, 3H), 3.25 (s, 3H).

[0310] Isopropylmagnesium chloride (2.0M, 0.48 mL, 0.95 mmol) was added dropwise to a solution of **18-7** (0.12 g, 0.38 mmol) and **18-2** (0.13 g, 0.50 mmol) in THF (1.0 mL). The solution was stirred for 2 h at r.t. The reaction was quenched with 1N HCl, diluted with EA and washed with brine. The organic solution was filtered to **18-8** (0.030 g, 20%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J =2.15, 1H), 7.38 (dd, J=2.15, 8.21, 1H), 7.03 (t, J=5.09, 1H), 4.93 (d, J=5.09, 2H), 4.74-4.96 (m, 2H), 4.28-4.37 (m, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.22 (s, 3H).

[0311] A solution of **18-8** (30 mg, 0.070 mmol), 3-chloro-4-fluorophenylboronic acid (24 mg, 0.14 mmol), potassium acetate (21 mg, 0.21 mmol) and $Pd(dppf)Cl_2$ (10 mg, 0.014 mmol) was heated under microwave irradiation for 1 h at 110°C. The mixture was concentrated and purified by chromatography on silica gel (EA/hexane) to give **18-9** (24 mg, 72%). LCMS: m/z 478.10 $[M+H]^+$.

[0312] Methylmagnesium bromide (0.33 mL, 0.46 mmol) was added to a solution of **18-9** (22 mg, 0.046 mmol) in THF (1.0 mL). The mixture was stirred for 2 h at r.t., and then quenched with 1M HCl. The mixture was extracted with EA, washed with brine, dried and concentrated. The residue purified by reverse phase HPLC to give **144** (3.8 mg, 17%). LCMS: m/z 494.15 $[M+H]^+$.

EXAMPLE 18
Preparation of Compound 145



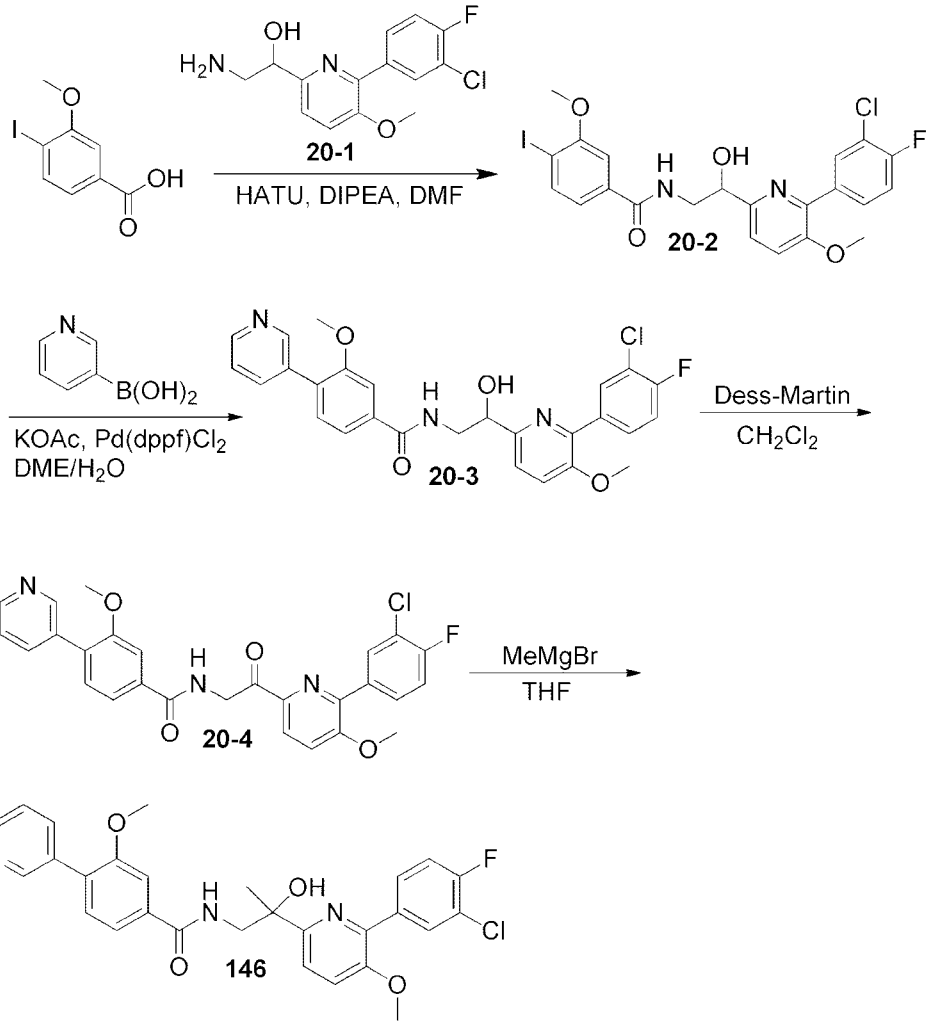
[0313] To a solution of 4(5)-methylimidazole (2 g, 24 mmol) in CH_2Cl_2 (150 mL) was added bromine (2.5 mL, 48 mmol) at 0°C. The solution was stirred for 1 H at r.t. The product was filtered and partitioned between EA and sat. $NaHCO_3$. The product was precipitated from $MeOH/CH_2Cl_2$ to provide **19-1** (4.31 g, 75 %). ^1H NMR (400 MHz, DMSO-d_6): δ 2.06 (s, 3H).

[0314] To a solution of **19-1** (3.6 g, 15 mmol) and K_2CO_3 (4.1 g, 30 mmol) in DMF (18 mL) was added iodomethane (1.4 mL, 23 mmol) at 25°C. The solution was stirred for 15 h. The mixture was poured into water and extracted with EA The combined organic phase was dried over anhydrous Na_2SO_4, and the residue was purified by chromatography on silica gel (EA/hexane) to give **19-2** (1.6 g, 41%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.52 (s, 3H), 2.21 (s, 3H).

[0315] Compound **145** was prepared using iodoethane and closely following the procedure for preparing of **144**. LCMS: m/z 476.10 $[M+H]^+$.

EXAMPLE 19

Preparation of Compound 146

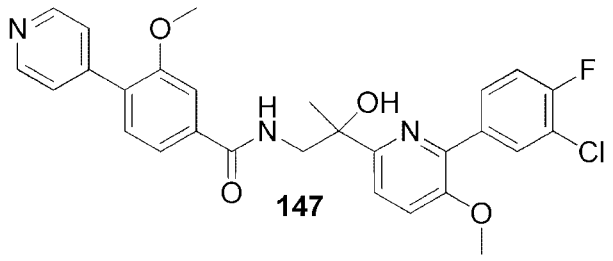


[0316] To a solution of 3-methoxy-4-iodobenzoic acid (0.45 g, 1.6 mmol), **20-1** (0.485 g, 1.6 mmol), HATU (0.75 g, 2.0 mmol) in DMF (3 mL) was added DIEA (0.71 mL, 4.1 mmol). The solution was stirred for 18 h at r.t. The mixture was diluted with EA. The organic phase was washed with water, 1N HCl, $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel ($MeOH/CH_2Cl_2$) to give **20-2** (0.176 g, 51%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (dd, J=2.15, 7.24, 1H), 7.81-7.85 (m, 1H), 7.75 (d, J=8.02, 1H), 7.37-7.42 (m, 2H), 7.26-7.27 (m, 1H), 7.25 (t, J=8.71, 1H), 6.93 (dd, J=1.96, 8.02), 6.83-6.86 (m, 1H), 4.97-4.99 (m, 1H), 3.99-4.13 (m, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.54-3.72 (m, 1H).

[0317] A solution of **20-2** (25 mg, 0.045 mmol), pyridine-3-boronic acid (11 mg, 0.09 mmol), potassium acetate (13 mg, 0.13 mmol) and $Pd(dppf)Cl_2$ (6 mg, 0.009 mmol) in DME (0.5 mL) and H_2O (0.05 mL) was heated under microwave irradiation for 1 h at 110°C. The mixture was concentrated and purified by chromatography on silica gel ($MeOH/CH_2Cl_2$) to give **20-3** (22 mg, 88%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.74-8.90 (br. s, 1H), 8.60-8.72 (br. s, 1H), 8.00, dd, J=2.15, 7.24), 7.85-7.88 (m, 2H), 7.34-7.45 (m, 5H), 7.17, (t, J=8.80, 1H), 6.94-6.97 (m, 1H), 4.98-5.01 (m, 1H), 4.00-4.09 (m, 1H), 3.88 (s, 3H), 3.82 (s, 3H0, 3.68-3.75 (m, 1H).

[0318] Dess-Martin periodinane (25 mg, 0.061 mmol) was added to a solution of **20-3** (22 mg, 0.043 mmol) in CH_2Cl_2, and stirred for 2 h. The mixture was diluted with CH_2Cl_2, washed with sat. Na_2CO_3, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EA/hexane) to give **20-4** (6.1 mg, 28%). LCMS: m/z 506.10 $[M+H]^+$.

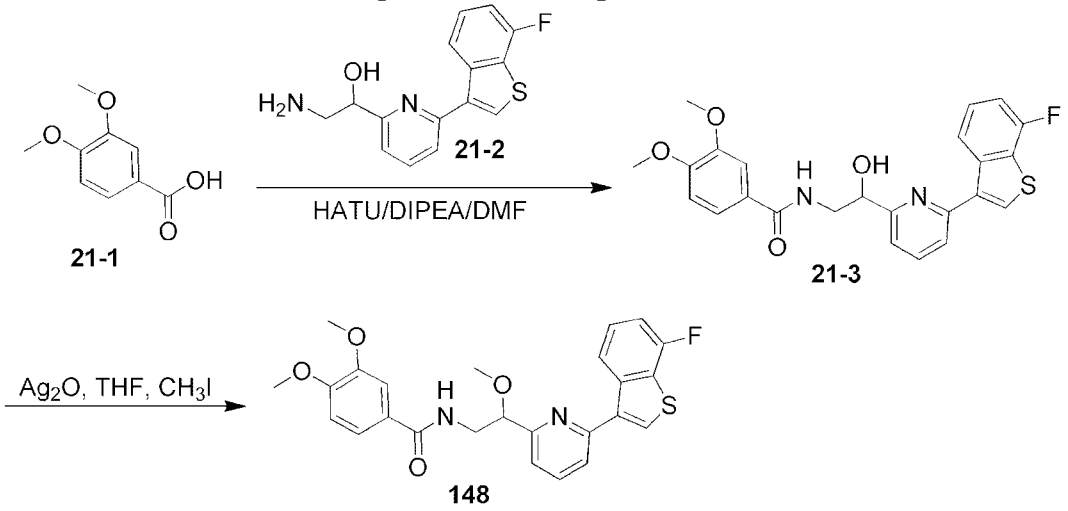
[0319] Methylmagnesium bromide (1.4 M in THF, 0.39 mL, 0.39 mmol) was added to a solution of **20-4** (20 mg, 0.039 mmol) in THF (1.0 mL) and stirred for 2 h. The mixture was diluted with quenched with 1N HCl and extracted with EA. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product purified by reverse phase HPLC to provide **146** (0.9 mg, 4%). LCMS: m/z 522.15 $[M+H]^+$.



147

[0320] Compound **147** was prepared using pyridine-4-boronic acid pinacol ester in the Suzuki reaction and by following a synthetic route, which closely follows that described for preparation of **146**. LCMS: m/z 522.15 $[M+H]^+$.

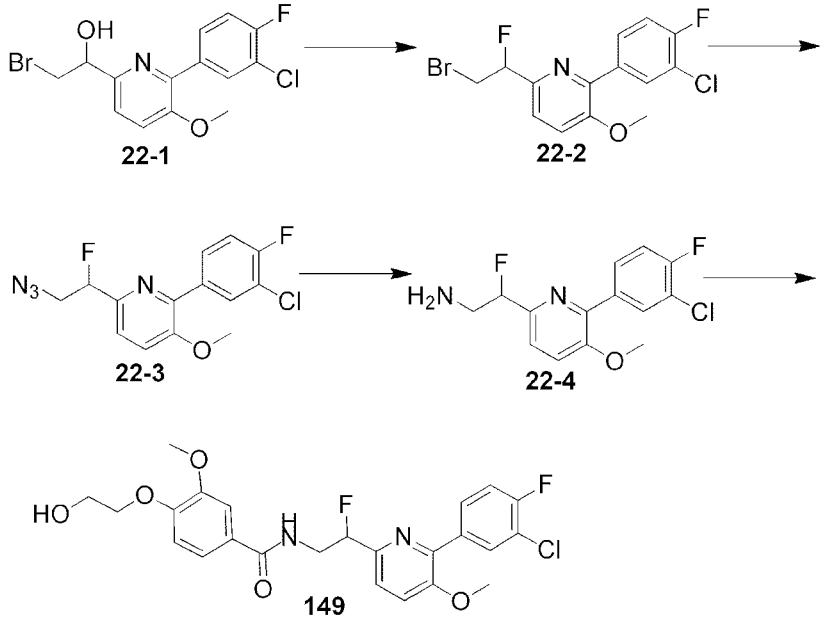
EXAMPLE 20
Preparation of Compound 148



[0321] To a solution of **21-1** (100 mg, 0.549 mmol), HATU (208 mg, 0.549 mmol) and DIPEA (142 mg, 1.1 mmol) in anhydrous DMF (2 mL) was added **21-2** (100 mg 0.347 mmol) at 25°C. The solution was stirred for 10 h at this temperature and then diluted with 1.0 N aqueous $NaHCO_3$ solution (2 x 40 mL), extracted with EA (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified on a silica gel column to give **21-3** (100 mg, 40.3%). +ESI-MS: m/z 433.1 $[M+H]^+$.

[0322] To a solution of **21-3** (100 mg, 0.22 mmol) in THF (2 mL) were added Ag_2O (20 mg) and CH_3I (100 mg, 0.72 mmol). The mixture was stirred for 15 h at 40°C. The solid was removed, and the filtrate was concentrated. The residue was purified by prep-HPLC (FA) to give **148** as a white solid (40 mg, 38.8 %). +ESI-MS: m/z 466.9 $[M+H]^+$.

EXAMPLE 21
Preparation of Compound 149

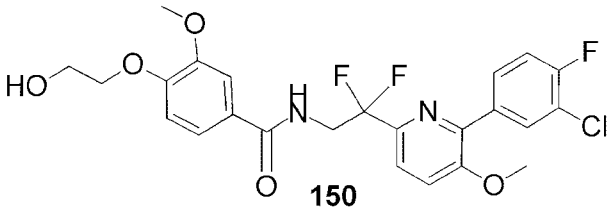


[0323] To a solution of **22-1** (1.1 g, 3.1 mmol) in DCM (3 mL) was added DAST (1.4 g; 8.7 mmol). The solution was stirred at r.t. for 1 h with TLC monitoring. The reaction was quenched with aq. $NaHCO_3$ at 0°C and extracted with DCM. The combined organic solution was dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (PE:EA=20:1 to 6:1) to give **22-2** (0.8 g).

[0324] To a solution of **22-2** (0.8 g, 2.2 mmol) in DMSO (5 mL) was added NaN_3 (300 mg 4.6 mmol). The solution was stirred at 60°C for 3 h with LCMS monitoring. The reaction was quenched with aq. $NaHCO_3$ and extracted with EA. The combined organic solution was dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to give crude **22-3** (0.7 g), which was used in next step directly without purification.

[0325] To a solution of **22-3** (0.7 g, 2.1 mmol) in EtOH (10 mL) and HCl (2 drops, 1.0 N) was added Pd/C (10%, 400 mg) under N_2. The suspension was degassed under vacuum and purged with H_2 3 times. The mixture was stirred under H_2 (40 psi) at r.t. for 1 h. The suspension was filtered through a pad of Celite and the pad cake was washed with EtOH. The combined filtrates were concentrated to give crude **22-4** (0.4 g) used for next step directly without purification

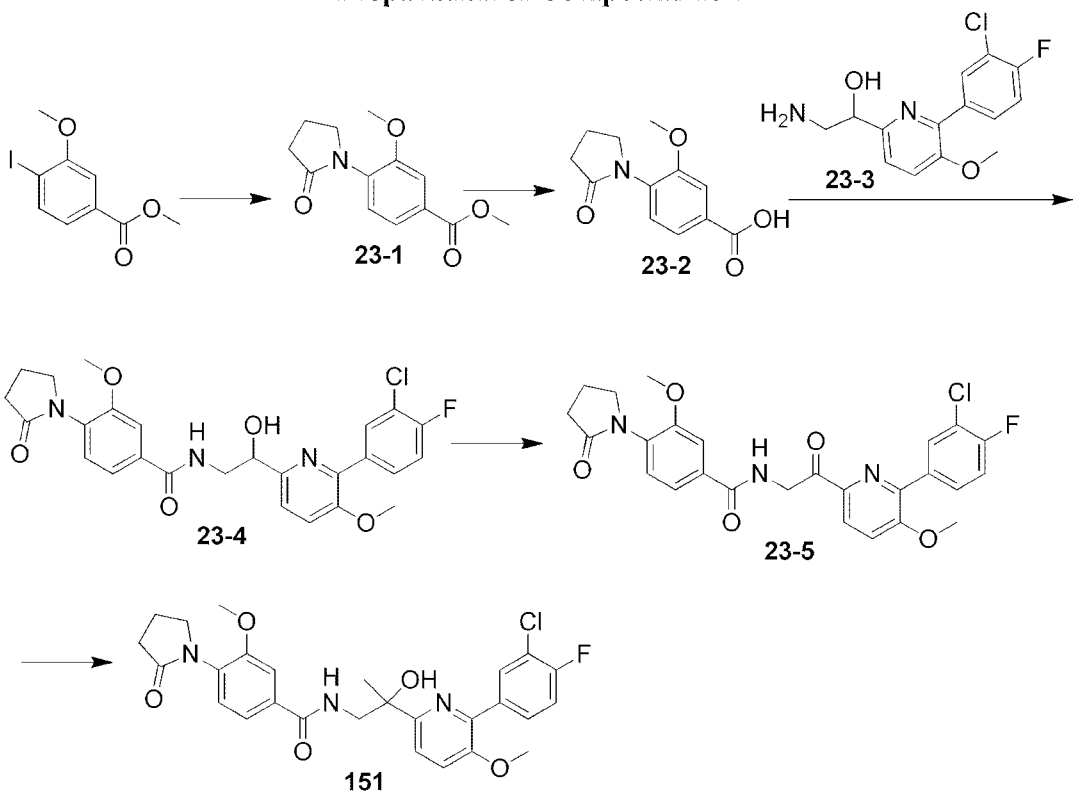
[0326] To a solution of 4-(2-hydroxyethoxy)-3-methoxybenzoic acid (212 mg, 1.0 mmol), HATU (570 mg, 1.5 mmol) and DIPEA (322 g, 2.5 mmol) in anhydrous DCM (5 mL) was added **22-4** (298 mg, 1.0 mmol) at 25°C. The solution was stirred for 3 h. at this temperature, diluted with 1.0 N aqueous $NaHCO_3$ solution, and extracted with DCM. The combined organic layers were washed by brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **149** (180 mg) as a white solid. +ESI-MS::m/z 493.0 $[M+H]^+$.



150

[0327] Compound **150** was prepared using 6-(2-bromo-1,1-difluoroethyl)-2-(3-chloro-4-fluorophenyl)-3-methoxypyridine, and by following a synthetic route, which closely follows that described for preparation of **149**. +ESI-MS: :m/z 510.9 $[M+H]^+$.

EXAMPLE 22
Preparation of Compound 151



[0328] To a solution of methyl 3-methoxy-4-iodobenzoate (250 mg, 0.85 mmol) in toluene (2 mL) was added pyrrolidinone (150 mg, 1.7 mmol), potassium phosphate (0.55 g, 2.2 mmol), xantphos (25 mg, 0.43 mmol) and tris(dibenzylideneacetone)dipalladium(0) (40 mg, 0.43 mmol). The mixture was heated at 110°C for 3 h. The mixture was then diluted with EA. The organic phase was washed with water, 1N HCl, $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **23-1** (0.178 g, 83%). LCMS: m/z 478.10 $[M+H]^+$.

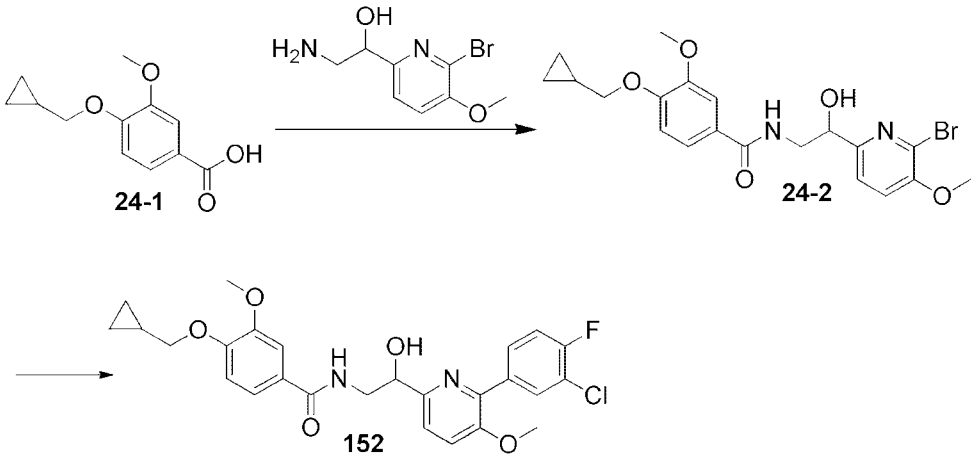
[0329] To a solution of **23-1** (0.178 g, 0.72 mmol) in methanol (6 mL) was added NaOH (2.0 M, 2.0 mL) at 25°C. The solution was stirred for 15 h, acidified with 2N HCl and extracted with EA. The combined organic phase was dried over anhydrous Na_2SO_4 to give **23-2** (0.152 g, 90%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, J=1.77, 8.22 Hz, 1H), 7.51 (d, J=1.77 Hz, 1H), 7.30 (d, J=8.22 Hz, 1H), 3.82 (s, 3H), 3.75 (t, J=7.04 Hz, 2H), 2.55 (t, J=8.02 Hz, 2H), 2.0-2.3 (m, 2H).

[0330] To a solution of **23-2** (0.152 g, 0.65 mmol), **23-3** (0.19 g, 0.65 mmol), HATU (0.37 g, 0.97 mmol) in DMF (1 mL) was added DIEA (0.23 mL, 1.3 mmol). The solution was stirred for 2 h at r.t. The mixture was diluted with EA. The organic phase was washed with water, 1N HCl, $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **23-4** (0.172 g, 51%). LCMS: m/z 478.10 $[M+H]^+$.

[0331] Dess-Martin periodinane (220 mg, 0.50 mmol) was added to a solution of **23-4** (172 mg, 0.34 mmol) in CH_2Cl_2, and the mixture was stirred for 2 h. The mixture was diluted with CH_2Cl_2 and washed with sat. Na_2CO_3, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EA/hexane) to give **23-5** (77 mg, 45%) as white solid. LCMS: m/z 512.10 $[M+H]^+$.

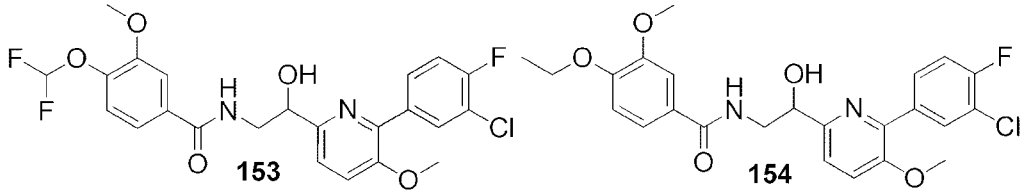
[0332] Methylmagnesium bromide (1.0 mL, 1.4 mmol) was added to a solution of **23-5** (72 mg, 0.14 mmol) in THF (1.0 mL). The mixture was stirred for 2 h at r.t., and then quenched with 1N HCl. The mixture was extracted with EA, washed with brine, dried and concentrated. The residue purified by reverse phase HPLC to give **151** (6.5 mg, 17%) as white solid. LCMS: m/z 528.15 $[M+H]^+$.

EXAMPLE 23
Preparation of Compound 152



[0333] To a stirring mixture of **24-1** (44 mg, 0.197 mmol) in DMF were added HATU (83 mg, 0.218 mmol) and DIPEA (51 mg, 0.4 mmol). The mixture was stirred at r.t. for 10 mins and a solution of 2-amino-1-(6-bromo-5-methoxypyridin-2-yl)ethan-1-ol was added. The mixture was stirred at r.t. for 1 h, diluted with EtOAc and quenched with a sat. $NaHCO_3$ solution. The mixture was stirred at r.t. for 10 mins and the layers were separated. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified via silica gel chromatography to afford **24-2**. LCMS: m/z 451.05 $[M+H]^+$.

[0334] To a stirring mixture of **24-2** (28 mg, 0.062 mmol) in DME/water (10:1, 2.2 mL) were added Cs_2CO_3 (60 mg, 0.19 mmol), $PdCl_2$dppf(10 mg, 0.012 mmol), and (3-chloro-4-fluorophenyl)boronic acid (11 mg, 0.062 mmol). The mixture was stirred under microwave conditions at 110°C for 1 h. The crude product mixture was cooled to r.t. and concentrated under reduced pressure. The crude mixture was purified via silica gel chromatography to afford **152**. LCMS: m/z 501.15 $[M+H]^+$.

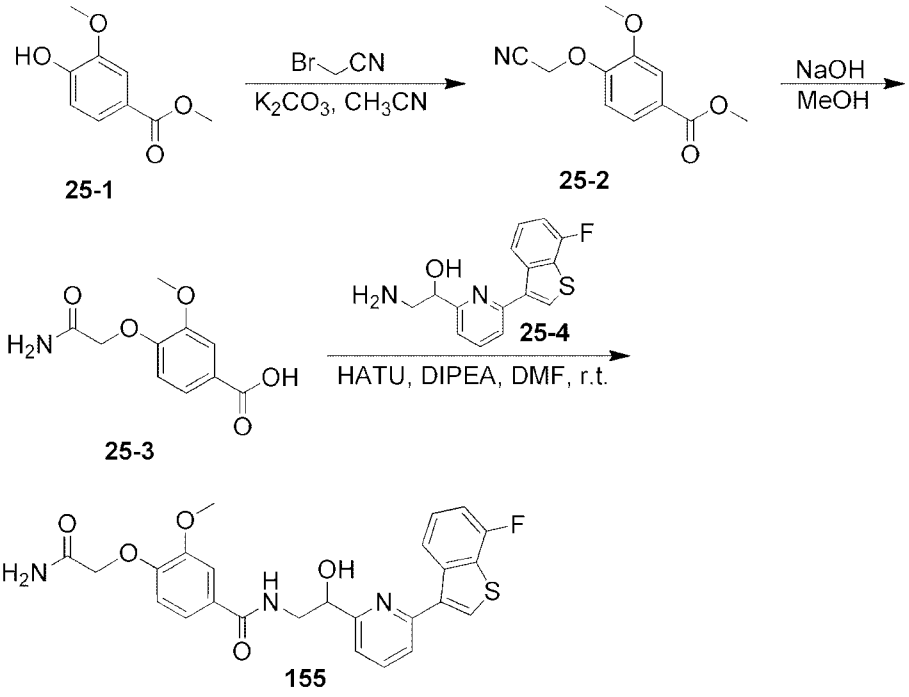


[0335] Compounds **153** and **154** were prepared using commercially available benzoic acids and 2-amino-1-(6-bromo-5-methoxypyridin-2-yl)ethan-1-ol in 2 or 3 steps, and

by following a synthetic route, which closely follows that described for preparation of the compound of Example 23. **153**: LCMS: m/z 497.05 $[M+H]^+$. **154**: LCMS: m/z 475.10 $[M+H]^+$.

EXAMPLE 24

Preparation of Compound 155



[0336] To a solution of **25-1** (1.82 g, 10 mmol) and K_2CO_3 (2.76 g, 20 mmol) in CH_3CN (20 mL) at r.t. was slowly added 2-bromoacetonitrile (2.4 g, 20 mmol). The mixture was heated to reflux and stirred for 15 h. The solvent were removed under reduced pressure. Purification by column chromatography on silica gel (PE:EA=3:1) provided **25-2** (2 g, 90%).

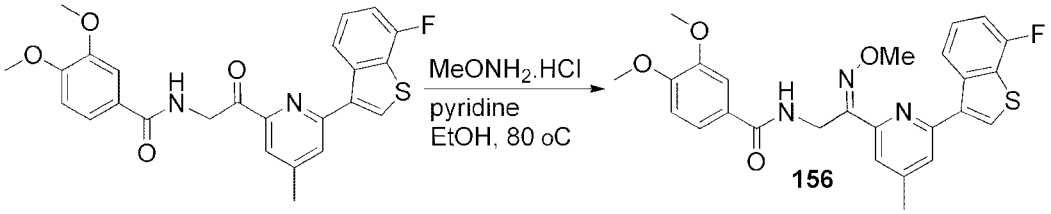
[0337] To a solution of **25-2** (2.21 g, 10 mmol) in methanol (10 mL) was added NaOH aqueous (10 mL, 1M). The mixture was stirred for 4 h at 60°C. The solution was cooled to r.t., acidified to pH=4 using 1N HCl solution and extracted with EtOAc. The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to provide **25-3** (1.1 g, 50%).

[0338] To a solution of **25-3** (226 mg, 0.1 mmol) in DMF (3 mL) were added HATU (570 mg, 1.5 mmol) and DIPEA (387 mg, 3 mmol) at r.t. The solution was stirred for 10 mins at r.t. Compound **25-4** (287 mg, 1 mmol) was added and stirred for 1 h. The solution was extracted with EtOAc and washed with H_2O. The organic phase was

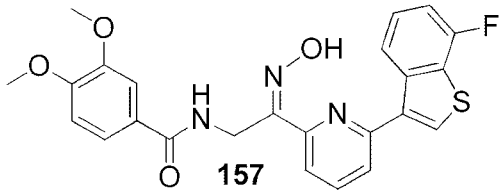
concentrated and purified by prep-TLC to give **155** (200 mg, 40%). +ESI-MS: m/z 495.9 $[M+H]^+$.

EXAMPLE 25

Preparation of Compound 156



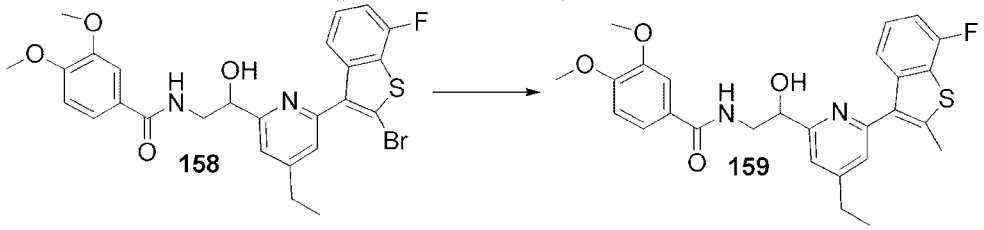
[0339] To a stirring mixture of N-(2-(6-(7-fluorobenzo[b]thiophen-3-yl)-4-methylpyridin-2-yl)-2-oxoethyl)-3,4-dimethoxybenzamide (20 mg, 0.043 mmol) in EtOH (0.25 mL) were added methoxy amine hydrochloride (4 mg, 0.048 mmol) followed by an addition of pyridine (34 mg, 0.43 mmol). The mixture was heated at 80°C for 30 mins and then cooled to r.t. The mixture was concentrated under reduced pressure. The crude mixture was purified via prep-HPLC to afford **156**. LCMS: m/z 494.10 $[M+H]^+$.



[0340] Compound **157** was prepared using N-(2-(6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)-2-oxoethyl)-3,4-dimethoxybenzamide and hydroxylamine hydrochloride, and by following a synthetic route, which closely follows that described for preparation of **156**. LCMS: m/z 466.25 $[M+H]^+$.

EXAMPLE 26

Preparation of Compound 158

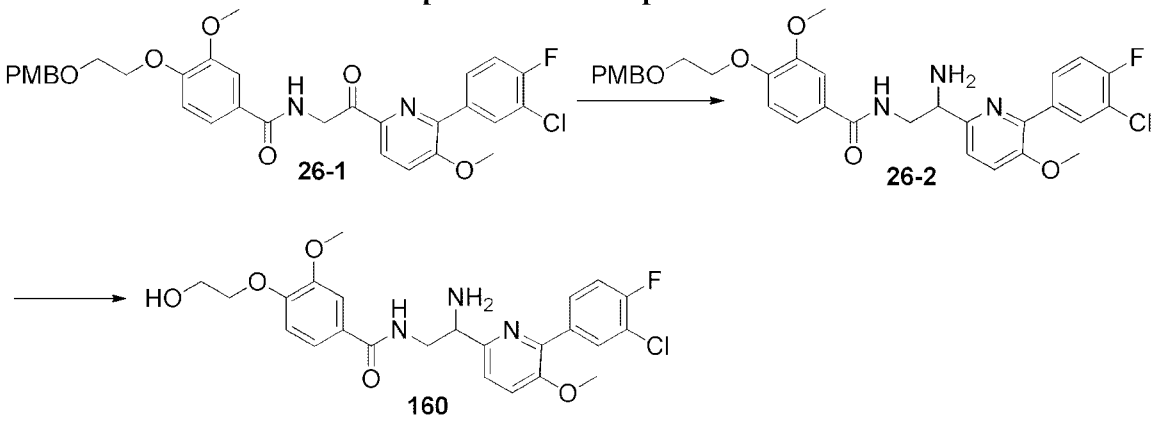


[0341] To a stirring mixture of **158** (20 mg, 0.036 mmol) in THF (1 mL) were added bis(tri-*tert*-butylphosphine)palladium(0) (3.6 mg, 0.008 mmol), and a solution of MeZnCl in THF (0.055 mL, 0.11 mmol). The mixture was stirred under microwave

condition at 100°C for 1 h. The mixture was cooled to r.t., diluted with EtOAc and slowly quenched with a sat. NH_4Cl solution. The mixture was stirred at r.t. for 20 mins and then the layers were separated. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product mixture was purified via silica gel column to afford **159** as a colorless oil. LCMS: m/z 495.1 $[M+H]^+$.

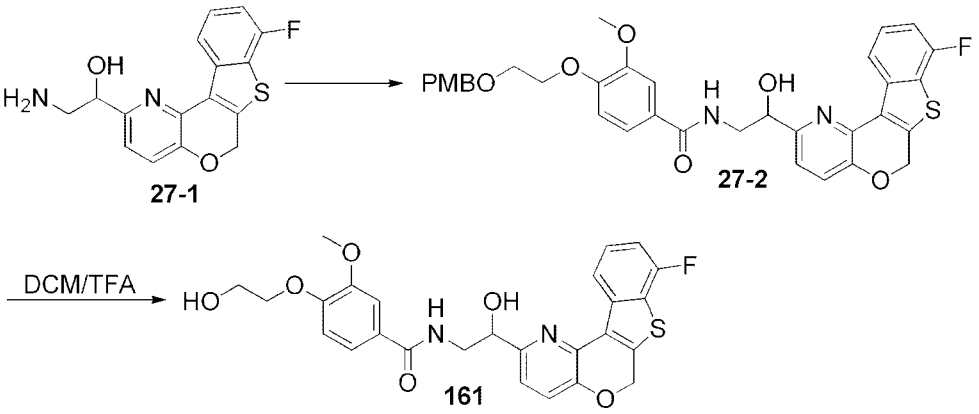
EXAMPLE 27

Preparation of Compound 160



[0342] To a stirring mixture of **26-1** (50 mg, 0.082 mmol) in MeOH (1 mL) were added amonium acetate (94 mg, 1.23 mmol), $NaCNBH_3$ (7.7 mg, 0.12 mmol). The mixture was heated at 70°C for 1 h and then cooled to room temperture. The mixtue was diluted wtih EtOAc and slowly quenched with a sat. NH_4Cl solution. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product mixture was purified via silica gel chromatography to afford **26-2**. The PMB ether was removed using TFA in DCM at r.t. The crude product was concentrated under reduced pressure and purified via prep-HPLC to afford **160** (3.1 mg) as a white solid. LCMS: m/z 490.15 $[M+H]^+$.

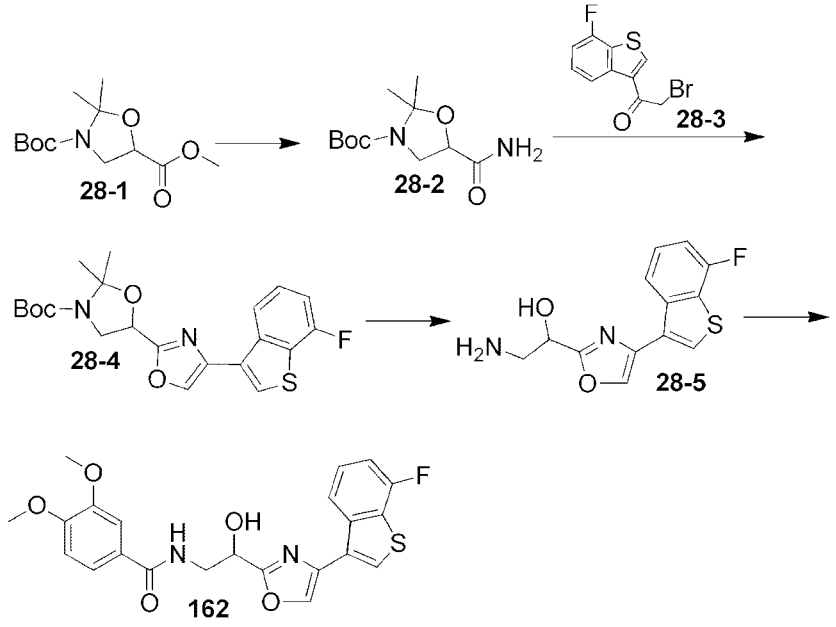
EXAMPLE 28
Preparation of Compound 161



[0343] To a solution of 3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzoic acid (205 mg, 0.62 mmol) in DMF (15 mL) were added DIPEA (320 mg, 2.48 mmol) and HATU (235.6 mg, 0.62 mmol). The mixture was stirred at r.t. for 30 mins, and **27-1** (195 mg, 0.62 mmol) was added. The mixture was stirred at r.t. overnight. The mixture was diluted with water and extracted with EA. The organic layer was dried over sodium sulfate, and concentrated in vacuum to give the crude product, which was purified by column chromatography to give **27-2** (180 mg). +ESI-MS: m/z 631.1 $[M+H]^+$.

[0344] Compound **27-2** (180 mg, 0.286 mmol) was dissolved in TFA/DCM (10 mL). The mixture was stirred at r.t. for 1 h (monitored by TLC). The mixture was extracted with EA, and washed with a sat. $NaHCO_3$ solution. The organic layer was dried over sodium sulfate, and concentrated in vacuum to give the crude product, which was purified by prep-HPLC to give **161** (50mg) as a white solid. +ESI-MS: m/z 511.1 $[M+H]^+$.

EXAMPLE 29
Preparation of Compound 162



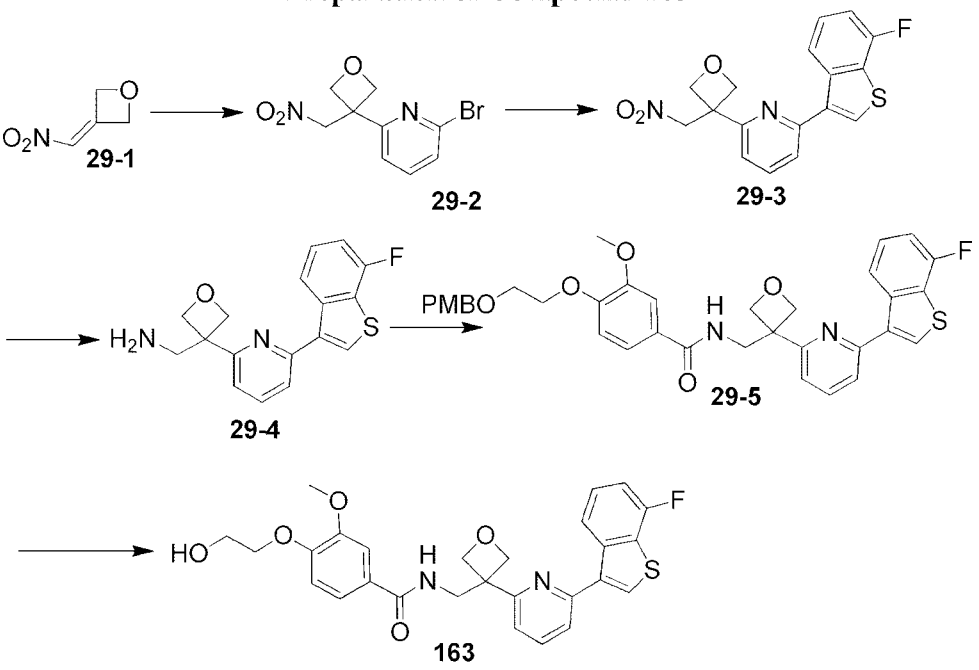
[0345] A solution of **28-1** (2.59 g, 0.01 mol) in NH_3/MeOH (20 mL) was stirred at r.t. for 30 mins. The solvent was removed by rotary evaporator. The residue, **28-2**, was used in next step.

[0346] A mixture of **28-2** (2.44 g, 0.01 mol) **28-3** (2.73 g, 0.01 mol) and $AgSbF_6$ (5.14 g, 0.015 mol) in DME (20 mL) was stirred for 2 h at 120°C under microwave irradiation. The mixture was filtered. The filtrate was concentrated by rotary evaporator to give crude **28-4** (5 g), which was used in next step without further purification.

[0347] To a solution of **28-4** (5 g) in EtOAc (10 mL) was added HCl-EtOAc (30 mL). The solution was stirred for 10 h. The solvent was concentrated by rotary evaporator. The product was purified by prep-HPLC to give **28-5** (250 mg). ESI-MS: m/z 278.8 $[M+H]^+$.

[0348] To a solution of **28-5** (145 mg, 0.8 mmol) in DMF (10 mL) was added HATU (343 mg, 0.9 mmol), DIEA (155 mg, 1.2 mmol), and stirred for 5 mins. 3,4-dimethoxybenzoic acid (250 mg, 0.8 mmol) was added and the mixture was stirred for 5 h. Water (100 mL) was poured into the solution, and a solid precipitated. The solid was purified by silica column chromatography (PE:EA=1:1) to give **162** (158 mg, 45%). ESI-MS: m/z 442.9 $[M+H]^+$.

EXAMPLE 30
Preparation of Compound 163



[0349] A 50 mL three-necked round bottle flask was charged with a solution of 2.6-dibromopyridine (1.15 g, 5 mmol, 5.0 eq.) in THF under nitrogen. The solution was cooled to -78°C, and *n*-BuLi (2 mL, 5 mmol, 5.0 eq.) was added dropwise. After addition, the mixture was stirred for 30 mins. A solution of **29-1** (115 mg, 1.0 mmol, 1.0 eq.) (prepared according to Wuitschik et al., *J. Med. Chem.* (2010) 53(8):3327-3246, which hereby is incorporated by reference for the limited purpose of preparing **29-1**) in THF (3~5 mL) was added dropwise. After addition, the mixture was stirred for 30 mins. The reaction was quenched with sat. NH_4Cl, and the mixture was extracted by EA (3 x 10 mL). The combined organic phase was concentrated to dryness, and the residue was purified by prep-TLC to give **29-2** as a yellow oil (80 mg). ^{1}H-NMR (400MHz, $CDCl_3$), δ = 7.67 - 7.60 (m, 1H), 7.55 (d, J=7.5 Hz, 1H), 7.44 (d, J=8.0 Hz, 1H), 5.23 (s, 2H), 4.99 (d, J=7.0 Hz, 2H), 4.89 (d, J=7.0 Hz, 2H).

[0350] A 50 mL round bottom flask was charged with a mixture of **29-2** (0.4 g, 1.46 mmol), boric ester (0.6 g, 2.16 mmol, 1.5 eq.), $Pd(dppf)Cl_2$ (107 mg, 0.146 mmol, 0.1 eq.) and Na_2CO_3 (320 mg, 3.0 mmol, 3.0 eq.) in dioxane/H_2O (10 mL/2 mL). The mixture was degassed and refilled with nitrogen. The mixture was heated to reflux overnight. The mixture was cooled to r.t. and concentrated to dryness. The residue was purified by column

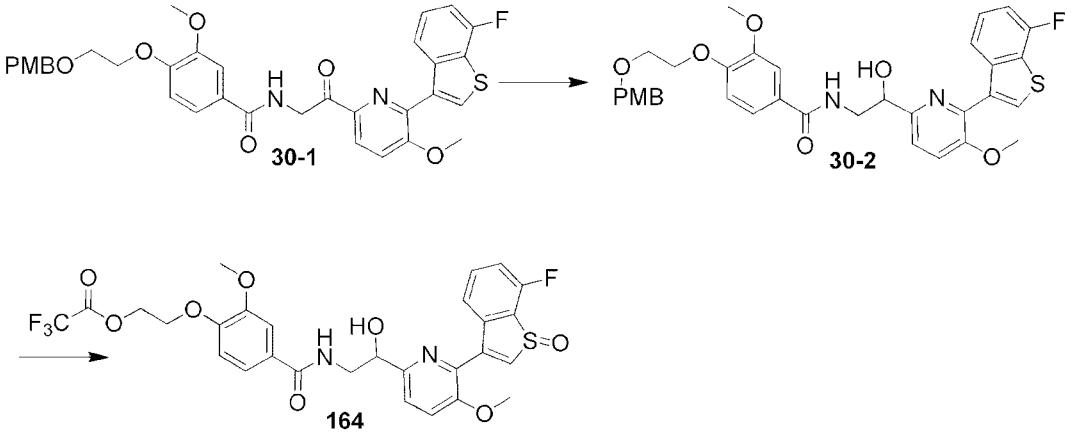
on silica gel (5~10% EA in PE) to give **29-3** as a pink oil (0.44 g, 87% yield). ^{1}H-NMR (400MHz, $CDCl_3$), δ = 8.02 (d, J=8.5 Hz, 1H), 7.92 (t, J=7.8 Hz, 1H), 7.81 (s, 1H), 7.67 (dd, J=7.8, 14.3 Hz, 2H), 7.42 (dt, J=5.5, 8.0 Hz, 1H), 7.16 - 7.07 (m, 1H), 5.33 (s, 2H), 5.10 (d, J=7.0 Hz, 2H), 5.00 (d, J=6.5 Hz, 2H).

[0351] A 250 mL round bottom flask was charged with a solution of **29-3** (0.4 g, 1.17 mmol) in EtOH (100 mL) and Pd/C (0.2 g). The mixture was stirred under hydrogen balloon overnight. The mixture was filtered, and concentrated to dryness. Crude **29-4** was used in the next step without further purification.

[0352] To a solution of **29-4** (270 mg, 0.86 mmol, 1.0 eq.), acid (313 mg, 0.942 mmol, 1.1 eq.) and DIEA (0.33 g, 3.0 eq.) in DMF (10 mL) was added HATU (360 mg, 0.942 mmol, 1.1 eq.), and the mixture was stirred at r.t. overnight. The mixture was diluted with EA and water. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness. The residue was purified by silica gel column (60% EA in PE) to give **29-5** as a pale yellow oil (0.4 g, 74%).

[0353] To a solution of **29-5** (0.35 g) in DCM (25 mL) was added TFA (5 mL), and the mixture was stirred at r.t. for 10 mins. The mixture was neutralized with sat. Na_2CO_3 solution. The organic phase was concentrated and purified by prep-TLC to give **163** as a white solid (70 mg). +ESI-MS: m/z 509.0 $[M+H]^+$.

EXAMPLE 31
Preparation of Compound 164

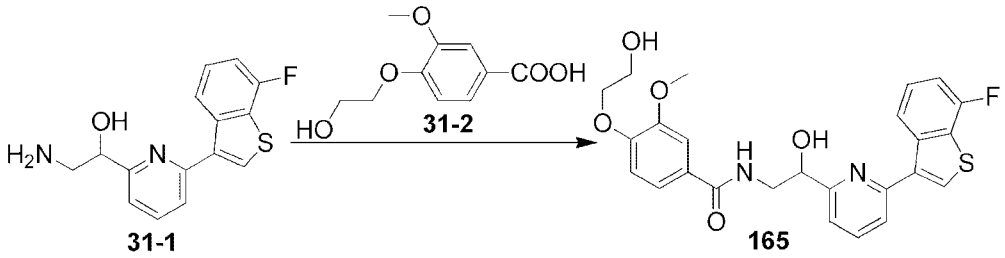


[0354] To a solution of **30-1** (190 mg, 0.30mmol) in THF (5 mL) was added $NaBH_4$ (20 mg, 0.6 mmol) at r.t. MeOH (1mL) was added, and the mixture was stirred at

20°C for 1 h. The residue was purified by column chromatography on silica gel (PE) to provide **30-2** (190 mg, 99 %).

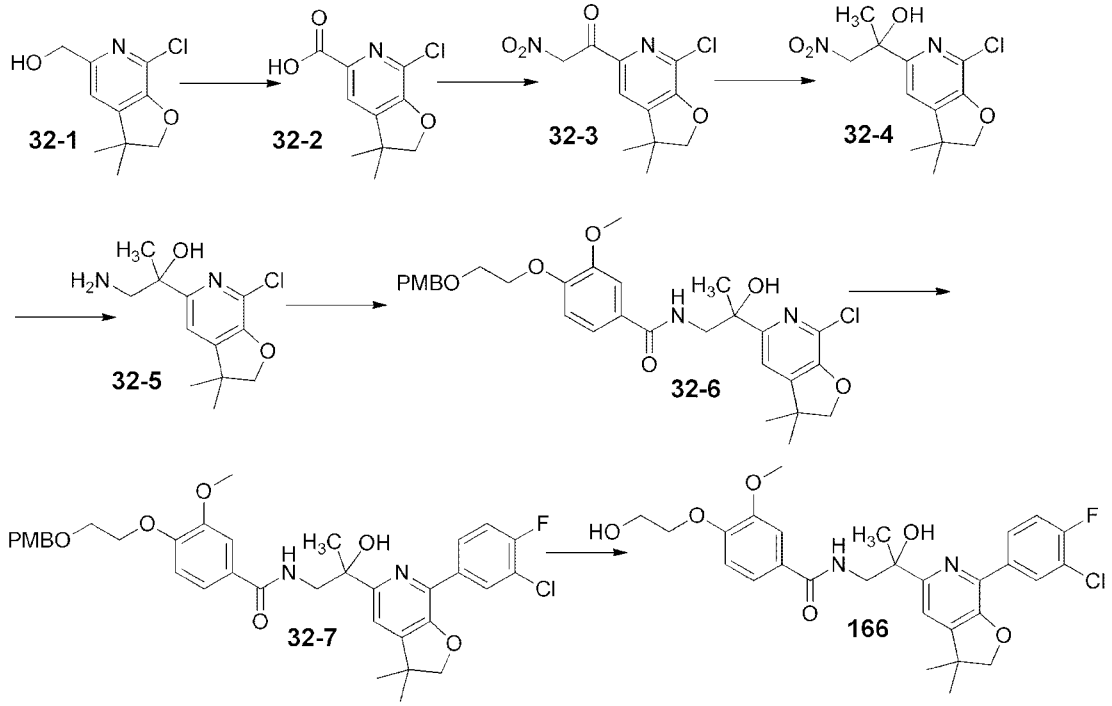
[0355] To a solution of **30-2** (190 mg, 0.3 mmol) in DCM (3 mL) was added TFA (0.5mL) and H_2O_2 (0.2 mL, 30%, 2eq), and the mixture was stirred for 30 mins. The mixture was neutralized with a sat. $NaHCO_3$ solution, and extracted with DCM (3 x 10mL). The solution was concentrated to give **164** in crude form (200 mg), +ESI-MS: m/z 625.0 $[M+H]^+$.

EXAMPLE 32
Preparation of Compound 165



[0356] Compound **31-2** (106 mg, 0.5 mmol), **31-1** (140 mg, 0.5 mmol) and triethylamine (1 mmol) were dissolved in DMF (5 mL). HATU (380 mg, 1 mmol) was added to the solution. After 15-30 mins, the mixture was treated with sat. NaCl solution (100 mL), and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with 2N HCl solution and 5% $NaHCO_3$ solution. The organic layer were dried over anhydrous $MgSO_4$, and concentrated in vacuum to give the crude product. The crude product was purified by silica gel column chromatography eluting with EtOAc/PE (1/1) to give **165** as a white solid (24 mg, 10%). +ESI-MS: m/z 483.0 $[M+H]^+$.

EXAMPLE 33
Preparation of Compound 166



[0357] Dess-Martin periodinane (1.49 g, 3.52 mmol) was added to a stirred solution of **32-1** (300 mg, 1.40 mmol) in dry DCM (6.5 mL). The mixture was stirred at r.t. for 1 h and quenched with a 1:1 mixture of 2M aq. $Na_2S_2O_3$ solution and sat. aq. $NaHCO_3$ solution (10 mL). The mixture was stirred vigorously for 30 mins and the layers were separated. The organic portion was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude aldehyde was progressed to the next step without further purification. The aldehyde was dissolved in *tert*-butanol (21 mL). To the solution, 2-methyl-2-butene (1.13 mL, 13.5 mmol) and a solution of sodium chlorite (244 mg, 2.70 mmol) and sodium phosphate monobasic dihydrate (1.36 g, 8.70 mmol) in water (21 mL) were added. The mixture was stirred at r.t. for 18 h. Brine was added and the mixture was extracted 3 times with EtOAc. The combined organic portions were dried (Na_2SO_4) and filtered. The volatiles were removed under reduced pressure. Acid **32-2** (310 mg) was progressed to the next step without further purification. UPLC/MS(ES^+): m/z 228.07 $[M+H]^+$.

[0358] 1,1'-Carbonyldiimidazole (1.17 g, 7.21 mmol) was added to a solution of **32-2** (250 mg) in THF (9.6 mL). The mixture was stirred at r.t. for 30 mins and then

nitromethane (671 mg, 11.0 mmol) and potassium carbonate (608 mg, 4.40 mmol) were added. After 3 h, the volatiles were removed under reduced pressure. The residue was taken up with EtOAc. The organic portion was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Crude **32-3** (300 mg) was progressed to the next step without further purification. UPLC/MS(ES^+): m/z 271.05 $[M+H]^+$.

[0359] Methylmagnesium bromide (3M solution in Et_2O, 204 uL, 0.612 mmol) was added to a solution of **32-3** (300 mg) in THF (8 mL), which had been pre-cooled to -40°C. The mixture was stirred at -40°C for 1 h, allowed to reach r.t. and then quenched with 1M aq. HCl solution. The aqueous portion was extracted twice with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Crude **32-4** was progressed to the next step without further purification. UPLC/MS(ES^+): m/z 287.10 $[M+H]^+$.

[0360] $NaBH_4$ (52.0 mg, 1.38 mmol) was added to a solution of $NiCl_2$-$6H_2O$ (109 mg, 0.460 mmol) in MeOH (10 mL). After 30 mins, nitro-derivative **32-4** (250 mg) dissolved in MeOH (2 mL) was added, followed by additional solid $NaBH_4$ (70 mg). The reaction was monitored by UPLC. When complete, the mixture was filtered through a pad of celite and the organic portion was concentrated under reduced pressure. Crude **32-5** (235 mg) was progressed to the next step without further purification. UPLC/MS(ES^+): m/z 257.17 $[M+H]^+$.

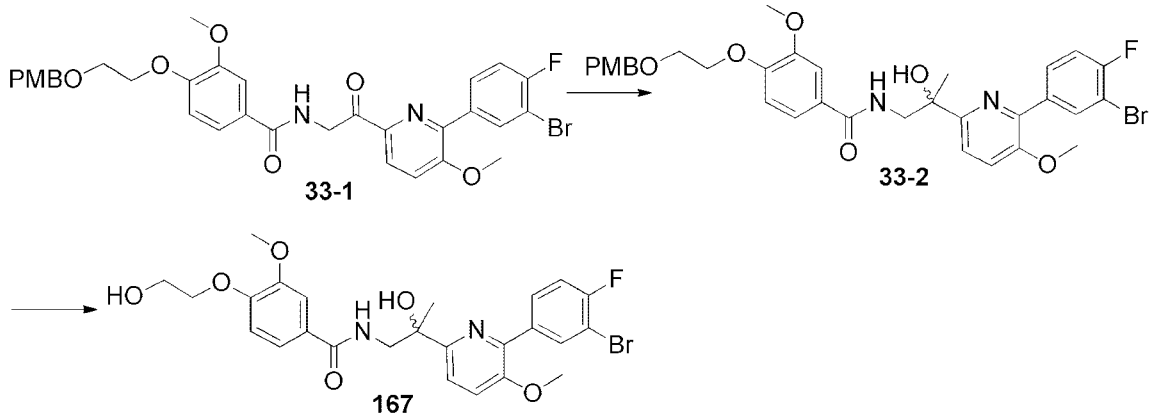
[0361] A mixture of **32-5** (235 mg), 3-methoxy-4-{2-[(4-methoxyphenyl)methoxy]ethoxy}benzoic acid (365 mg, 1.10 mmol), EDC (263 mg, 1.38 mmol), HOBT (186 mg, 1.38 mmol) and TEA (255 uL, 1.84 mmol) in DCM (8 mL) was stirred at r.t. for 3 h. The mixture was washed twice with 1M aq. HCl solution. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 60:40 to 10:90) afforded **32-6** as an off-white solid (60 mg, 12% starting from **32-1**). UPLC/MS(ES^+): m/z 571.20 $[M+H]^+$.

[0362] A mixture of **32-6** (60 mg, 0.100 mmol), (3-chloro-4-fluorophenyl)boronic acid (91.0 mg, 0.500 mmol), $Pd(dppf)Cl_2$ (3.6 mg, 0.005 mmol) and aq. Na_2CO_3 (2M solution, 0.500 mmol, 250 uL) in DCE (1 mL) was degassed and then stirred with heat to 85°C for 4 h. Water and DCM were added, and the layers were separated. The organic phase

was dried with Na_2SO_4, filtered and evaporated. Chromatography of residue (cyclohexane:EtOAc, 100:0 to 20:80) afforded **32-7** (46 mg, 69%). UPLC/MS(ES^+): m/z 665.47 $[M+H]^+$.

[0363] A solution of **32-7** (46.0 mg, 0.069 mmol) in 10:1 DCM-TFA (1.1 mL) was stirred at room temperatire for 1 h. 1M aq. NaOH solution was added and the mixture was stirred for 15 mins. The layers were separated. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN, 100:0 to 50:50) to afford **166** as a white solid (racemic mixture, 18 mg, 33%). UPLC/MS(ES^+): m/z 545.33 $[M+H]^+$.

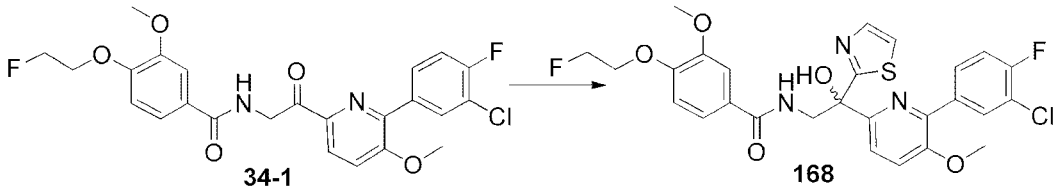
EXAMPLE 34
Preparation of Compound 167



[0364] To a stirring mixture of **33-1** (40 mg, 0.061 mmol) in THF (1.0 mL) at r.t. under argon was added a solution of MeMgBr (1.4 M) in THF (0.5 mL) dropwise. The mixture was reacted at r.t. for 1 h. The mixture was diluted with EtOAc and quenched with a sat. NH_4Cl solution. The mixture was stirred at r.t. for 10 mins and the layers were separated. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude mixture was purified via silica gel column to afford **33-2** as a white solid. LCMS: m/z 669.1 $[M+H]^+$.

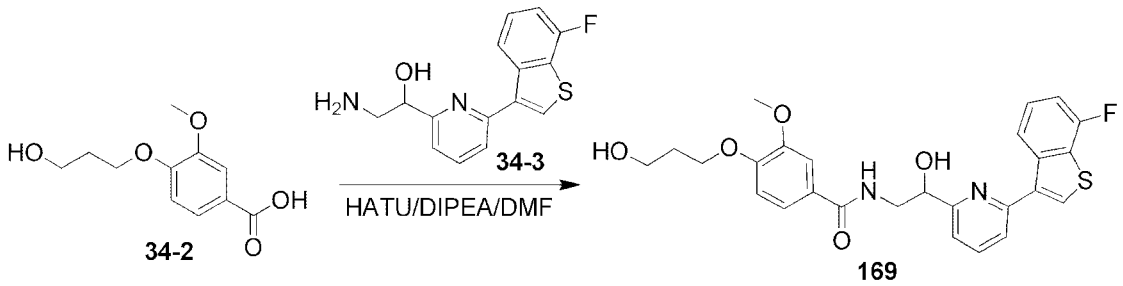
[0365] To a stirring mixture of **33-2** (20 mg, 0.0299 mmol) in DCM (1.0 mL) at r.t. was added dropwise TFA (0.2 mL). The mixture was stirred at r.t. for 10 mins and then concentrated under reduced pressure. The crude product mixture was purified via prep-HPLC to afford **167**. LCMS: m/z 549.05 $[M+H]^+$.

EXAMPLE 35
Preparation of Compound 168



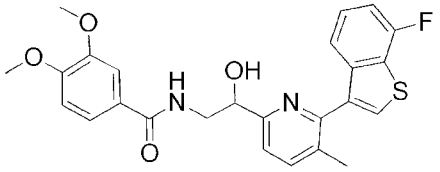
[0366] To a stirring mixture of 2-bromothiazole (0.2 g, 1.22 mmol) in THF under Ar at -78°C was added dropwise a solution of n-BuLi (2.5 M) in hexane (0.49 mL, 1.22 mmol). The mixture was stirred at -78°C for 15 mins and then a solution of **34-1** (40 mg, 0.081 mmol) in THF (0.5 mL) was added. The mixture was stirred at -78°C for 1 h and then warmed to r.t. for 10 mins. The mixture was diluted with EtOAc and quenched with a sat. NH_4Cl solution. The mixture was stirred at r.t. for 10 mins and then the layers were separated. The aqueous layer was extracted with EtOAc (2 x 15 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude mixture was purified via silica gel chromatography and further purified via prep-HPLC to afford **168** as a tan solid. LCMS: m/z 576.1 $[M+H]^+$.

EXAMPLE 36
Preparation of Compound 169



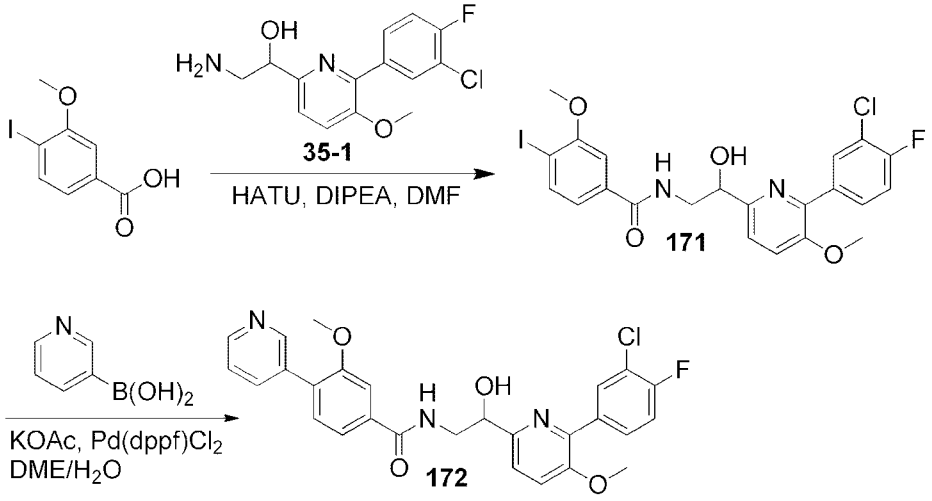
[0367] To a solution of **34-2** (100 mg, 0.442 mmol), HATU (251 mg, 0.66 mmol) and DIPEA (170 mg, 1.32 mmol) in anhydrous DMF (2 mL) was added **34-3** (127 mg 0.442 mmol) at 25°C. The solution was stirred for 10 h at r.t. and then diluted with 1.0 N aqueous $NaHCO_3$ solution (2 x 40 mL), extracted with EA (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified on a silica gel column to give **169** (120 mg, 54.8%). +ESI-MS: m/z 497.1 $[M+H]^+$.

EXAMPLE 37
Preparation of Compound 170



[0368] Compound **170** was prepared using 2,6-dichloro-3-methylpyridine, 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 3,4-dimethoxybenzoic acid, and by closely following a synthetic route, which closely follows that described for the preparation of **1**. +ESI-MS:m/z 464.9 $[M+H]^+$.

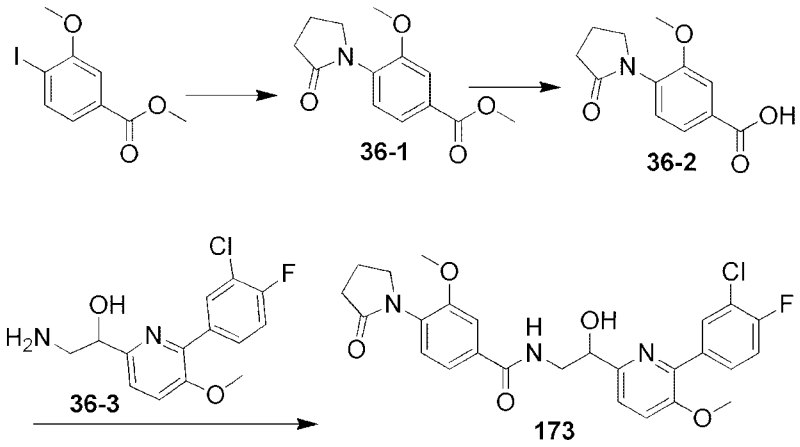
EXAMPLE 38
Preparation of Compounds 171 and 172



[0369] To a solution of 3-methoxy-4-iodobenzoic acid (0.45 g, 1.6 mmol), **35-1** (0.485 g, 1.6 mmol), HATU (0.75 g, 2.0 mmol) in DMF (3 mL) was added DIEA (0.71 mL, 4.1 mmol). The solution was stirred for 18 h at r.t. The mixture was diluted with EA. The organic phase was washed with water, 1N HCl, $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel ($MeOH/CH_2Cl_2$) to give **171** (0.176 g, 51%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (dd, J=2.15, 7.24, 1H), 7.81-7.85 (m, 1H), 7.75 (d, J=8.02, 1H), 7.37-7.42 (m, 2H), 7.26-7.27 (m, 1H), 7.25 (t, J=8.71, 1H), 6.93 (dd, J=1.96, 8.02), 6.83-6.86 (m, 1H), 4.97-4.99 (m, 1H), 3.99-4.13 (m, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.54-3.72 (m, 1H).

[0370] A solution of **171** (25 mg, 0.045 mmol), pyridine-3-boronic acid (11 mg, 0.09 mmol), potassium acetate (13 mg, 0.13 mmol) and $Pd(dppf)Cl_2$ (6 mg, 0.009 mmol) in DME (0.5 mL) and H_2O (0.05 mL) was heated under microwave irradiation for 1 h at 110°C. The mixture was concentrated and purified by chromatography on silica gel ($MeOH/CH_2Cl_2$) to give **172** (22 mg, 88%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.74-8.90 (br. s, 1H), 8.60-8.72 (br. s, 1H), 8.00, dd, J=2.15, 7.24), 7.85-7.88 (m, 2H), 7.34-7.45 (m, 5H), 7.17, (t, J=8.80, 1H), 6.94-6.97 (m, 1H), 4.98-5.01 (m, 1H), 4.00-4.09 (m, 1H), 3.88 (s, 3H), 3.82 (s, 3H0, 3.68-3.75 (m, 1H).

EXAMPLE 39
Preparation of Compound 173



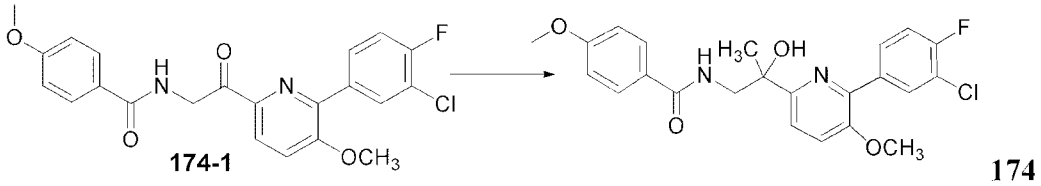
[0371] To a solution of methyl 3-methoxy-4-iodobenzoate (250 mg, 0.85 mmol) in toluene (2 mL) was added pyrrolidinone (150 mg, 1.7 mmol), potassium phosphate (0.55 g, 2.2 mmol), xantphos (25 mg, 0.43 mmol) and tris(dibenzylideneacetone)dipalladium(0) (40 mg, 0.43 mmol). The mixture was heated at 110°C for 3 h. The mixture was then diluted with EA. The organic phase was washed with water, 1N HCl, $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **36-1** (0.178 g, 83%). LCMS: m/z 478.10 $[M+H]^+$.

[0372] To a solution of **36-1** (0.178 g, 0.72 mmol) in methanol (6 mL) was added NaOH (2.0 M, 2.0 mL) at 25°C. The solution was stirred for 15 h, acidified with 2N HCl and extracted with EA. The combined organic phase was dried over anhydrous Na_2SO_4 to give **36-2** (0.152 g, 90%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, J=1.77, 8.22 Hz, 1H), 7.51 (d,

J=1.77 Hz, 1H), 7.30 (d, J=8.22 Hz, 1H), 3.82 (s, 3H), 3.75 (t, J=7.04 Hz, 2H), 2.55 (t, J=8.02 Hz, 2H), 2.0-2.3 (m, 2H).

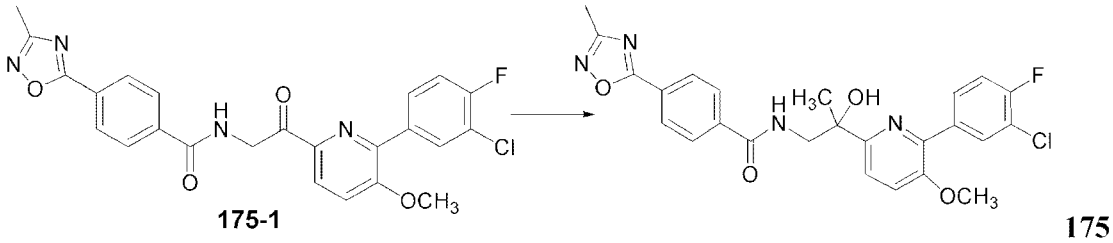
[0373] To a solution of **36-2** (0.152 g, 0.65 mmol), **36-3** (0.19 g, 0.65 mmol), HATU (0.37 g, 0.97 mmol) in DMF (1 mL) was added DIEA (0.23 mL, 1.3 mmol). The solution was stirred for 2 h at r.t. The mixture was diluted with EA. The organic phase was washed with water, 1N HCl, $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **173** (0.172 g, 51%). LCMS: m/z 478.10 $[M+H]^+$.

EXAMPLE 40
Preparation of Compound 174



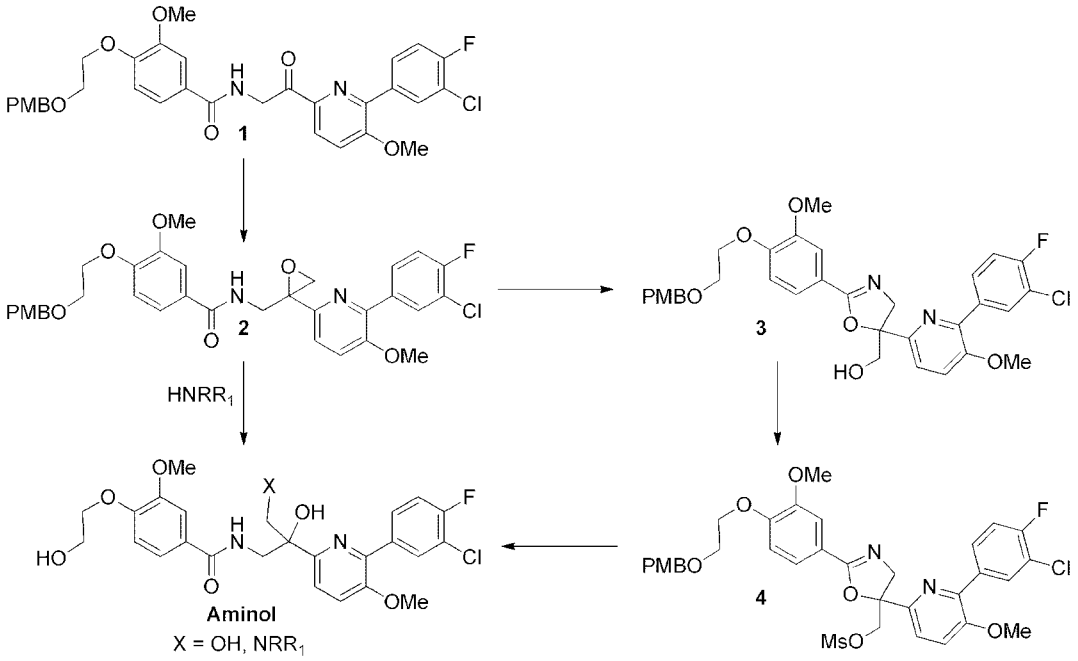
[0374] Addition of MeMgBr to **174-1** afforded **174** as a white solid (50%). UPLC/MS(ES^+): m/z 445.27 $[M+H]^+$.

EXAMPLE 41
Preparation of Compound 175



[0375] Addition of MeMgBr to **175-1** afforded **175** as a white solid (10%). UPLC/MS(ES^+): m/z 497.1 $[M+H]^+$.

EXAMPLE 42



[0376] Trimethylsulfoxonium iodide (1.19 g, 5.41 mmol) was added to a solution of potassium *tert*-butoxide (551 mg, 4.92 mmol) in DMSO (10 mL). The mixture was stirred at r.t. for 30 mins. A solution of N-{2-[6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl]-2-oxoethyl}-3-methoxy-4-{2-[(4-methoxyphenyl)methoxy]ethoxy}benzamide (**1**, 3.00 g, 4.92 mmol) in DMSO (20 mL) was added. The mixture was stirred at r.t. for 10 mins. The mixture was diluted with EtOAc and water. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure to afford the crude epoxide **2** (3.34 g). Epoxide **2**:UPLC/MS(ES^+): m/z 623.40 [$M+H^+$]. With chromatography (cyclohexane-EtOAc, 75:25 to 50:50), epoxide **2** quantitatively rearranged to oxazoline **3** (1.92 g recovered from 3 g of crude **2**). Oxazoline **3**: UPLC/MS(ES^+): m/z 623.29 [$M+H^+$].

[0377] Method A: A mixture of epoxide **2** (100 mg, crude) and an amine (10 eq.) in MeOH (1 mL) was stirred at r.t. or heated to 100 °C. When complete, the reaction was concentrated under reduced pressure. The residue was dissolved in a 10:1 DCM:TFA mixture (2.2 mL). After 30 mins of stirring at r.t., a 2M aq. NaOH solution was added. The mixture was stirred at r.t. for 10 mins. The layers were separated, and the aqueous portion

extracted with DCM. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue afforded the aminol.

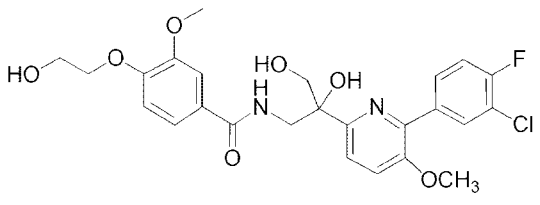
[0378] Method B: A mixture of epoxide **2** (150 mg, crude), an amine (2 eq.) and K_2CO_3 (66.0 mg, 2 eq.) in DMF (2 mL) was stirred at 50 °C. When complete, the reaction was diluted with EtOAc. The organic portion was washed twice with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in DCM (2 mL) and treated with TFA (300 uL). After 1 h, the reaction was quenched with 2M aq. NaOH solution. The layers were separated, and the organic portion was concentrated under reduced pressure. Chromatography of the residue afforded the aminol.

[0379] Method C: TEA (270 uL, 1.93 mmol) and MsCl (150 uL, 1.93 mmol) were added to a solution of **3** (600 mg, 0.964 mmol) in DCM (4 mL). The mixture was stirred at r.t. for 2 h. The mixture was poured into 1M aq. HCl solution and extracted with DCM. The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure to afford the crude mesylate **4**, which was directly used in the next step. A mixture of **4** (80 mg) and an amine (50 uL) in MeOH (2 mL) was heated to 85 °C in a sealed vial. When complete, the reaction was concentrated under reduced pressure. The residue was dissolved in MeOH (1.5 mL) and treated with a 6M aq. HCl solution (1.5 mL). The mixture was heated to 65 °C for 2 h. After cooling to r.t., the mixture was purified by reverse phase chromatography to afford the aminol.

[0380] Method D: A mixture of epoxide **2** (50 mg, crude) and an amine (10 eq.) was heated to 60 °C under microwave irradiation. When complete, the reaction was concentrated under reduced pressure. The residue was dissolved in DCM (2 mL) and treated with TFA (300 uL). After 1 h, the reaction was quenched with 2M aq. NaOH solution. The layers were separated, and the organic portion was concentrated under reduced pressure. Chromatography of the residue afforded the aminol.

EXAMPLE 43

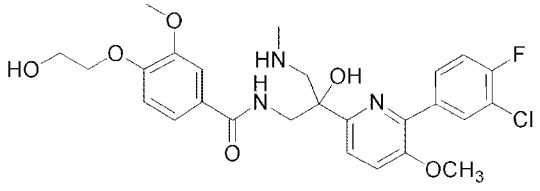
Preparation of Compound 176



176

[0381] Epoxide **2** (200 mg, crude) was dissolved in a 1:1 MeOH:6M aq. HCl solution (2 mL), and the mixture was stirred at 60 °C for 2 h. The mixture was basified with 6M aq. NaOH solution and purified by reverse phase chromatography (water:CH_3CN, 100:0 to 50:50) to afford **176** as an off-white solid (40.2 mg). UPLC/MS(ES^+): m/z 521.10 $[M+H]^+$.

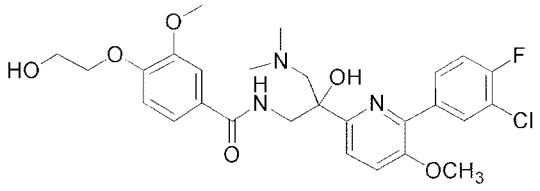
EXAMPLE 44
Preparation of Compound 177



177

[0382] Reaction of epoxide **2** with a 2M $MeNH_2$-MeOH solution followed by PMB-group removal according to Method A afforded **177** as a white solid (13% over 3 steps). UPLC/MS(ES^+): m/z 534.30 $[M+H]^+$.

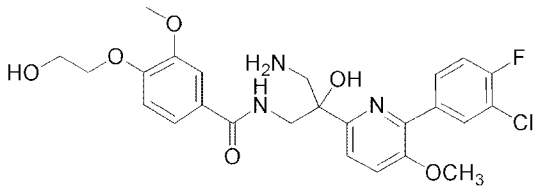
EXAMPLE 45
Preparation of Compound 178



178

[0383] Reaction of epoxide **2** with a 2M Me_2NH-MeOH solution followed by PMB-group removal according to Method A afforded **178** as a white solid (37% over 3 steps). UPLC/MS(ES^+): m/z 548.30 $[M+H]^+$.

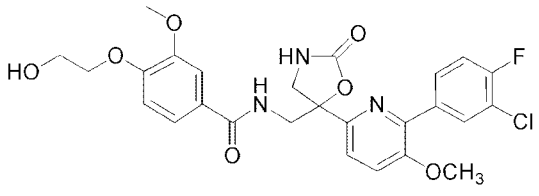
EXAMPLE 46
Preparation of Compound 179



179

[0384] Reaction of epoxide **2** with a 7M NH_3-MeOH solution followed by PMB-group removal according to Method A afforded **179** as a white solid (24% over 3 steps). UPLC/MS(ES^+): m/z 520.40 $[M+H]^+$.

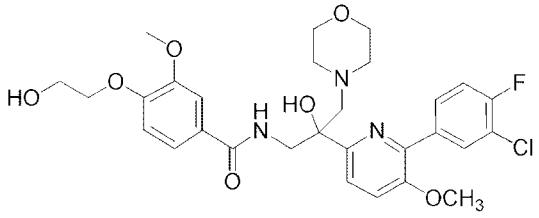
EXAMPLE 47
Preparation of Compound 180



180

[0385] A solution of **179** (10.0 mg, 0.019 mmol) and triphosgene (5.0 mg, 0.019 mmol) in a 1:1 5% aq. $NaHCO_3$:MeOH mixture (1 mL) was stirred and heated at 40 °C for 3 h. The volatiles were removed under reduced pressure to afford a 30:70 mixture of **180** and the corresponding methyl carbamate. This mixture was dissolved in DMF (0.5 mL) and treated with NaH (60% oil dispersion, 1 mg). After 30 mins, the reaction was quenched with MeOH, and the volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (0.1% HCOOH:water-0.1% HCOOH:CH_3CN, 100:0 to 30:70) to afford **180** as a white solid (4.0 mg, 39%). UPLC/MS(ES^+): m/z 546.30 $[M+H]^+$.

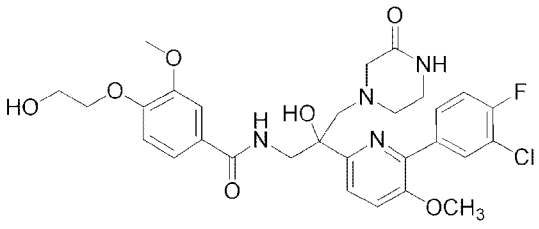
EXAMPLE 48
Preparation of Compound 181



181

[0386] Reaction of epoxide **2** with morpholine followed by PMB-group removal according to Method B afforded **181** as a white solid (10% over 3 steps). UPLC/MS(ES^+): m/z 590.40 $[M+H]^+$.

EXAMPLE 49
Preparation of Compound 182

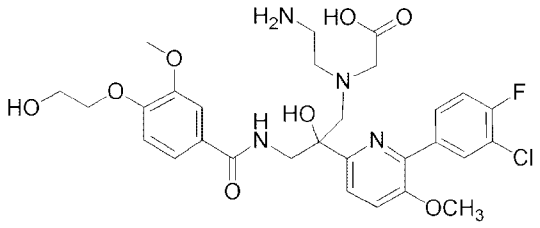


182

[0387] A mixture of epoxide **2** (100 mg, crude), ketopiperazine (80 mg, 0.80 mmol) and K_2CO_3 (155 mg, 1.13 mmol) in DMF (2 mL) was stirred at 60 °C for 18 h. The

mixture was diluted with EtOAc, and the organic portion was washed with water (2x), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH (2 mL) and treated with 3M aq. HCl solution (500 uL). The mixture was heated to 80 °C and stirred at 80 °C for 30 mins. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water-CH_3CN, 100:0 to 0:100) to afford **182** as a light yellow solid (14% over 3 steps). UPLC/MS(ES^+): m/z 603.30 $[M+H]^+$.

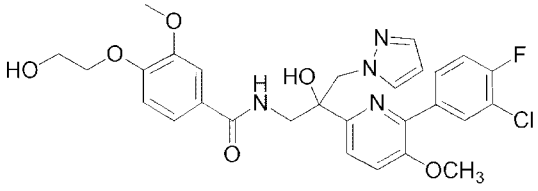
EXAMPLE 50
Preparation of Compound 183



183

[0388] Reaction of epoxide **2** with ketopiperazine followed by PMB-group removal according to Method B afforded **183** as a light yellow solid (10% over 3 steps). UPLC/MS(ES^+): m/z 621.40 $[M+H]^+$.

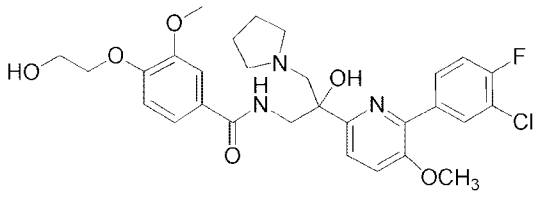
EXAMPLE 51
Preparation of Compounds 184, 185 and 186



184, 185 and 186

[0389] Reaction of epoxide **2** with pyrazole followed by PMB-group removal according to Method B afforded **184** as a racemic mixture (32% over 3 steps). This mixture was resolved by using a prep-HPLC separation [Chiralpak AD-H (25 x 2.0 cm), 5 μM; mobile phase: Ethanol + 0.1% isopropylamine 30%, flow rate: 46 mL/min, UV detection DAD 220 nm] to afford the two separated enantiomers **185** (t_R= 11.0 min) and **186** (t_R= 12.5 min). Analytical data for the single enantiomers: white solid. UPLC/MS(ES^+): m/z 571.36 $[M+H]^+$.

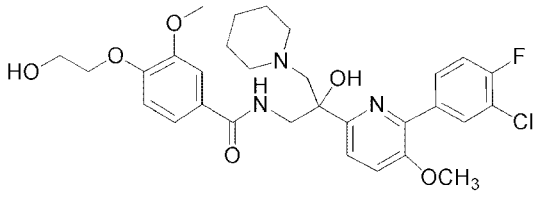
EXAMPLE 52
Preparation of Compound 187



187

[0390] Reaction of mesylate **4** with pyrrolidine followed by PMB-group removal according to Method C afforded **187** as a white solid (55% over 3 steps). UPLC/MS(ES^+): m/z 574.20 $[M+H]^+$.

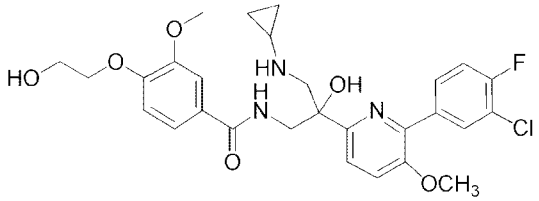
EXAMPLE 53
Preparation of Compound 188



188

[0391] Reaction of mesylate **4** with piperidine followed by PMB-group removal according to Method C afforded **188** as a white solid (6% over 3 steps). UPLC/MS(ES^+): m/z 588.20 $[M+H]^+$.

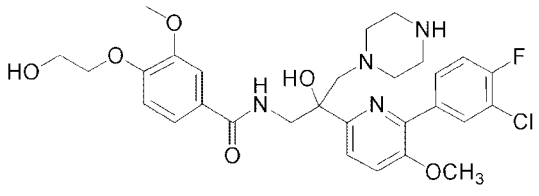
EXAMPLE 54
Preparation of Compound 189



189

[0392] Reaction of epoxide **2** with cyclopropylamine followed by PMB-group removal according to Method D afforded **189** as a white solid (11% over 3 steps). UPLC/MS(ES^+): m/z 560.10 $[M+H]^+$.

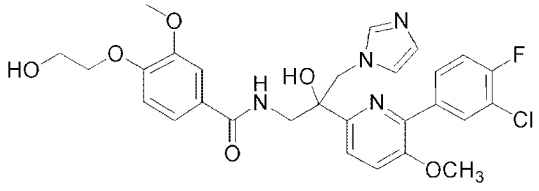
EXAMPLE 55
Preparation of Compound 190



190

[0393] Reaction of epoxide **2** with 1-Boc-piperazine followed by PMB-group removal according to Method C afforded **190** (17% over 3 steps). UPLC/MS(ES^+): m/z 589.30 $[M+H]^+$.

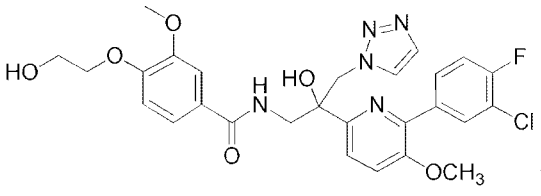
EXAMPLE 56
Preparation of Compound 191



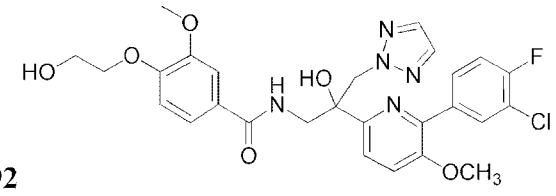
191

[0394] Reaction of epoxide **2** with imidazole followed by PMB-group removal according to Method B afforded **191** as a white solid (12% over 3 steps). UPLC/MS(ES^+): m/z 571.30 $[M+H]^+$.

EXAMPLE 57
Preparation of Compounds 192 and 193



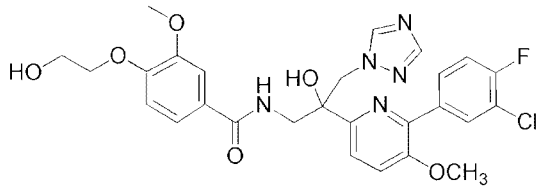
192



193

[0395] Reaction of epoxide **2** with 1H-1,2,3-triazole followed by PMB-group removal according to Method B afforded compounds **192** (10% over 3 steps) and **193** (18% over 3 steps). **192**: UPLC/MS(ES^+): m/z 572.30 $[M+H]^+$. **193**: UPLC/MS(ES^+): m/z 572.30 $[M+H]^+$.

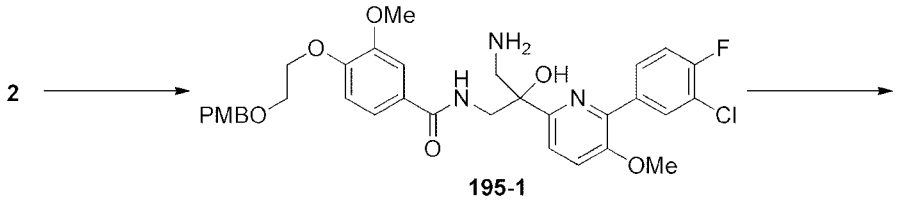
EXAMPLE 58
Preparation of Compound 194



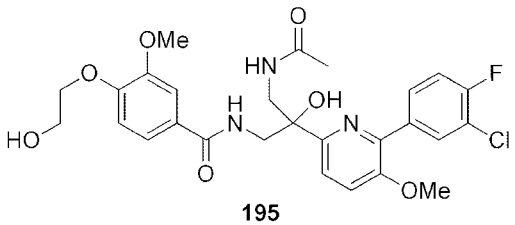
194

[0396] Reaction of epoxide **2** with 1H-1,2,4-triazole followed by PMB-group removal according to Method B afforded compound **194** (24% over 3 steps). UPLC/MS(ES$^+$): m/z 572.30 $[M+H]^+$.

EXAMPLE 59
Preparation of Compound 195



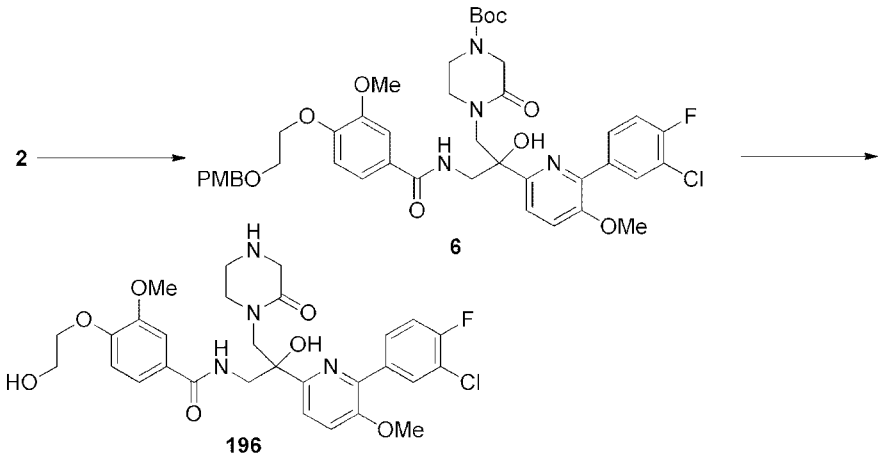
195-1



195

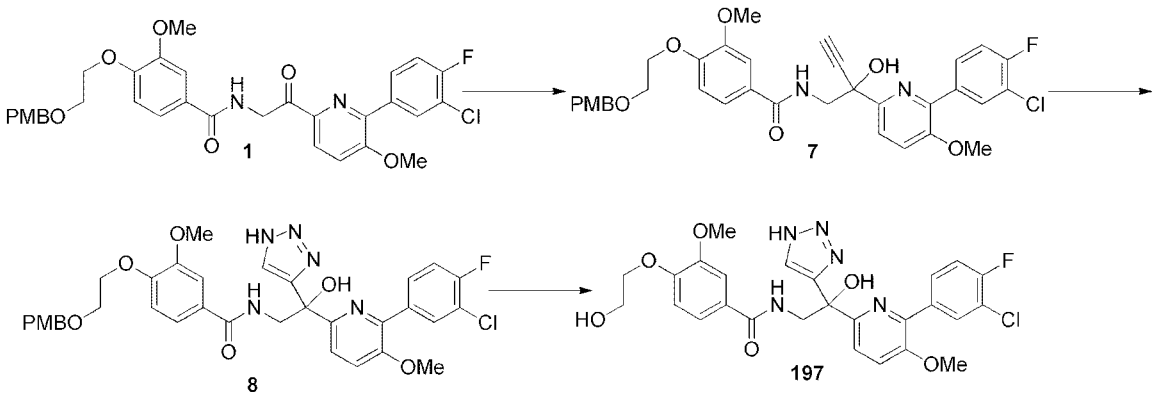
[0397] A mixture of epoxide **2** (80 mg, crude) and 7M NH_3-MeOH (1.5 mL) in MeOH (2 mL) was stirred at r.t. for 18 h. The volatiles were removed under reduced pressure. The resulting crude **195-1** was dissolved in DCM (1 mL) and treated with TEA (15 uL) and AcCl (11 uL). The mixture was stirred at r.t. for 1 h. The volatiles were removed under reduced pressure. Deprotection of the PMB-ether using TFA:DCM afforded **195** as a white solid (7% overall). UPLC/MS(ES$^+$): m/z 562.30 $[M+H]^+$.

EXAMPLE 60
Preparation of Compound 196



[0398] *n*-BuLi (1.6M solution in hexanes, 650 μL, 1.04 mmol) was added to a suspension of tert-butyl 3-oxopiperazine-1-carboxylate (160 mg, 0.800 mmol) in dry THF (2 mL), which had been pre-cooled to 0 °C. The mixture was stirred for 5 mins at 0 °C and then warmed to r.t. After 5 mins, a solution of epoxide 2 (200 mg, crude) in THF (1 mL) was added. The mixture was heated to 50 °C and stirred at 50 °C for 12 h. Water and EtOAc were added. The layers were separated, and the aqueous portion was extracted with EtOA. The combined organic portions were dried with Na2SO4 and filtered. The volatiles were removed under reduced pressure. The crude 6 was dissolved in MeOH (5 mL) and treated with 6M aq. HCl solution (2 mL). The mixture was heated to 60 °C and stirred at 60 °C for 1.5 h. A majority of the volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 40:60) to afford **196** as a white solid (31 mg, 16% over 3 steps). UPLC/MS(ES^+): m/z 603.30 $[M+H]^+$.

EXAMPLE 61
Preparation of Compound 197



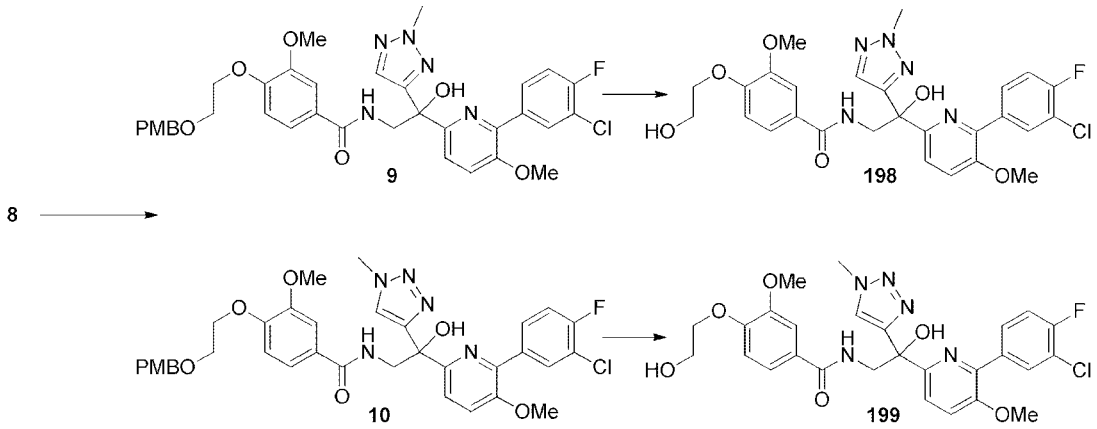
[0399] Bromo(ethynyl)magnesium (4.90 mL, 2.46 mmol) was added to a solution of **1** (300 mg, 0.493 mmol) in THF (15 mL), which had been warmed to 55 °C. The mixture was stirred for 30 mins and quenched with sat. aq. NH4Cl solution. The aqueous portion was extracted with EtOAc (2x). The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (DCM:EtOAc, 100:0 to 80:20) afforded **7** as a light yellow solid (130 mg, 41%). UPLC/MS(ES+): m/z 635.20 $[M+H]^+$.

[0400] A mixture of aq formaldehyde (37% solution, 630 uL, 0.780 mmol) and glacial AcOH (7 uL, 0.117 mmol) in THF (500 uL) was stirred at r.t. for 15 mins. Sodium azide (7.6 mg, 0.117 mmol) and 7 (50.0 mg, 0.078 mmol) were sequentially added. After 10 mins, aq. sodium ascorbate (0.5 M solution, 32 uL, 0.016 mmol) and $CuSO_4$ (1.2 mg, 0.008 mmol) were added. The mixture was stirred at r.t. for 18 h. The volatiles were removed under reduced pressure. The residue was treated with a 3:1 MeOH:2N aq NaOH solution (4 mL), and the mixture was stirred at r.t. for 18 h. The volatiles were removed under reduced pressure, and the residue was partitioned between EtOAc and water. The layers were separated, and the organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **8** (34 mg), which was used in next step without further purification. UPLC/MS(ES^+): m/z 678.25 $[M+H]^+$.

[0401] A solution of **8** (34 mg) in 10:1 DCM-TFA (5 mL) was stirred at r.t. for 20 mins. The reaction was quenched with 2M aq. NaOH solution. The layers were separated, and the organic portion was concentrated under reduced pressure. The residue was purified

by reverse phase chromatography (water:CH_3CN, 95:5 to 0:100) to afford **197** as a white solid (5.5 mg, 13% over 2 steps). UPLC/MS(ES^+): m/z 558.11 $[M+H]^+$.

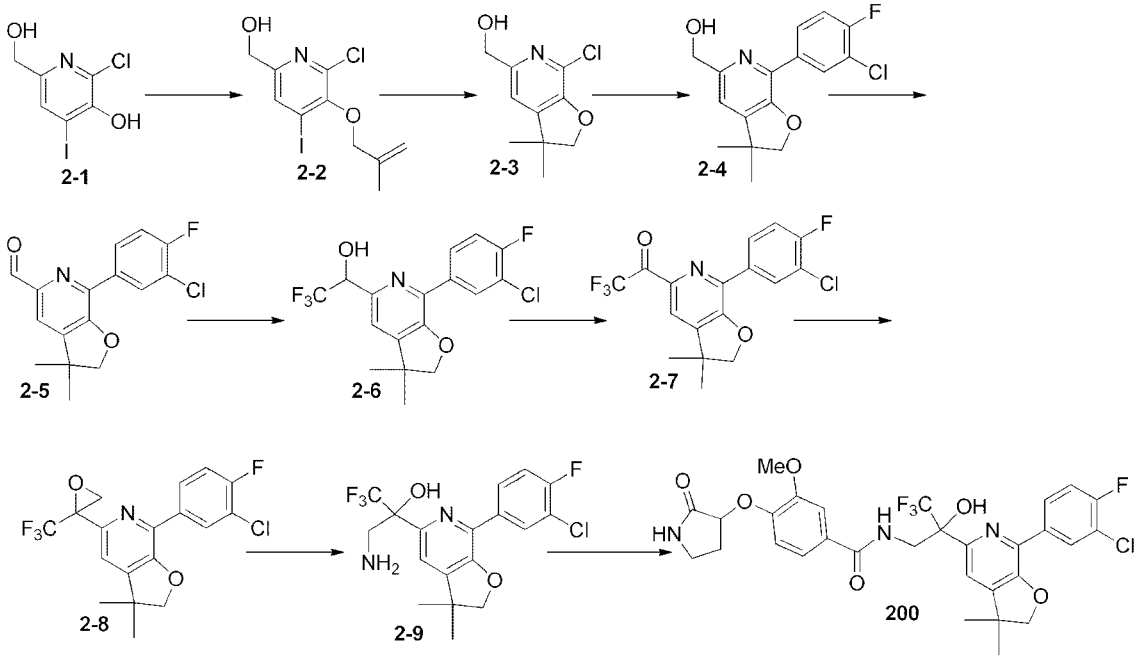
EXAMPLE 62
Preparation of Compounds 198 and 199



[0402] Potassium carbonate (40.0 mg, 0.295 mmol) and MeI (20.0 mg, 0.141 mmol) were added to a solution of **8** (80.0 mg, 0.118 mmol) in CH_3CN (4 mL). The mixture was stirred at r.t. for 4 h, diluted with water and extracted with EtOAc (3x). The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (DCM:EtOAc, 70:30 to 0:100) afforded the two separated regioisomers **9** (21 mg, 25%) and **10** (24 mg, 29%). **9**: UPLC/MS(ES+): m/z 692.29 $[M+H]^+$. **10**: UPLC/MS(ES+): m/z 692.28 $[M+H]^+$.

[0403] General procedure for PMB-removal: A solution of PMB-ether (0.1 mmol) in 10:1 DCM:TFA (3 mL) was stirred at r.t. for 30 mins. The reaction was quenched with 2M aq. NaOH solution. The layers were separated, and the organic portion was concentrated under reduced pressure. Chromatography of the residue (EtOAc:MeOH, 100:0 to 90:10) afforded the product. **198**. (derived from **9**) UPLC/MS(ES^+): m/z 572.38 $[M+H]^+$. **199**: (derived from **10**) UPLC/MS(ES^+): m/z 572.43 $[M+H]^+$.

EXAMPLE 63
Preparation of Compounds 200, 201, 202, 203 and 204



[0404] Sodium hydride (1.80 g, 44.7 mmol) was added to a stirred solution of **2-1** (11.6 g, 40.7 mmol) in dry DMF (75 mL), which had been pre-cooled to 0° C. The mixture was stirred at 0° C for 10 mins, and then warmed to r.t. The mixture was then stirred for 30 mins. The reaction was cooled to 0° C and 3-bromo-2-methylprop-1-ene (5.70 g, 42.7 mmol) was added dropwise. The mixture was allowed to gradually reach r.t., and stirring was continued for 20 h. EtOAc and sat. aq. NH_4Cl solution were added. The layers were separated, and the organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **2-2** (12.1 g, 87%). UPLC/MS(ES^+): m/z 339.80 $[M+H]^+$.

[0405] A mixture of **2-2** (12.0 g, 35.4 mmol), sodium formate (2.70 g, 40.7 mmol), tetrabutylammonium chloride (9.80 g, 35.4 mmol), $Pd(OAc)_2$ (396 mg , 1.7 mmol) and TEA (14.7 mL, 106 mmol) in dry DMF (300 mL) was degassed and heated to 100 °C for 3 h. EtOAc and sat. aq. NH_4Cl solution were added. The layers were separated, and the organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **2-3** as a pale yellow wax (6.15 g, 81%). UPLC/MS(ES^+): m/z 213.91 $[M+H]^+$.

[0406] A mixture of **2-3** (1.80 g, 8.45 mmol), (3-chloro-4-fluorophenyl)boronic acid (2.94 g, 16.9 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (618 mg, 0.84 mmol) and aq. Na_2CO_3 (2M solution, 8.45 mL, 16.9 mmol) in DCE (80 mL) was degassed and heated to 100 °C under microwave irradiation. Water and DCM were added. The layers were separated, and the organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **2-4** as a white solid (1.97 g, 76%). UPLC/MS(ES^+): m/z 307.18 $[M+H]^+$.

[0407] Dess-Martin periodinane (6.8 g, 16.0 mmol) was added to a stirred solution of **2-4** (1.97 g, 6.40 mmol) in dry DCM (28 mL). The mixture was stirred at r.t. under N_2 atmosphere for 1 h. The reaction was quenched with a 1:1 2M aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$ solution (30 mL), the mixture was vigorously stirred for 30 mins. The layers were separated, and the organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc 100:0 to 70:30) afforded **2-5** as a white solid (1.40 g, 72%). UPLC/MS(ES^+): m/z 306.15 $[M+H]^+$.

[0408] $TMSCF_3$ (810 uL, 5.50 mmol) was added to a solution of **2-5** (1.40 g, 4.60 mmol) in dry DCM (25 mL). The mixture was cooled 0 °C and TBAF (1M sol in THF, 5.5 mL, 5.50 mmol) was added dropwise. The mixture was allowed to gradually reach r.t. and stirring was continued for 1 h. Water and DCM were added. The layers were separated, and the organic portion was dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc 100:0 to 80:20) afforded **2-6** (1.43 g, 82%). UPLC/MS(ES^+): m/z 376.16 $[M+H]^+$.

[0409] Dess-Martin periodinane (3.25 g, 7.68 mmol) was added to a stirred solution of **2-6** (1.43 g, 3.84 mmol) in dry DCM (17 mL). The mixture was stirred at r.t. for 1 h. A 1:1 2M aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$ solution was added. The mixture was stirred at r.t. for 30 mins. The layers were separated, and the aqueous portion was extracted with DCM (2x). The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc 100:0 to 70:30) afforded **2-7** as a white solid (1.20 g, 84%). UPLC/MS(ES^+): m/z 392.16 $[M+H_3O]^+$

[0410] Trimethylsulfoxonium iodide (695 mg, 3.16 mmol) was added to a solution of potassium *tert*-butoxide (354 mg, 3.16 mmol) in DMSO (6 mL). The mixture was stirred at r.t. for 30 mins. A solution of **2-7** (1.18 g, 3.16 mmol) in DMSO (20 mL) was added, and the mixture was stirred at r.t. for 30 mins. EtOAc and water were added, and the layers were separated. The aqueous portion was extracted with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc 100:0 to 70:30) afforded **2-8** as a colourless wax (530 mg, 43%). UPLC/MS(ES^+): m/z 388.18 $[M+H]^+$.

[0411] A solution of **2-8** (530 mg, 1.37 mmol) in 7M NH_3-MeOH (50 mL) was stirred at 45 °C for 1 h. The volatiles were removed under reduced pressure. The crude was purified by reverse phase chromatography (water:CH_3CN 95:5 to 0:100) to afford **2-9** as a white solid (498 mg, 90%). UPLC/MS(ES^+): m/z 405.21 $[M+H]^+$.

[0412] Racemate **2-9** was resolved by using a prep-HPLC separation [Chiralpak AD-H (25 x 3 cm, 5 um), mobile phase: n-Hexane/(EtOH/MeOH+0.1% ipa) 96/4 % v/v, flow rate: 32 mL/min, UV detection DAD 220 nm] to obtain the two separated enantiomers **2-9a** (t_R=10.9 min) and **2-9b** (t_R=14.5 min). UPLC and ^1H NMR analyses for the two enantiomers were superimposible.

[0413] General amide coupling conditions-Method A: A mixture of **2-9** (50.0 mg, 0.124 mmol), EDC (31.0 mg, 0.161 mmol), HOBT (22.0 mg, 0.161 mmol) and acid (0.124 mmol) in DCM:DMF (5:1, 6 mL) was stirred at 45 °C for 2 h. DCM was added. The organic portion was washed with sat. aq. NH_4Cl solution and brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue afforded the product.

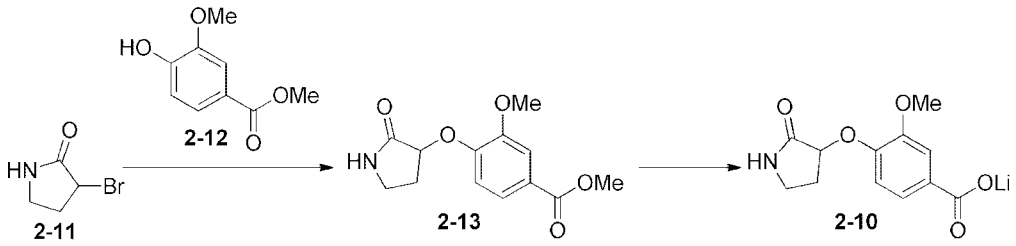
[0414] General amide coupling conditions-Method B: DIPEA (281 uL, 1.62 mmol) was added to a solution of acid (1.06 mmol) and HATU (461 mg, 1.21 mmol) in dry DMF (5 mL). After 20 mins, a solution of **2-9** (330 mg, 0.81 mmol) in DMF (5 mL) was added. The mixture was stirred at r.t. until complete. EtOAc and sat. aq. NH_4Cl solution were added. The layers were separated, and the aqueous portion was extracted with EtOAc.

The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue afforded the product.

[0415] Coupling of **2-9** with acid **2-10** according to Method A afforded **200** as a white solid (30%, mixture of 4 isomers). UPLC/MS(ES+): m/z 638.18 $[M+H]^+$. Racemate **200** was resolved by using a prep-HPLC separation [Chiralpak AD-H (25 x 2 cm, 5 um), mobile phase: Ethanol+0.1% isopropylamine 20% v/v, flow rate: 45 mL/min, UV detection DAD 220 nm] to obtain the four separated isomers **201** (t_R=12.9 min), **203** (t_R=14.8 min), **202** (t_R=16.6 min) and **204** (t_R=23.6 min).

[0416] Alternatively, **2-9a** and **2-9b** were separately coupled with **2-10** according to Method B. Each diastereomeric mixture was resolved by chiral HPLC. **2-9a** provided a mixture of **204** (t_R=6.5 min) and **202** (t_R=14.1 min) [Whelk O1 (R,R) (25 x 2.0 cm), 5 μ, mobile phase: n-Hexane/(Ethanol+0.1% isopropylamine) 30/70 % v/v, flow rate: 17 mL/min, UV detection DAD 220 nm]. **2-9b** provided a mixture of **201** and **203** (t_R 6.4 min and 12.3 min) [Whelk O1 (R,R) (25 x 2.0 cm), 5 μ, mobile phase: n-Hexane/(Ethanol+0.1% isopropylamine) 30/70 % v/v, flow rate: 17 mL/min, UV detection DAD 220 nm].

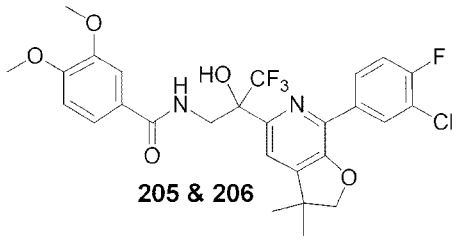
EXAMPLE 64
Preparation of 2-10



[0417] Compound **2-12** (4.86 g, 26.7 mmol) was added to a stirring suspension of cesium carbonate (15.4 g, 47.5 mmol) in DCM (120 mL). A solution of **2-11** (3.13 g, 19.0 mmol) in DCM (20 mL) was added. The mixture was stirred at r.t. for 5 h. The mixturew was filtered through a pad of Celite, washed thoroughly with DCM and concentrated. The residue was dissolved in EtOAc. The organic portion was washed with water and brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc 100:0 to 0:100) afforded **2-13** as a white solid (4.50 g, 89%). UPLC/MS(ES^+): m/z 266.15 $[M+H]^+$.

[0418] Lithium hydroxide monohydrate (258 mg, 6.10 mmol) was added to a suspension of **2-13** (1.50 g, 5.60 mmol) in a 1:1:6 THF:MeOH:H_2O mixture (40 mL). The mixture was stirred at r.t. for 3 h, loaded on a reverse phase cartridge and eluted with water to afford **2-10** as a white solid (1.10 g, 78%). UPLC/MS(ES^+): m/z 252.13 $[M+H]^+$.

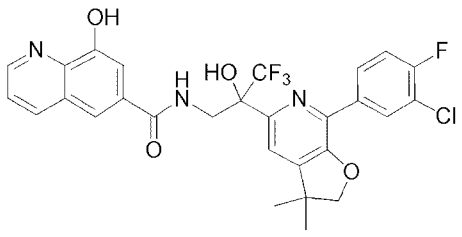
EXAMPLE 65
Preparation of Compounds 205 and 206



205 & 206

[0419] Coupling of **2-9a** with 3,4-dimethoxybenzoic acid according to Method A afforded **205** as a white solid (51%). UPLC/MS(ES^+): m/z 569.40 $[M+H]^+$. Using **2-9b** and 3,4-dimethoxybenzoic acid according to Method A afforded **206** as a white solid (50%). UPLC/MS(ES^+): m/z 569.40 $[M+H]^+$.

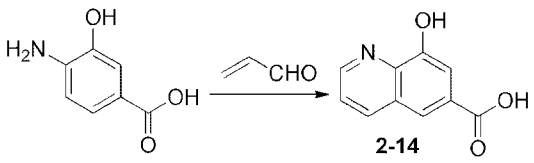
EXAMPLE 66
Preparation of Compounds 207



207

[0420] Coupling of **2-9** with **2-14** according to Method A afforded **207** as a white solid (43%). UPLC/MS(ES^+): m/z 576.32 $[M+H]^+$.

EXAMPLE 67
Preparation of 2-14

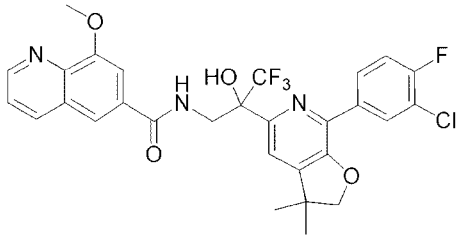


2-14

[0421] Acrolein (21.8 mL, 326 mmol) was added to a mixture of 4-amino-3-hydroxybenzoic acid (5.00 g, 33.0 mmol) in 12 N aq. HCl solution (50 mL). The mixture was refluxed for 1 h. After cooling to r.t., the mixture was concentrated under reduced

pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 50:50) to afford **2-14** (561 mg, 9%). UPLC/MS(ES^+): m/z 190.04 $[M+H]^+$.

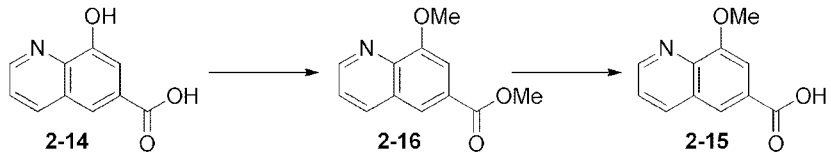
EXAMPLE 68
Preparation of Compound 208



208

[0422] Coupling of **2-9** with **2-15** according to Method A afforded **208** as a white solid (67%). UPLC/MS(ES^+): m/z 590.25 $[M+H]^+$.

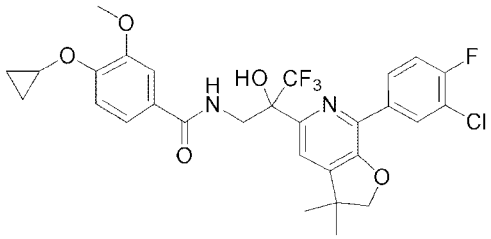
EXAMPLE 69
Preparation of 2-15



2-14 **2-16** **2-15**

[0423] Cesium carbonate (2.58 g, 7.92 mmol) and MeI (822 uL, 13.2 mmol) were sequentially added to a solution of **2-14** (500 mg, 2.64 mmol) in DMF (30 mL). The mixture was stirred at r.t. for 18 h. EtOAc was added. The organic portion was washed with 2M aq. HCl solution and water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Crude **2-16** was dissolved in a 2:1:1 THF:MeOH:H_2O mixture (8 mL). Lithium hydroxide monohydrate (332 mg, 7.92 mmol) was added, and the mixture was stirred at r.t. for 1 h. The volatiles were removed under reduced pressure. The residue was dissolved in water, and the pH of the solution was adjusted to 6 with 1M aq. HCl solution. The aqueous portion was extracted with DCM (2x). The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-15** (227 mg), which was used in the next step without further purification. UPLC/MS(ES^+): m/z 204.10 $[M+H]^+$.

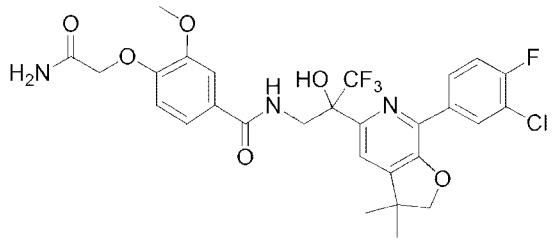
EXAMPLE 70
Preparation of Compound 209



209

[0424] Coupling of **2-9** with 4-cyclopropoxy-3-methoxybenzoic acid according to Method A afforded **209** as a white solid (41%). UPLC/MS(ES^+): m/z 595.30 $[M+H]^+$.

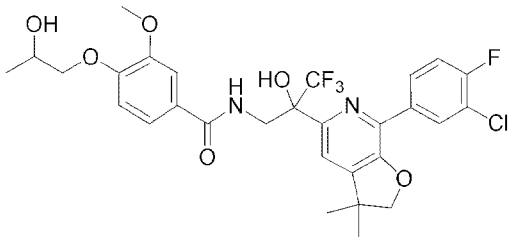
EXAMPLE 71
Preparation of Compound 210



210

[0425] Coupling of **2-9** with 4-(carbamoylmethoxy)-3-methoxybenzoic acid according to Method B afforded **210** as a white solid (51%). UPLC/MS(ES^+): m/z: 612.21 $[M+H]^+$.

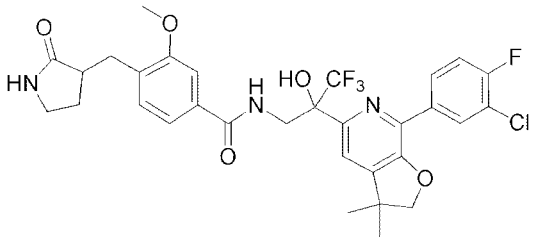
EXAMPLE 72
Preparation of Compound 211



211

[0426] Coupling of **2-9** with 4-[(2R)-2-hydroxypropoxy]-3-methoxybenzoic acid according to Method B afforded **211** as a white solid (45%). UPLC/MS(ES^+): m/z 613.27 $[M+H]^+$.

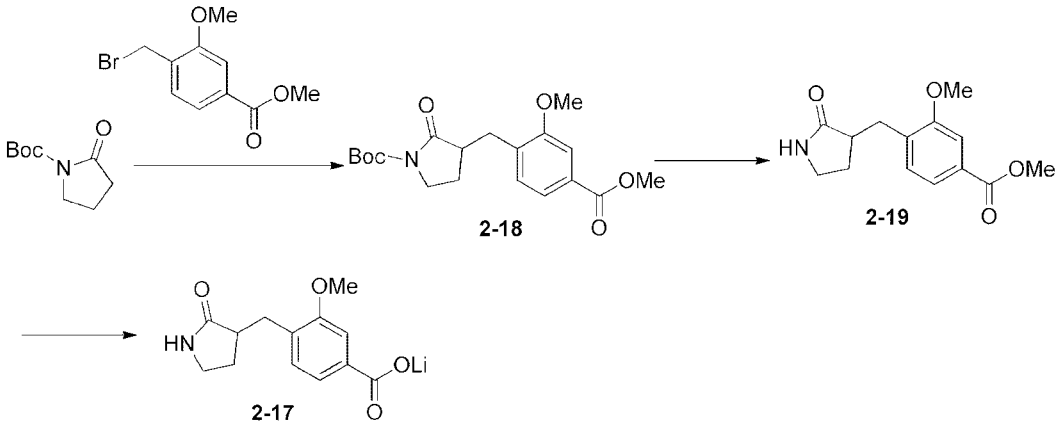
EXAMPLE 73
Preparation of Compound 212



212

[0427] Coupling of **2-9** with **2-17** according to Method B afforded **212** as a white solid (33%). UPLC/MS(ES^+): m/z 636.00 $[M+H]^+$.

EXAMPLE 74
Preparation of 2-17



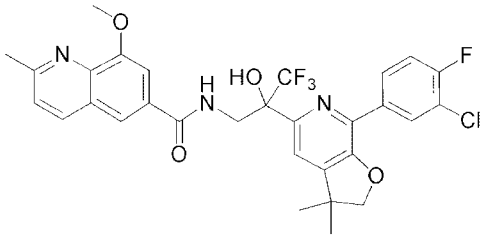
[0428] LDA (2M solution in THF, 1.05 mL, 2.10 mmol) was added to a stirred solution of 1-(tert-butoxycarbonyl)-2-pyrrolidinone (276 uL, 1.62 mmol) in THF (1 mL), which had been pre-cooled to -78 °C. After 15 mins, a solution of methyl 4-(bromomethyl)-3-methoxybenzoate (460 mg, 1.78 mmol) in THF (1 mL) was added dropwise to the mixture and stirring at 78 °C was continued for 1 h. The reaction was quenched with water. The aqueous portion was extracted with EtOAc (2x). The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc 70:30) afforded **2-18** (199 mg, 34%). UPLC/MS(ES^+): m/z 364.20 $[M+H]^+$.

[0429] A solution of **2-18** (199 mg, 0.547 mmol) in 5:1 DCM:TFA (3 mL) was stirred at r.t. for 5 mins. The mixture was diluted with DCM. The organic portion was washed with a sat. aq. $NaHCO_3$ solution, dried with Na_2SO_4, filtered and concentrated under

reduced pressure. The residue was purified by reverse phase chromatography (0.1% HCOOH:water:0.1% HCOOH:CH_3CN 100:0 to 0:100) to afford **2-19**.

[0430] Compound **2-19** was dissolved in a 2:1:1 THF:MeOH:H_2O mixture (10 mL). Lithium hydroxide monohydrate (45 mg, 1.10 mmol) was added. The mixture was stirred at r.t. for 2 h. The volatiles were removed under reduced pressure to afford crude **2-17**, which was directly used in the next step without further purification. UPLC/MS(ES^+): m/z 250.20 $[M+H]^+$.

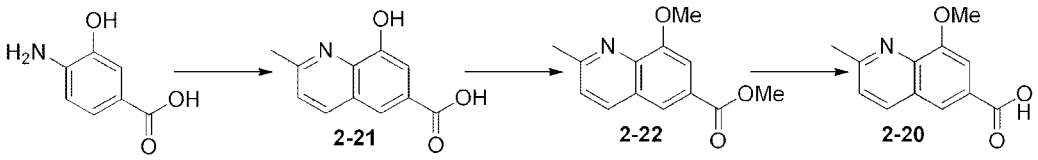
EXAMPLE 75
Preparation of Compound 213



213

[0431] Coupling of **2-9** with **2-20** according to Method B afforded **213** as a white solid (73%). UPLC/MS(ES^+): m/z 604.00 $[M+H]^+$.

EXAMPLE 76
Preparation of 2-20



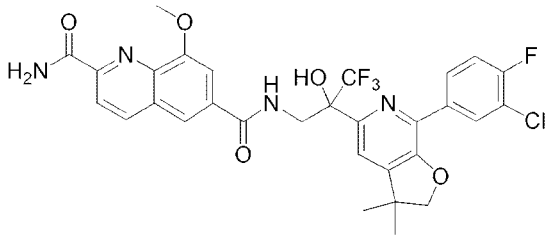
[0432] Crotonaldehyde (4.01 g, 48.9 mmol) was added dropwise to a mixture of 4-amino-3-hydroxybenzoic acid (5.00 g, 33.1 mmol) and 6M aq. HCl solution (60 mL, 360 mmol). The mixture was refluxed for 18 h. After cooling to r.t. a precipitate formed. The solid was filtered off, dried and collected. Acid **2-21** (3.44 g) was used in the next step without further purification. UPLC/MS(ES^+): m/z 204.10 $[M+H]^+$.

[0433] Cesium carbonate (15.8 g, 48.6 mmol) and MeI (5.88 mL, 94.5 mmol) were sequentially added to a solution of **2-21** (3.04 g) in DMF (80 mL). The mixture was stirred at r.t. for 12 h. DMF was removed under reduced pressure, and the residue was taken up with EtOAc. The organic portion was washed with water, dried with Na_2SO_4, filtered and

concentrated under reduced pressure to afford crude **2-22** (2.76 g), which was used in the next step without further purification. UPLC/MS(ES$^+$): m/z 232.10 $[M+H]^+$.

[0434] Lithium hydroxide monohydrate (0.272 g, 6.49 mmol) was added to a stirred suspension of **2-22** (500 mg, 2.16 mmol) in a 2:1:2 THF:MeOH:H_2O mixture. The mixture was stirred at r.t. for 3 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **2-20** (291 mg). UPLC/MS(ES$^+$): m/z 218.10 $[M+H]^+$.

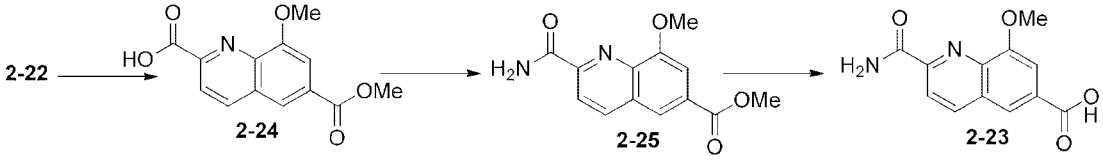
EXAMPLE 77
Preparation of Compound 214



214

[0435] Coupling of **2-9** with **2-23** according to Method B afforded **214** as a white solid (49%). UPLC/MS(ES$^+$): m/z 633.26 $[M+H]^+$.

EXAMPLE 78
Preparation of 2-23

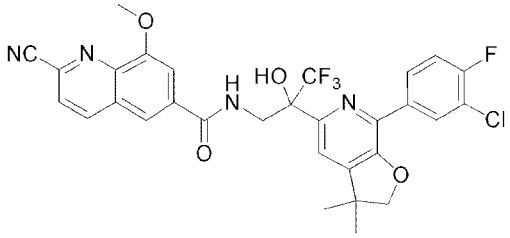


[0436] Ester **2-22** (1.50 g, 6.48 mmol) was added to a suspension of selenium dioxide (1.44 g, 13.0 mmol) in pyridine (24 mL). The mixture was refluxed for 3 h. The volatiles were removed under reduced pressure, and the residue was triturated with EtOAc. The solid was dried and collected to provide **2-24** (595 mg, 35%). UPLC/MS(ES$^+$): m/z 262.10 $[M+H]^+$.

[0437] Oxalyl chloride (100 uL, 1.14 mmol) and DMF (1 drop) were added to a solution of **2-24** (230 mg, 0.880 mmol) in DCM (7 mL). The mixture was stirred at r.t. for 30 mins. HMDS (400 uL, 1.89 mmol) and then MeOH were added. The mixture was concentrated under reduced pressure. Chromatography of the residue (EtOAc-DCM, 100:0 to 0:100) afforded **2-25**. UPLC/MS(ES$^+$): m/z 261.10 $[M+H]^+$.

[0438] Lithium hydroxide monohydrate (44.0 mg, 1.05 mmol) was added to a stirred suspension of **2-25** (91.0 mg, 0.350 mmol) in a 2:1:2 THF:MeOH:H_2O mixture. The mixture was stirred at r.t. for 2 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **2-23** (76 mg, 89%). UPLC/MS(ES^+): m/z 247.20 $[M+H]^+$.

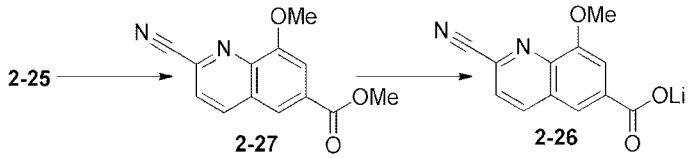
EXAMPLE 79
Preparation of Compound 215



215

[0439] Coupling of **2-9** with **2-26** according to Method B afforded **215** as a white solid (41%). UPLC/MS(ES^+): m/z 615.26 $[M+H]^+$.

EXAMPLE 80
Preparation of 2-26

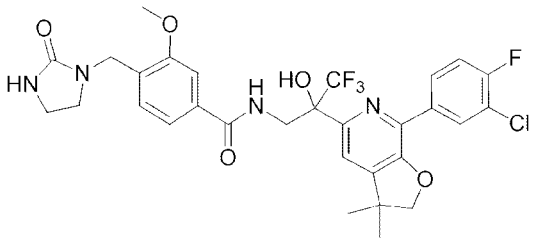


[0440] $SOCl_2$ (420 uL, 5.76 mmol) and TEA (800 uL, 5.76 mmol) were added to a solution of **2-25** (150 mg, 0.576 mmol) in DCE (10 mL), which had been pre-cooled to 0 °C. The mixture was stirred at 0 °C for 3 h. The reaction was quenched with a sat. aq. $NaHCO_3$ solution. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **2-27** (100 mg, 71%). UPLC/MS(ES^+): m/z 243.18 $[M+H]^+$.

[0441] Lithium hydroxide monohydrate (21.0 mg, 0.49 mmol) was added to a stirred suspension of **2-27** (100 mg, 0.413 mmol) in a 2:2:1 THF:MeOH:H_2O mixture (10 mL). The mixture was stirred at r.t. for 2 h. The volatiles were removed under reduced

pressure. Crude **2-26** was used in the next step without further purification. UPLC/MS(ES$^+$): m/z 229.14 $[M+H]^+$.

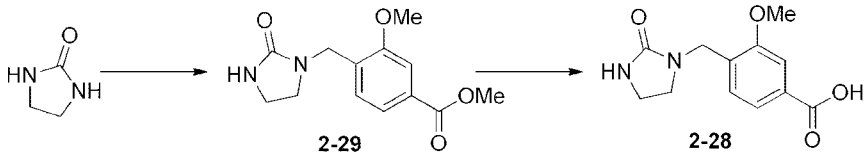
EXAMPLE 81
Preparation of Compound 216



216

[0442] Coupling of **2-9** with **2-28** according to Method B afforded **216** as a white solid (46%). UPLC/MS(ES$^+$): m/z 637.30 $[M+H]^+$.

EXAMPLE 82
Preparation of 2-28

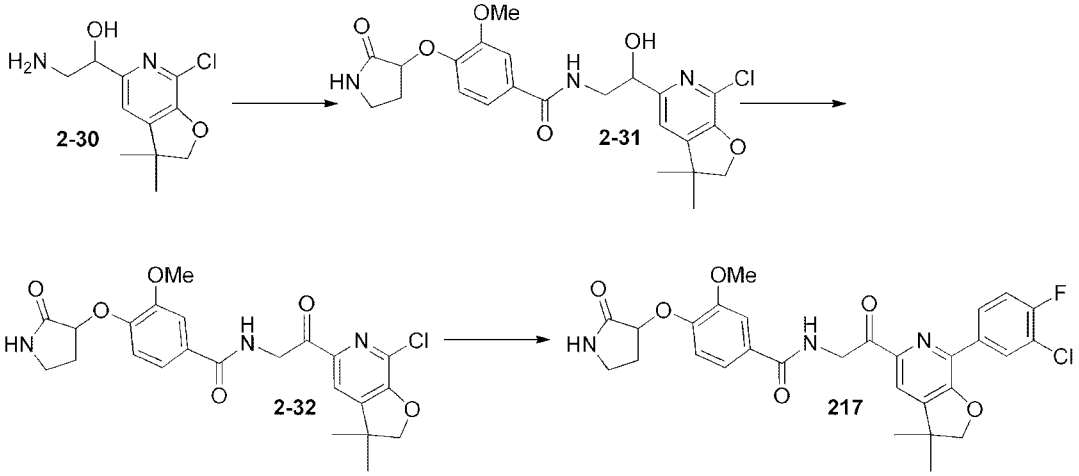


2-29 **2-28**

[0443] NaH (153 mg, 3.83 mmol) was added to a solution of imidazolidin-2-one (300 mg, 3.48 mmol) in THF (3 mL), which had been pre-cooled to 0 °C. After 1 h, methyl 4-(bromomethyl)-3-methoxybenzoate (899 mg, 3.48 mmol) was added. The mixture was stirred at r.t. for 18 h, poured in to water and extracted with EtOAc (3x). The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc:MeOH 100:0 to 80:20) afforded **2-29** as a white solid (40 mg, 4%). UPLC/MS(ES$^+$): m/z 265.20 $[M+H]^+$.

[0444] Lithium hydroxide monohydrate (19.0 mg, 0.454 mmol) was added to a stirred suspension of **2-29** (40.0 mg, 0.151 mmol) in a 2:2:1 THF:MeOH:H_2O mixture (8 mL). The mixture was stirred at r.t. for 18 h. The volatiles were removed under reduced pressure. The residue was taken up with water, and the aqueous portion was extracted with EtOAc (2x). The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc:MeOH 100:0 to 80:20) afforded **2-28** as a white solid (32 mg, 84%). UPLC/MS(ES$^+$): m/z 251.20 $[M+H]^+$.

EXAMPLE 83
Preparation of Compound 217



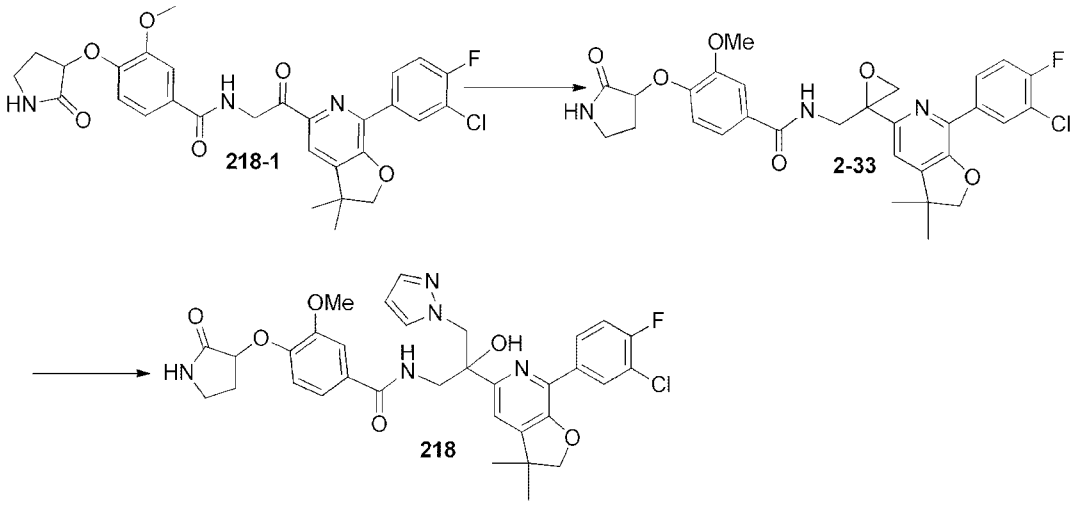
[0445] Triethylamine (0.240 mL, 1.72 mmol) was added to a mixture of 3-methoxy-4-[(2-oxopyrrolidin-3-yl)oxy]benzoic acid (130 mg, 0.517 mmol), HOBT (87.3 mg, 0.646 mmol), EDC (124 mg, 0.646 mmol) and **2-30** (104 mg, 0.431 mmol) in a 4:1 DCM:DMF (5 mL). The mixture was warmed to 45 °C and stirred at 45 °C for 18 h. A 1M aq. HCl solution was added, and the mixture was stirred at r.t. for 10 mins. The layers were separated. The organic portion was washed with 1M aq. HCl solution, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-31** (203 mg), which was used in the next step without further purification. UPLC/MS(ES$^+$): m/z 476.30 $[M+H]^+$.

[0446] Dess-Martin periodinane (453 mg, 1.07 mmol) was added to a stirred solution of **2-31** (203 mg) in dry DCM (10 mL). The mixture was stirred at r.t. for 2 h, and the reaction was quenched with a 1:1 1M aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$ solution (3 mL). The mixture was stirred vigorously for 30 mins. The layers were separated, and the organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc:MeOH, 100:0 to 75:25) afforded **2-32** (80 mg, 39% over two steps). UPLC/MS(ES$^+$): m/z 474.30 $[M+H]^+$.

[0447] A mixture of **2-32** (10.0 mg, 0.021 mmol), (3-chloro-4-fluorophenyl)boronic acid (18.4 mg, 0.105 mmol), $Pd(dppf)Cl_2$ (2.0 mg, 0.003 mmol) and aq. Na_2CO_3 (2M solution, 0.105 mmol, 0.05 mL) in DCE (0.3 mL) was degassed and stirred while heated to 85 °C under microwave irradiation (4 cycles for 10 mins each). After each run, a further aliquot of $Pd(dppf)Cl_2$ (2.0 mg, 0.003 mmol) was added. The reaction was

diluted with water, and DCM were added. The layers were separated, and the organic portion was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **217**. UPLC/MS(ES^+): m/z 568.30 $[M+H]^+$.

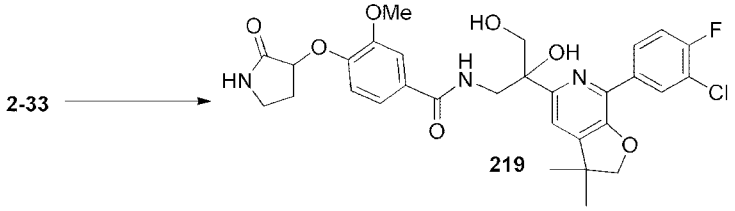
EXAMPLE 84
Preparation of Compound 218



[0448] Trimethylsulfoxonium iodide (21.0 mg, 0.097 mmol) was added to a solution of potassium tert-butoxide (9.8 mg, 0.086 mmol) in DMSO (0.6 mL). The mixture was stirred at r.t. for 30 mins. A solution of **218-1** (50.0 mg, 0.088 mmol) in DMSO (0.6 mL) was added, and the mixture was stirred at r.t. for a further 30 mins. The mixture was diluted with EtOAc and water. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-33** (50 mg), which was used next step without further purification. UPLC/MS(ES^+): m/z 582.34 $[M+H]^+$.

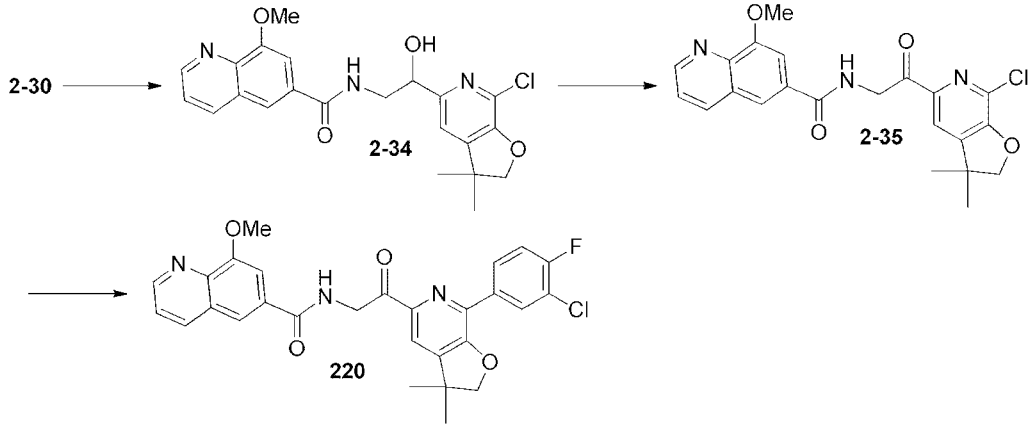
[0449] A mixture of **2-33** (50 mg), potassium carbonate (24.0 mg, 0.170 mmol) and pyrazole (24.0 mg, 0.350 mmol) in DMF (1 mL) was stirred at 40 °C for 18 h. The mixture was diluted with EtOAc and water. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 50:50) to afford **218** as a white solid (10 mg, 17% over two steps). UPLC/MS(ES^+): m/z 650.40 $[M+H]^+$.

EXAMPLE 85
Preparation of Compound 219



[0450] Epoxide **2-33** (60 mg, crude) was dissolved in a 1:1 3M aq. HCl sol:MeOH mixture (5 mL). The mixture was heated to 50 °C for 3 h. After cooling to r.t., the mixture was basified with 1M aq. NaOH solution and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 95:5 to 0:100) to afford **219** as a white solid (18 mg, 26% over two steps). UPLC/MS(ES^+): m/z 600.36 $[M+H]^+$.

EXAMPLE 86
Preparation of Compound 220

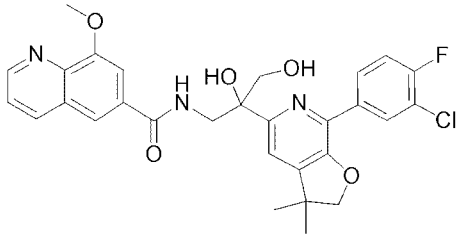


[0451] Triethylamine (0.35 mL, 2.51 mmol) was added to a mixture of 8-methoxyquinoline-6-carboxylic acid (286 mg, 1.18 mmol), HOBT (223 mg, 1.65 mmol), EDC (316 mg, 1.65 mmol) and **2-30** (239 mg, 1.18 mmol) in DCM (7 mL). The mixture was stirred at r.t. for 60 h. A 1M aq. HCl solution was added, and the mixture was stirred at r.t. for 10 mins. The layers were separated. The organic portion was washed with 1M aq. HCl solution, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-34**, which was used in the next step without further purification. UPLC/MS(ES^+): m/z 428.30 $[M+H]^+$.

[0452] Dess-Martin periodinane (1.20 g, 2.82 mmol) was added to a stirred solution of **2-34** in dry DCM (6 mL). The mixture was stirred at r.t. for 2 h, and the reaction quenched with a 1:1 1M aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$ solution. The mixture was stirred vigorously for 30 mins. The layers were separated, and the organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 80:20 to 0:100) to afford **2-35** (11.0 mg, 2% overall). UPLC/MS(ES^+): m/z 426.20 $[M+H]^+$.

[0453] A mixture of **2-35** (11.0 mg, 0.026 mmol), (3-chloro-4-fluorophenyl)boronic acid (11.2 mg, 0.065 mmol), $Pd(dppf)Cl_2$ (1.3 mg, 0.002 mmol) and aq. Na_2CO_3 (2M solution, 39 uL, 0.078 mmol) in DCE (1 mL) was degassed and heated to 85 °C for 24 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 30:70) to afford **220** as an off-white solid (2.3 mg, 17%). UPLC/MS(ES^+): m/z 520.30 $[M+H]^+$.

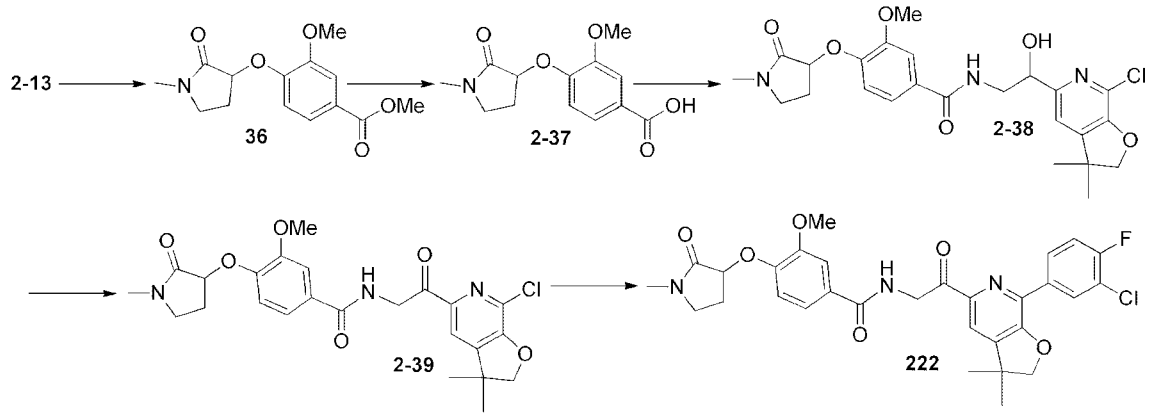
EXAMPLE 87
Preparation of Compound 221



221

[0454] Trimethylsulfoxonium iodide (18.3 mg, 0.087 mmol) was added to a solution of potassium tert-butoxide (9.3 mg, 0.083 mmol) in DMSO (0.3 mL). The mixture was stirred at r.t. for 30 mins. A solution of **220** (43.0 mg, 0.083 mmol) in DMSO (0.7 mL) was added, and the mixture was stirred at r.t. for a further 30 mins. The mixture was partitioned between EtOAc and water. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in a 1:1 3M aq. HCl sol:MeOH mixture (3 mL), and the mixture was heated to 50 °C for 3 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **221** as an off-white solid. UPLC/MS(ES^+): m/z 552.38 $[M+H]^+$.

EXAMPLE 88
Preparation of Compound 222



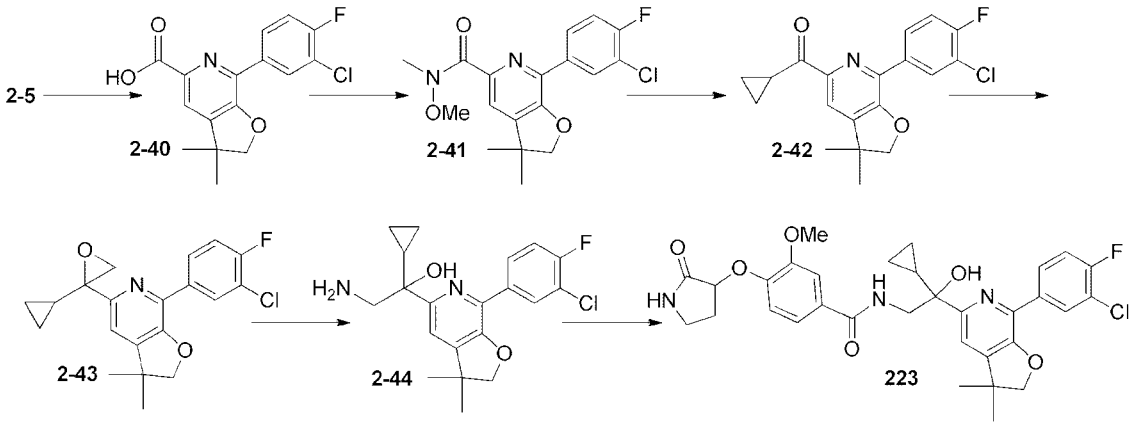
[0455] NaH (59.0 mg, 1.47 mmol) was added to a solution of **2-13** (300 mg, 1.13 mmol) in dry THF (4.5 mL). After 5 mins of stirring at r.t., MeI (192 mg, 1.35 mmol) was added. The reaction was stirred at r.t. for 3 h. EtOAc and 1M aq. HCl solution were added. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure to afford crude **2-36**, which was in the next step without further purification. Lithium hydroxide monohydrate (95.0 mg, 2.26 mmol) was added to a stirred mixture of **2-36** in 2:1:1 THF:MeOH:H_2O (8 mL). The reaction was stirred at r.t. for 3 h. Additional lithium hydroxide monohydrate (95 mg) was added and stirring was continued for 2 h. The mixture was poured in to 6M aq. HCl solution. The aqueous portion was saturated with NaCl and extracted with EtOAc and DCM. The combined organic portions were dried with Na_2SO_4, and filtered. The volatiles were removed under reduced pressure to afford crude **2-37**, which was in the next step without further purification. UPLC/MS(ES^+): m/z 266.20 $[M+H]^+$.

[0456] A mixture of **2-37**, **2-30** (273 mg, 1.13 mmol), EDC (282 mg, 1.47 mmol), HOBT (198 mg, 1.47 mmol) and TEA (267 uL, 1.92 mmol) in DMF (8 mL) was stirred at r.t. for 18 h. EtOAc and 2M aq. HCl solution were added. The layers were separated, and the organic portion was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **2-38** as a colorless wax (90 mg, 16% over 3 steps). UPLC/MS(ES^+): m/z 490.30 $[M+H]^+$.

[0457] Dess-Martin periodinane (195 mg, 0.46 mmol) was added to a stirred solution of **2-38** (90.0 mg, 0.184 mmol) in dry DCM (2 mL). The mixture was stirred at r.t. for 2 h. The reaction was quenched with a 1:1 1M aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$ solution. The mixture was stirred vigorously for 30 mins. The layers were separated, and the organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-39** (92 mg), which was in the next step without further purification. UPLC/MS(ES^+): m/z 488.30 $[M+H]^+$.

[0458] A mixture of **2-39** (92 mg), (3-chloro-4-fluorophenyl)boronic acid (83.0 mg, 0.475 mmol), $Pd(dppf)Cl_2$ (27.6 mg, 0.038 mmol) and aq. Na_2CO_3 (2M solution, 285 uL, 0.570 mmol) in DCE (3 mL) was degassed and heated to 100 °C under microwaive irradiation for 1.5 h. Water and DCM were added. The layers were separated, and the organic portion was dried wtih Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **222** as an off-white solid (27.0 mg, 25% over two steps). UPLC/MS(ES^+): m/z 582.30 $[M+H]^+$.

EXAMPLE 89
Preparation of Compound 223



[0459] 2-Methyl-2-butene (16.9 mL, 33.7 mmol, 2M solution in THF) was added to a solution of **2-5** (1.03 g, 3.37 mmol) in tert-butanol (60 mL). A solution of sodium chlorite (609 mg, 6.74 mmol) and sodium phosphate monobasic dihydrate (3.41 g, 21.9 mmol) in water (60 mL) was then added. The mixture was stirred at r.t. for 18 h. Brine was added, and the aqueous portion was extracted with EtOAc (3x). The combined organic portions were were dried with Na_2SO_4, filtered and concentrated under reduced pressure.

Chromatography of the residue (cyclohexane:EtOAc 100:0 to 0:100) afforded **2-40** as an off-white solid (688 mg, 63%). UPLC/MS(ES^+): m/z 322.10 $[M+H]^+$.

[0460] Triethylamine (0.160 mL, 1.12 mmol) was added to a mixture of **2-40** (200 mg, 0.622 mmol), HOBT (151 mg, 1.12 mmol), EDC (167 g, 0.870 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (91.1 mg, 0.934 mmol) in DCM (15 mL). The mixture was stirred at r.t. for 18 h. A 1M aq. HCl solution was added, and the mixture was stirred at r.t. for 10 mins. The layers were separated. The organic portion was washed with 1M aq. HCl solution, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-41** (255 mg) which was used in the next step without further purification. UPLC/MS(ES^+): m/z found 365.20 $[M+H]^+$.

[0461] Cyclopropylmagnesium bromide (1M solution in 2-methyl tetrahydrofuran, 1.96 mL, 1.96 mmol) was added to a solution of **2-41** (255 mg) in THF (10 mL). The mixture was stirred at r.t. for 1 h. The reaction was quenched with sat. aq. NH_4Cl solution and extracted with DCM (3x). The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 50:50) afforded **2-42** (146 mg, 68% over 2 steps). UPLC/MS(ES^+): m/z: 346.20 $[M+H]^+$.

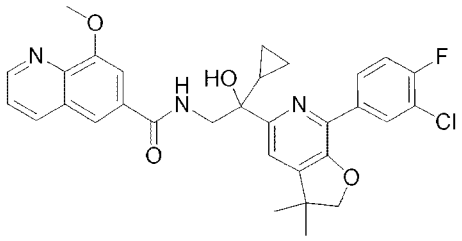
[0462] A mixture of trimethylsulfoxonium iodide (93.0 mg, 0.423 mmol) and NaH (16.9 mg, 0.423 mmol) in 1:1 DMSO:THF (1 mL) was stirred at r.t. for 1 h. A solution of **2-42** (146 mg, 0.423 mmol) in THF (1 mL) was added, and the mixture was stirred at r.t. for 18 h. The mixture was partitioned between EtOAc and water. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-43** (180 mg), which was used in the next step without further purification.

[0463] A solution of **2-43** (180 mg) in 7M NH_3:MeOH (4 mL) was stirred at r.t. for 18 h and at 35 °C for an addition 24 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **2-44** (13 mg, 8% over 2 steps). UPLC/MS(ES^+): m/z 377.20 $[M+H]^+$.

[0464] A mixture of **2-10** (39.9 mg 0.159 mmol), HOBT (25.8 mg, 0.191 mmol), EDC (28.4 mg, 0.148 mmol), TEA (0.027mL, 0.191 mmol) and **2-44** (40.0 mg, 0.106 mmol)

in DMF (2 mL) was stirred at r.t. for 18 h. A 1M aq. HCl solution was added, and the mixture was stirred at r.t. for 10 mins. The layers were separated. The organic portion was washed with 1M aq. HCl solution, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **223** (8 mg, 12%). UPLC/MS(ES^+): m/z 610.50 $[M+H]^+$.

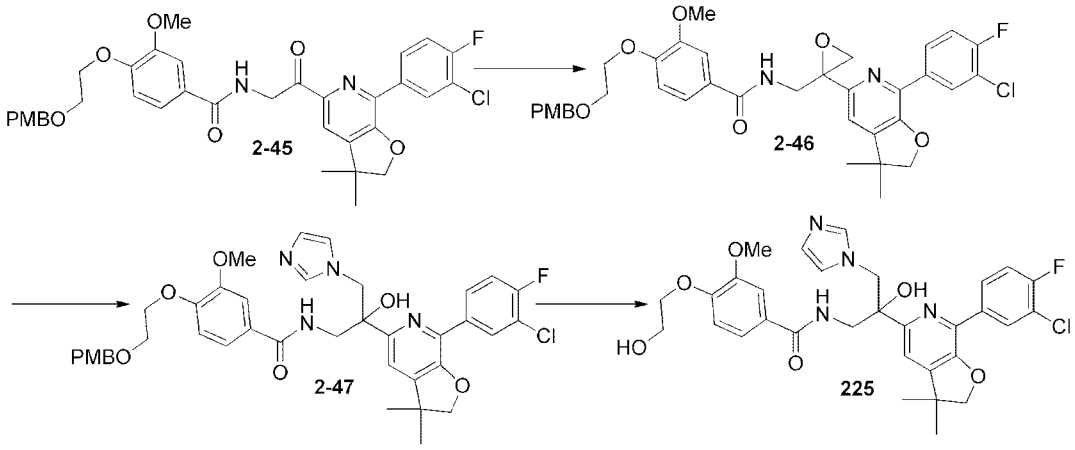
EXAMPLE 90
Preparation of Compound 224



224

[0465] Coupling of **2-44** with **2-14** using conditions reported for the preparation of **223** (EDC, HOBT) afforded **224** as a white solid. UPLC/MS(ES^+): m/z 562.40 $[M+H]^+$.

EXAMPLE 91
Preparation of Compound 225

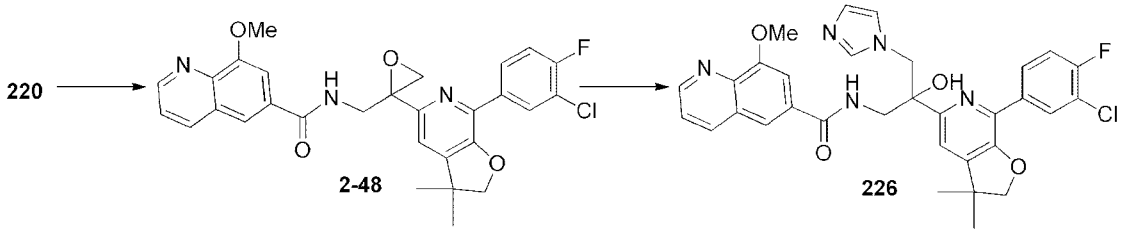


[0466] Trimethylsulfoxonium iodide (21.5 mg, 0.098 mmol) was added to a mixture of potassium tert-butoxide (9.98 mg, 0.089 mmol) in DMSO (2 mL). After 30 mins, **2-45** (57.8 mg, 0.089 mmol) was added, and the mixture was stirred at r.t. for 1.5 h. The mixture was partitioned between EtOAc and water. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-46**, which was used in the next step without purification. Crude **2-46** was dissolved in DMF (1 mL). K_2CO_3

(24.6 mg, 0.178 mmol) and imidazole (12.1 mg, 0,178 mmol) were then sequentially added. The mixture was heated to 80 °C and stirred at 80 °C for 48 h. The volatiles were removed under reduced pressure to afford crude **2-47**, which was used in the next step without purification.

[0467] A solution of **2-47** in 1:1 TFA:DCM (0.9 mL) was stirred at r.t. for 1 h. The reaction was quenched with a 1M aq. NaOH solution. After 30 mins of stirring at r.t., the layers were separated. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography to afford **225** as a white solid (1 mg, 2% overall). UPLC/MS(ES^+): m/z 611.30 $[M+H]^+$.

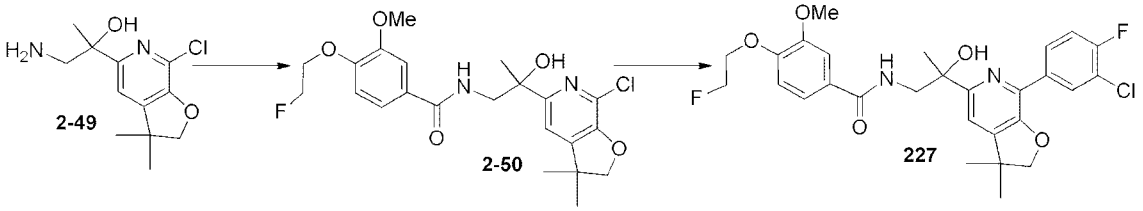
EXAMPLE 92
Preparation of Compound 226



[0468] NaH (9.0 mg, 0.226 mmol) was added to a solution of trimethylsulfoxonium iodide (49.7 mg, 0.226 mmol) in DMSO (2 mL). After 40 mins a solution of **220** (117 mg, 0.226 mmol) in THF (2 mL) was added, and the mixture was stirred at r.t. for 6 h. The mixture was partitioned between water and EtOAc. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-48**, which was used in the next step without purification. UPLC/MS(ES^+): m/z 534.30 $[M+H]^+$.

[0469] Potassium carbonate (31.3 mg, 0.452 mmol) and imidazole (30.8 mg, 0.452 mmol) were sequentially added to a solution of **2-48** in DMF (2 mL). The mixture was heated to 120 °C for 18 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **226** as a white solid (10 mg, 7% over 2 steps). UPLC/MS(ES^+): m/z 602.50 $[M+H]^+$.

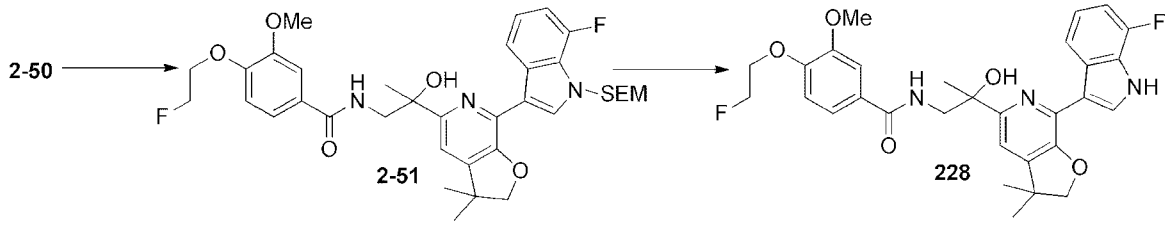
EXAMPLE 93
Preparation of Compound 227



[0470] A mixture of **2-49** (110 mg, 0.0 mmol), HOBT (86.0 mg, 0.640 mmol), EDC (122 mg, 0.640 mmol), TEA (120 uL, 0.860 mmol) and 4-(2-fluoroethoxy)-3-methoxybenzoic acid (110 mg, 0.510 mmol) in DCM (4 mL) was stirred at r.t. for 3 h. The reaction was quenched with 1M aq. HCl solution, and the mixture was stirred at r.t. for 10 mins. The layers were separated, and the organic portion was washed with 1M aq. HCl solution, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc 60:40 to 10:90) afforded **2-50** as a white solid (95 mg, 48%). UPLC/MS(ES^+): m/z 453.09 $[M+H]^+$.

[0471] A mixture of **2-50** (45.0 mg, 0.100 mmol), (3-chloro-4-fluorophenyl)boronic acid (87.0 mg, 0.500 mmol), $Pd(dppf)Cl_2$ (3.6 mg, 0.005 mmol) and aq. Na_2CO_3 (2M solution, 250 uL, 0.500 mmol) in DCE (1 mL) was degassed and stirred with heating to 85 °C for 3 h. Water and DCM were added. The layers were separated, and the organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 50:50) to afford **227** (10.5 mg, 19%). UPLC/MS(ES^+): m/z 547.30 $[M+H]^+$.

EXAMPLE 94
Preparation of Compound 228

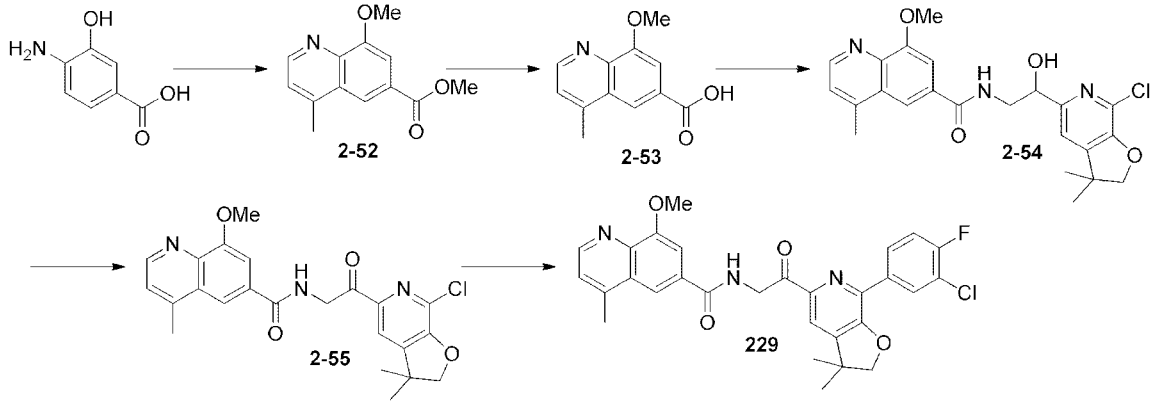


[0472] A mixture of **2-50** (50.0 mg, 0.110 mmol), 7-fluoro-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-indole (108 mg, 0.270 mmol), $Pd(dppf)Cl_2$ (4.0 mg, 0.005 mmol) and aq. Na_2CO_3 (2M solution, 135 uL, 0.270 mmol) in

DCE (1 mL) was degassed and stirred with heating to 85 °C for 5 h. Water and DCM were added, and the layers were separated. The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **2-51**.

[0473] A solution of **2-51** in 10:1 DCM:TFA (1.1 mL) was stirred at r.t. for 3 h. A 1M aq. NaOH solution was added, and the mixture was stirred at r.t. for 18 h. The layers were separated, and the organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 50:50) to afford **228** (4.2 mg, 7% over 2 steps). UPLC/MS(ES^+): m/z 552.40 $[M+H]^+$.

EXAMPLE 95
Preparation of Compound 229



[0474] A mixture of 4-amino-3-hydroxybenzoic acid (2.01 g, 13.1 mmol), 12M aq. HCl solution (20mL, 240 mmol) and 3-buten-2-one (1.59 mL, 19.6 mmol) was refluxed for 4 h. The volatiles were removed under reduced pressure, and the residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford 8-hydroxy-4-methylquinoline-6-carboxylic acid (830 mg, 31%). This was dissolved in DMF (35 mL). Cesium carbonate (4.42 g, 13.6 mmol) and iodomethane (1.28 mL, 20.5 mmol) were sequentially added to the solution. The mixture was stirred at r.t. for 4 h. The volatiles were removed under reduced pressure, and the residue was taken up with EtOAc. The organic portion was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-52** (860 mg), which was used in the next step without further purification. UPLC/MS(ES^+): m/z 232.10 $[M+H]^+$.

[0475] Lithium hydroxide monohydrate (280 mg, 6.73 mmol) was added to a stirred suspension of **2-52** (220 mg) in a 2:1:1 THF:MeOH:H_2O mixture (4 mL). The mixture was stirred at r.t. for 1 h. The volatiles were removed under reduced pressure. The residue was dissolved in water, and the pH of the aqueous portion was adjusted to 6 with 1M aq. HCl solution. The mixture was purified by reverse phase chromatography (water:CH_3CN 100:0 to 0:100) to afford **2-53** (80 mg, 31%). UPLC/MS(ES^+): m/z 218.10 $[M+H]^+$.

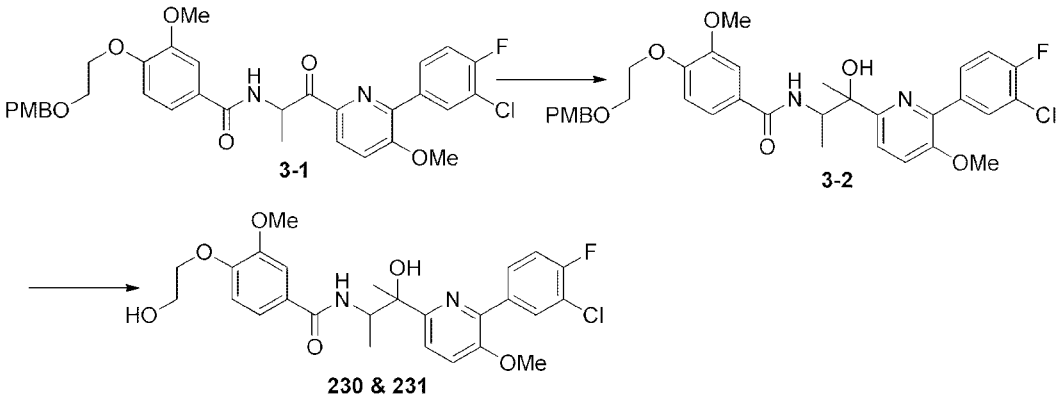
[0476] Coupling of **2-53** with **2-30** according to Method A afforded **2-54**, which was used in the next step without further purification.

[0477] Dess-Martin periodinane (127 mg, 0.299 mmol) was added to a stirred solution of **2-54** (66 mg) in dry DCM (32 mL). The mixture was stirred at r.t. for 1 h. The reaction was quenched with a 1:1 1M aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$ solution, and the mixture was stirred vigorously for 30 mins. The layers were separated, and the organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **2-55**, which was used in the next step without further purification.

[0478] A mixture of **2-55**, (3-chloro-4-fluorophenyl)boronic acid (52.0 mg, 0.299 mmol), $Pd(dppf)Cl_2$ (16.0 mg, 0.022 mmol) and aq. Na_2CO_3 (2M solution, 222 uL, 0.447 mmol) in DCE (31 mL) was degassed and heated to 100 °C under microwave irradiation. After 2.5 h, the volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN 100:0 to 50:50) to afford **229** (10.0 mg). UPLC/MS(ES^+): m/z 534.30 $[M+H]^+$.

EXAMPLE 96

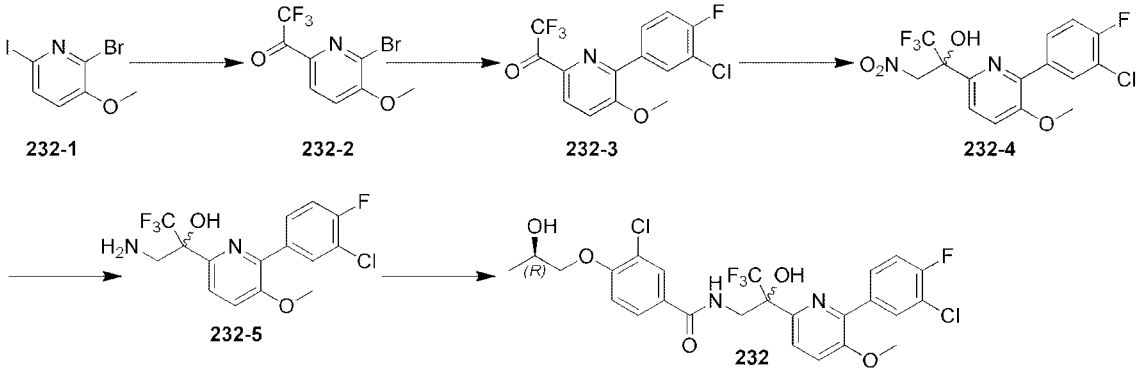
Preparation of Compounds 230 and 231



[0479] Methyl magnesiumbromide (3M solution in hexane, 300 uL, 0.892 mmol) was added to a solution of **3-1** (185 mg, 0.297 mmol) in dry THF (5 mL). The mixture was stirred at r.t. for 1 h. The reaction was quenched with 1M aq. HCl solution and EtOAc was added. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **3-2** (201 mg), which was used in the next step without further purification.

[0480] A solution of **3-2** (201 mg) in a 10:1 DCM:TFA (3 mL) was stirred at r.t. for 40 mins. The reaction was quenched with 1M aq. NaOH solution, and the mixture was stirred at r.t. for 10 mins. The layers were separated, and the aqueous portion was extracted with DCM. The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (EtOAc:MeOH 100:0 to 80:20) afforded the two separated diastereomers (each as a racemic mixture, relative stereochemistry arbitrarily assigned). **230**: white solid (10 mg, 7% overall) and UPLC/MS(ES^+): m/z 519.30 $[M+H]^+$. **231**: white solid (37 mg, 24% overall) and UPLC/MS(ES^+): m/z 519.30 $[M+H]^+$.

EXAMPLE 97
Preparation of Compound 232



[0481] To a solution of **232-1** (21.8 g, 69.9 mmol) and ethyl 2,2,2-trifluoroacetate (12.9 g, 90.8 mmol) in THF (500 mL) was added isopropyl-magnesium chloride (46.0 mL, 2.3 N in THF) at 0°C. The mixture was stirred at 0°C for 30 mins. The reaction was quenched with sat. NH_4Cl solution and extracted with EA. The combined organic phases were dried over anhydride $MgSO_4$ and evaporated under reduced pressure. The residue was

purified by column chromatography on silica gel (PE:EA, 5:1) to give **232-2** as an oil (16.5 g, 83.8%).

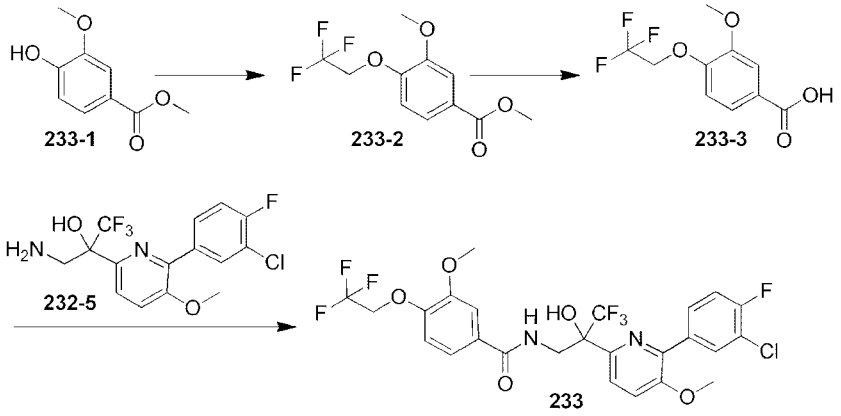
[0482] To a solution of **232-2** (16.5 g, 58.5 mmol), (3-chloro-4-fluorophenyl)boronic acid (10.51 g, 58.6 mmol), KF (7.1 g, 117 mmol) in dioxane (300 mL) and H_2O (30 mL) was added $Pd(dppf)Cl_2$ (4.7 g, 5.8 mmol). The mixture was degassed and then charged with nitrogen (3x). The mixture was stirred at 70 °C in an oil bath for 6 h under N_2. The mixture was cooled to r.t., diluted with EA and separated from the water layer. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA, 10:1) to give **232-3** as a white solid (17.0 g, 87.2%). ESI-MS: m/z 351.8 $[M+H_2O]^+$.

[0483] A mixture of **232-3** (17.0 g, 51.1 mmol) and K_2CO_3 (13.8 g, 100 mmol) in nitro-methane (100 mL) was stirred at r.t. for 10 h. The solution was extracted with EA (3 x 200 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using 15% EA in PE to give **232-4** as a white solid (16.0 g, 80.0%).

[0484] To a solution of **232-4** (16.0g, 40.6 mmol) and $NiCl_2.6H_2O$ (9.5 g, 40.4 mmol) in anhydrous MeOH (150 mL) and anhydrous THF (150 mL) was added $NaBH_4$ (15.2 g, 400.6 mmol) in portions at 0 °C. After addition was complete, the solution was stirred at 0 °C for 1 h. The reaction was quenched with H_2O and then extracted with EA (3 x 200 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using EA to give **232-5** as an oil (11.0 g, 74.8%). ESI-MS: m/z 365 $[M+H]^+$.

[0485] To a solution of (R)-3-chloro-4-(2-hydroxypropoxy)benzoic acid (115 mg, 0.5 mmol), HATU (260 mg, 0.7 mmol) and DIPEA (320 mg, 2.5 mmol) in anhydrous DCM (5 mL) was added **232-5** (180 mg, 0.5 mmol) at 25 °C. The solution was stirred for 1 h at 25 °C. The mixture was diluted with 1.0 N aqueous $NaHCO_3$ solution, and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **232** as a white solid (80 mg, 27.5%). ESI-MS: m/z 576.9 $[M+H]^+$.

EXAMPLE 98
Preparation of Compound 233

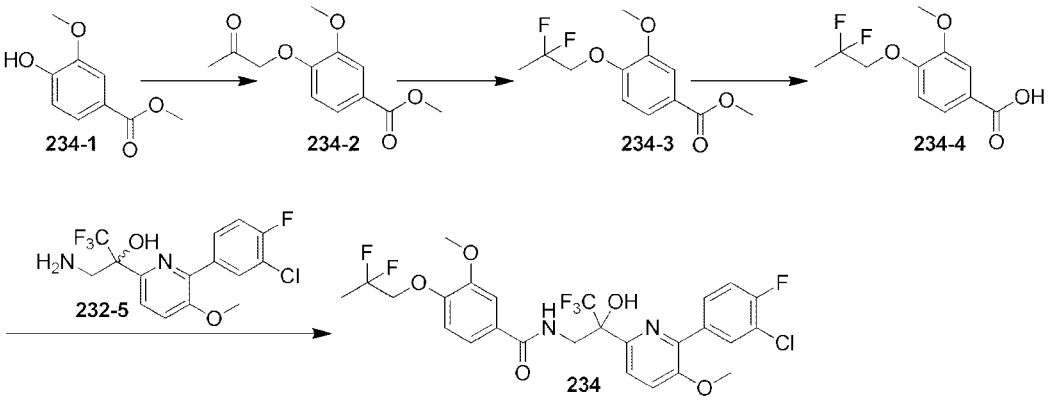


[0486] To a solution of **233-1** (1.8 g, 10.0 mmol) and F_3CCH_2I (2 g, 10.0 mmol) in DMF (100 mL) was added K_2CO_3 (2.6 g, 20.0 mmol). The mixture was stirred at 80 °C for 3 h. The mixture was concentrated at low pressure, and the reidue was dissolved in EA (50 mL). The mixture was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude product was purified by column chromatography using 10% EA in PE to give **233-2** (1.6 g, 60%).

[0487] To a solution of **233-2** (1.5 g, 5.7 mmol) in CH_3OH and water (120 mL and 30 mL) was added LiOH (270 mg, 11.3 mmol). The mixture was stirred at 70 °C for 2 h, and then cooled to r.t. The mixture was extracted with EA, and the residue was neutralized using 2.0 N HCl solution. The mixture was extracted with EA (3 x 30 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated at low pressure to give **233-3** as a white solid (1.3 g, 85%).

[0488] Compound **233** was prepared essentially as described in the preparation of **232** by using **233-3** and **232-5**. Compound **233** was obtained as a white solid. (100 mg, 67%) +ESI-MS:m/z 596.1 $[M+H]^+$.

EXAMPLE 99
Preparation of Compound 234

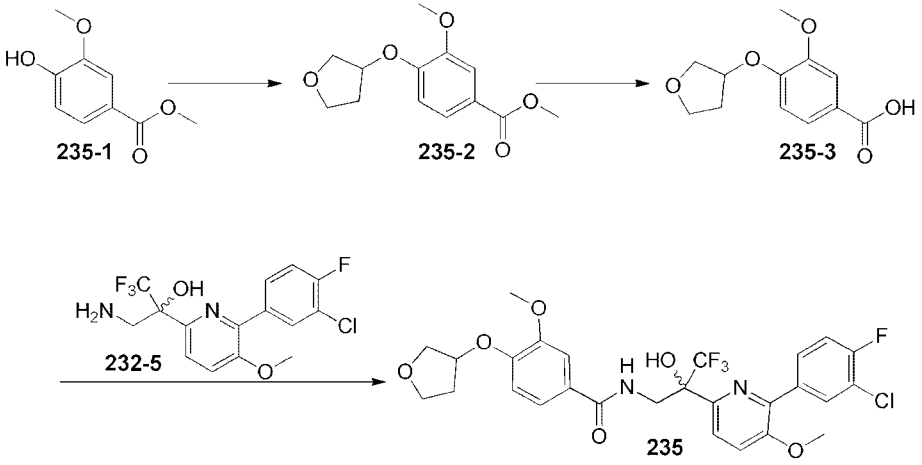


[0489] To a solution of **234-1** (1.0 g, 5.4 mmol) in MeCN (10 mL) were added 1-chloro-2-propanone (1.0 g, 10.0 mmol) and K_2CO_3 (3.5 g, 20.0 mmol). The mixture was stirred at 80 °C for 1 h. After filtration, the filtrate was concentrated at low pressure. The residue was purified by chromatography to give **234-2** (850 mg, 65.4%).

[0490] A mixture of **234-2** (500 mg, 2.1 mmol) and DAST (5 mL) was stirred at 50 °C for 12 h. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with EA (3 x 20 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography using 10% EA in PE to give **234-3** (310 mg, 56.8%).

[0491] Compound **234-4** was prepared essentially as described in the preparation of **233-3**. Compound **234** was prepared essentially as described in the preparation of **232** by using **234-4** and **232-5**. Compound **234** was obtained as white solid (58 mg, 24.1%). +ESI-MS:m/z 593.1 $[M+H]^+$.

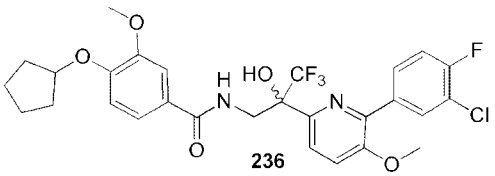
EXAMPLE 100
Preparation of Compound 235



[0492] To a solution of **235-1** (1.82 g, 10.0 mmol), tetrahydrofuran-3-ol (880 mg, 10.0 mmol) and PPh_3 (2.62 g, 10.0 mmol) in THF (30 mL) at 0 °C was added DIAD (2.02 g, 10.0 mmol) dropwise. The mixture was stirred at 50 °C for 2 h, and the reaction was then quenched with sat. $NaHCO_3$ solution. The aqueous layer was extracted by DCM (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated at low pressure. The residue was purified by flash column chromatography on silica gel to give **235-2** (2.4 g, 89.6%).

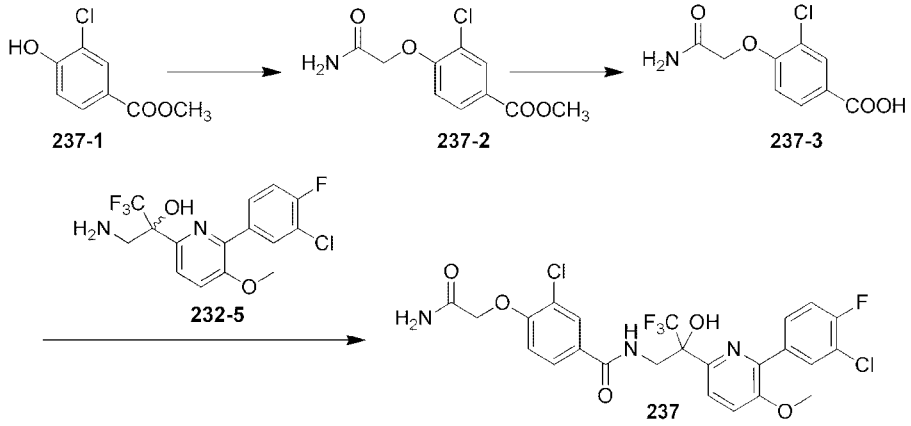
[0493] Compound **235-3** was prepared essentially as described in the preparation of **233-3**. Compound **235** was prepared essentially as described in the preparation of compound **232** by using **235-3** and **232-5**. Compound **235** was obtained as white solid (75 mg, 62.3%). +ESI-MS:m/z 585.2 $[M+H]^+$.

EXAMPLE 101
Preparation of Compound 236



[0494] Compound **236** was prepared essentially as described in the preparation of compound **235** by using methyl 4-hydroxy-3-methoxybenzoate. Compound **236** was obtained as white solid (56 mg, 22.7 %). +ESI-MS:m/z 583.1 $[M+H]^+$.

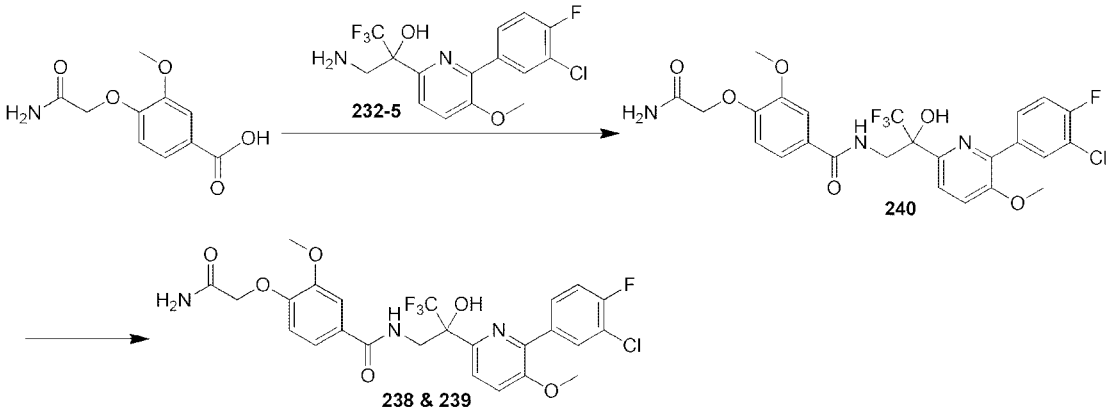
EXAMPLE 102
Preparation of Compound 237



[0495] To a solution of **237-1** (0.93 g, 5 mmol) in acetone (30 mL) was added K_2CO_3 (2.08 g, 15 mmol) and 2-iodoacetamide (1.39 g, 7.5 mmol). The mixture was stirred at r.t. overnight. The mixture was diluted with water and extracted with EA (4 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum to give crude **237-2**, which was further purified by column chromatography on silica gel (PE:EA= 2:1) to **237-2** (1.01 g, 83.1%) as a white solid.

[0496] Compound **237-3** was prepared essentially as described in the preparation of **233**. Compound **237** was prepared essentially as described in the preparation of **236** by using **237-3** and **232-5**. Compound **237** was obtained as white solid (32 mg, 22.2%). +ESI-MS:m/z 576.1 $[M+H]^+$.

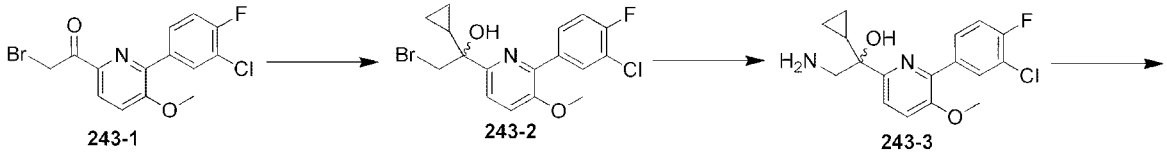
EXAMPLE 103
Preparation of Compounds 238, 239 and 240

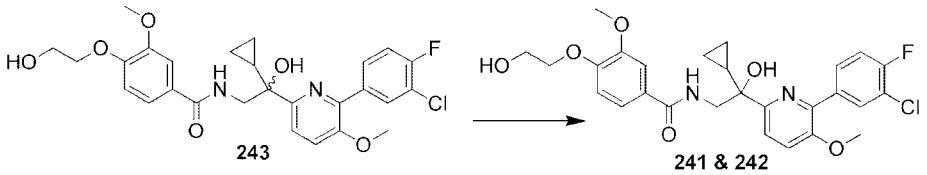


[0497] Compound **240** was prepared essentially as described in the preparation of **232** by using 4-(2-amino-2-oxoethoxy)-3-methoxybenzoic acid and **232-5**. Compound **240** was obtained as a white solid (300 mg, 52.5%).

[0498] Compound **240** (300 mg, 0.53 mmol) was separated via SFC to give two enantiomers: **238** (140 mg, 93.3%) and **239** (100 mg, 66.7%). Compound **238**: +ESI-MS:m/z 572.1 $[M+H]^+$. Compound **239**: +ESI-MS:m/z 572.0 $[M+H]^+$.

EXAMPLE 104
Preparation of Compounds 241, 242 and 243





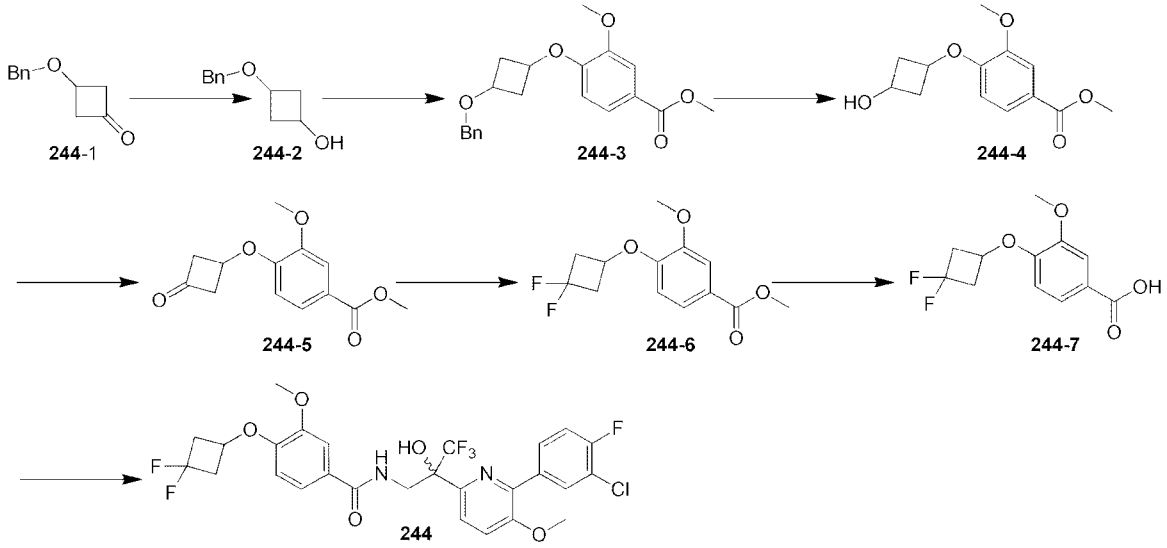
[0499] To a solution of **243-1** (714 mg, 2.0 mmol) in THF (4 mL) was added cyclopropylmagnesium bromide (4 mL, 0.5 M in THF). The mixture was stirred at 0 °C for 1 h. The reaction was quenched with water, and extracted with EA (3 x 20 mL). The combined organic layers was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. Crude **243-2** was directly used in the next step. +ESI-MS: m/z 399.0 $[M+H]^+$.

[0500] Compound **243-2** (600 mg), $NH_3 \cdot H_2O$ (10 mL) and ethanol (10 mL) were put in an autoclave. After sealing, the reaction was stirred at r.t. for 10 h. The mixture was extracted by EA (3 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated at low pressure to give **243-3**, which was used without further purification. +ESI-MS: m/z 336.1 $[M+H]^+$.

[0501] Compound **243** was prepared essentially as described in the preparation of **232** by using 4-(2-hydroxyethoxy)-3-methoxybenzoic acid and **243-3**. Compound **243** was obtained as a white solid (152 mg, 23%). +ESI-MS: m/z 531.2 $[M+H]^+$.

[0502] Compound **243** (152 mg, 0.28 mmol) was separated via SFC to give two isomers: **242** (40.0 mg, 26%) and **241** (43.0 mg, 26%). **241**: +ESI-MS: m/z 531.1 $[M+H]^+$. **242**: +ESI-MS: m/z 531.1 $[M+H]^+$.

EXAMPLE 105
Preparation of Compound 244



[0503] Compound **244-2** was prepared as described in Franck et al., *Bioorganic & Medicinal Chemistry*, (2013) 21(3):643-652. Compound **244-3** was prepared essentially as described in the preparation of **235** by using **244-4** and methyl 4-hydroxy-3-methoxybenzoate. Compound **244-3** was obtained as a white solid (2.8 g, 73.7%).

[0504] To a solution of **244-3** (2.8 g, 8.2 mmol) in methanol (15 mL) was added $Pd(OH)_2$ on charcoal (10%, 500 mg) under N_2. The suspension was degassed under vacuum and purged with H_2 (3x). The mixture was stirred under H_2 (40 psi) at r.t. for 3 h. The suspension was filtered through a pad of Celite, and the pad cake was washed with methanol. The combined filtrates were concentrated to give crude **244-4** (1.7 g, 84.5%), which was used in the next step without purification.

[0505] To a solution of **244-4** (1.3 g, 5.2 mmol) in DCM (10 mL) was added DMP (3.4 g, 8.0 mmol). The mixture was stirred at r.t. for 40 mins. The reaction was quenched by sat. $Na_2S_2O_3$ solution and extracted with EA. The combined organic layers were washed with sat. $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The solution was

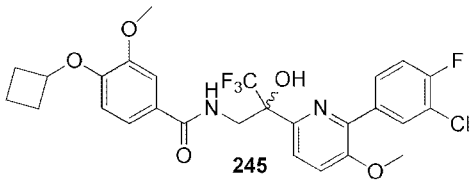
concentrated to dryness, and the residue was purified by column chromatography on a silica gel column (PE:EA, 5:1) to give **244-5** as a white solid (0.8 g, 61.6%).

[0506] Compound **244-5** (500 mg, 2.0 mmol) was treated with DAST (5 mL), and stirred at 0 °C for 30 mins. The reaction was quenched by a sat. $NaHCO_3$ solution at 0 °C, and then extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE:EA, 10:1) to give **244-6** as a white solid (605 mg, 81.2%). +ESI-MS: m/z 273.1 $[M+H]^+$.

[0507] To a solution of **244-6** (300 mg, 1.1 mmol) in MeOH (35 mL) was added NaOH solution (2 N, 35 mL). The reaction was stirred under reflux for 1 h. The mixture was neutralized with 2.0 N HCl solution, and extracted with EA (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give **244-7** as a white solid (250 mg, 88.1%). +ESI-MS: m/z 259 $[M+H]^+$.

[0508] Compound **244** was prepared essentially as described in the preparation of compound **232** by using **244-7** and **232-5**. Compound **244** was obtained as a white solid (60 mg, 25.5%). +ESI-MS: m/z 606.1 $[M+H]^+$.

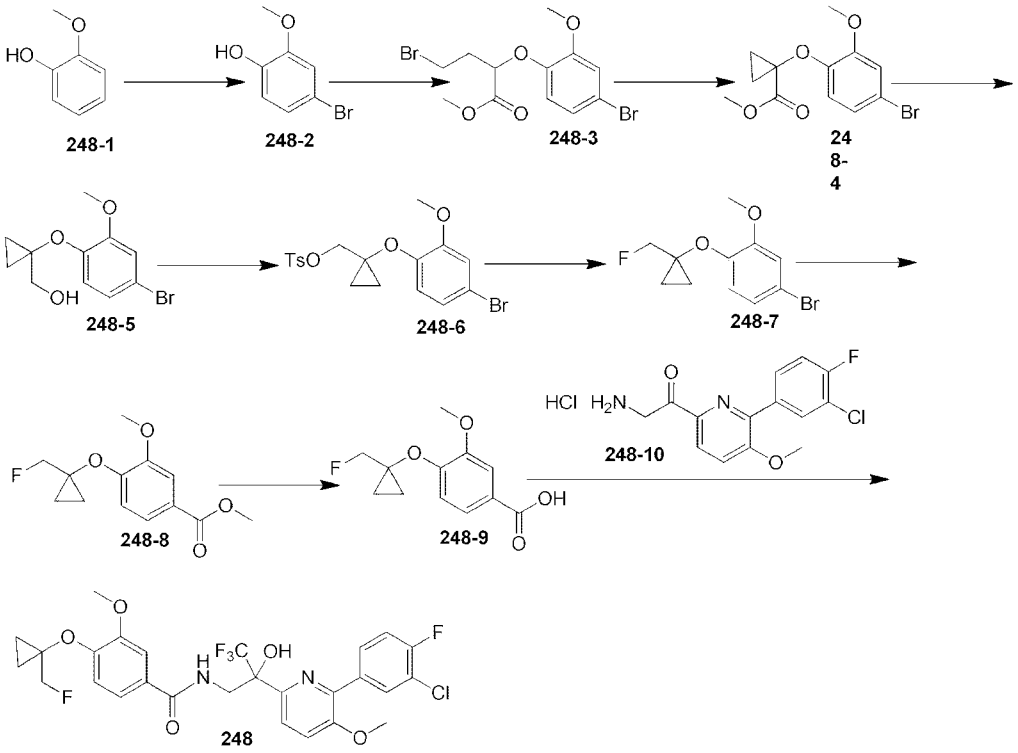
EXAMPLE 106
Preparation of Compound 245



245

[0509] Compound **245** was prepared essentially as described in the preparation of **235**. Compound **245** was obtained as a white solid (70 mg, 54.8%). +ESI-MS:m/z 569.1 $[M+H]^+$.

EXAMPLE 107
Preparation of Compound 248



[0510] Compound **248-2** was prepared as described in Rye et al., *Eur. J. Med. Chem.* (2013) 60:240-248. To a solution of **248-2** (6.0 g, 29.41 mmol) and K_2CO_3 (5.28 g, 38.23 mmol) in DMF (50 mL) was added methyl 2,4-dibromobutanoate (9.86 g, 38.23 mmol). The mixture was stirred at 80 ^{0}C for 12 h, and then diluted with water and extracted with EA (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography on silica gel crude **248-3** (9.8 g).

[0511] To a solution of **248-3** (9.8 g, 25.8 mmol) in THF (100 mL) was added t-BuOK (28.37 mL, 28.37 mmol, 1 N in THF) at 0 ^{o}C. The mixture was stirred at r.t. for 3 h. The mixture was diluted with water and extracted with EA (3 x 60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography to give **248-4** (6.0 g, 78.0%).

[0512] To a solution of **248-4** (6.0 g, 20.0 mmol) in EtOH (20 mL) was added $NaBH_4$ (2.10 g, 30.0 mmol) at r.t. The mixture was stirred at r.t. for 10 mins. The mixture was heated to reflux for 10 h and then cooled to r.t. The mixture was diluted with EA (60

mL) and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by chromatography to give **248-5** (4.5 g) as a white solid.

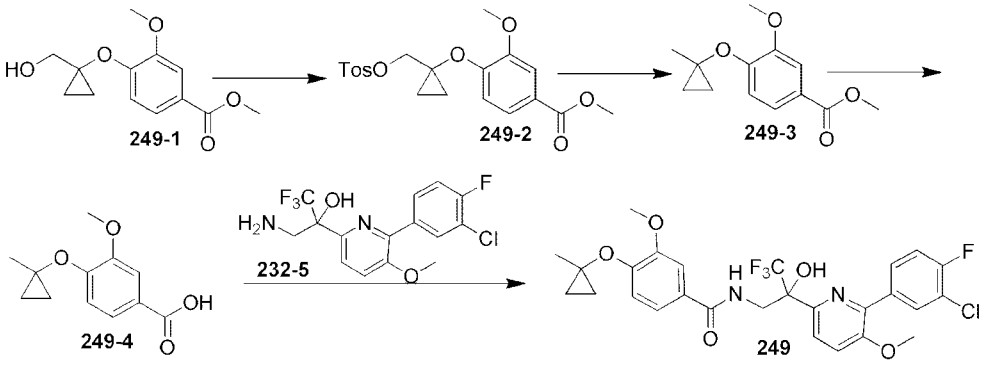
[0513] To a solution of **248-5** (500 mg, 1.84 mmol) in DCM (10 mL) was added Et_3N (370 mg, 3.68 mmol) and DMAP (10.0 mg, 0.082 mmol). TsCl (459 mg, 2.41 mmol) was added portionwise. The mixture was stirred at r.t. overnight. The reaction was quenched with water, and extracted with EA (3 x 30 mL). The combined organic layer were dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography on silica gel to give **248-6** as a white solid (730 mg, 93.1%).

[0514] To a solution of **248-6** (730 mg, 1.80 mmol) in anhydrous THF (10 mL) was added TBAF (1M in THF) (5.0 mL, 5.0 mmol). The mixture was stirred at r.t. overnight. The mixture was diluted with EA (20 mL) and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography on silica gel to give **248-7** as a white solid (330 mg, 67.0%).

[0515] To a solution of **248-7** (330 mg, 1.2 mmol) in anhydrous THF (10 mL) was added *n*-BuLi (0.63 mL, 1.6 mmol) at -78 ^oC dropwise. The mixture was stirred at -78 ^oC for 0.5 h. $ClCOOCH_3$ (0.69 g, 7.2 mmol) was added in one portion and stirred at -78 ^oC for 1 h. The mixture was diluted with EA (20 mL) and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by chromatography to give **248-8** as a white solid (203 mg, 66.0%).

[0516] Compound **248-9** was prepared essentially as described in the preparation of **233**. Compound **248** was prepared essentially as described in the preparation of **232** by using **248-9** and **248-10**. Compound **248** was obtained as a white solid (12 mg, 3.7%). +ESI-MS:m/z 587.1 $[M+H]^+$.

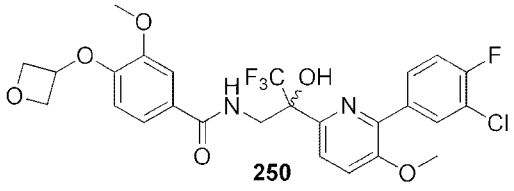
EXAMPLE 108
Preparation of Compound 249



[0517] Compound **249-2** was prepared essentially as described in the preparation of **248**. To a solution of **249-2** (1.02 mg, 2.5 mmol) in DMSO (10 mL) was added $NaBH_4$ (285 mg, 7.5 mmol) at r.t. under N_2 atmosphere. The solution was heated to 80 °C and stirred for 1 h. The solution was cooled to r.t. The reaction was quenched with water (20 mL) and extracted with EA (2 x 20 mL). The organic phase was concentrated at low pressure, and the residue was purified by column chromatography on silica gel (PE:EA=20:1) to give **249-3** as a colorless oil (280 mg, 47.4%)

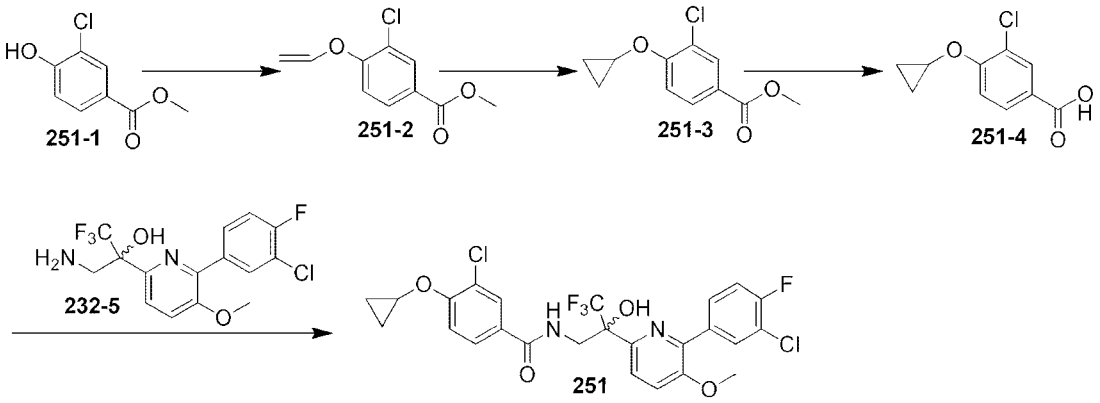
[0518] Compound **249-4** was prepared essentially as described in the preparation of **233**. Compound **249** was prepared essentially as described in the preparation of **232** by using **249-4** and **232-5**. Compound **249** was obtained as a white solid (7 mg, 13.7%). +ESI-MS: m/z 569.0$[M+H]^+$.

EXAMPLE 109
Preparation of Compound 250



[0519] Compound **250** was prepared essentially as described in the preparation of **235** by using methyl 4-hydroxy-3-methoxybenzoate and **232-5**. Compound **250** was obtained as white solid (19.8 mg, 8.7%). +ESI-MS: m/z 571.0$[M+H]^+$.

EXAMPLE 110
Preparation of Compound 251

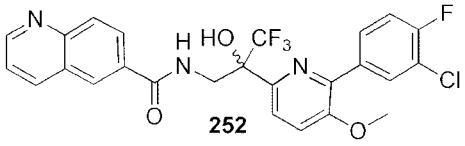


[0520] To a suspension of $[IrCl(cod)]_2$ (18 mg, 0.03 mmol) and sodium carbonate (171 mg, 1.6 mmol) in toluene (10 mL) was added **251-1** (500 mg, 2.68 mmol) and vinyl acetate (457 mg, 5.38 mmol) under Ar. The mixture was stirred at 100 °C for 2 h. The mixture was cooled to r.t., and treated with PE. The precipitate was removed by filtration, and the organic phase was concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA = 30:1) to give **251-2** (410 mg, 72%).

[0521] TFA (468 mg, 4.1 mmol) was slowly added to anhydrous DCM (5 mL) and Et_2Zn (4.2 mL, 4.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 mins, followed by the addition of CH_2I_2 (1.9 g, 7.1 mL). The resulting solution was stirred at 0 °C for 10 mins, and then **251-2** (300 mg, 1.42 mmol) was added. The mixture was allowed to warm to r.t., and stirred at r.t. overnight. The reaction was quenched with sat. NH_4Cl solution and extracted with EA (3 x 20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA=20:1) to give **251-3** (210 mg, 65.8%).

[0522] Compound **251-4** was prepared essentially as described in the preparation of **233**. Compound **251** was prepared essentially as described in the preparation of **232** by using **251-4** and **232-5**. Compound **251** was obtained as white solid (23 mg, 10.1%). +ESI-MS: m/z 559.0$[M+H]^+$.

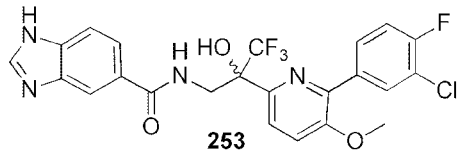
EXAMPLE 111
Preparation of Compound 252



252

[0523] Compound **252** was prepared essentially as described in the preparation of **232** by using quinoline-6-carboxylic acid and **232-5**. Compound **252** was obtained as a white solid (70 mg, 33%). +ESI-MS:m/z 520.1 $[M+H]^+$.

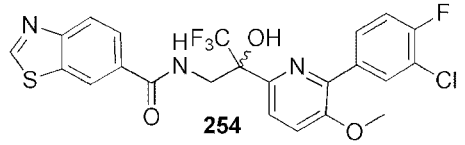
EXAMPLE 112
Preparation of Compound 253



253

[0524] Compound **253** was prepared essentially as described in the preparation of **232** by using 1H-benzo[d]imidazole-5-carboxylic acid and **232-5**. Compound **253** was obtained as a white solid (70 mg, 28%). +ESI-MS:m/z 509.1 $[M+H]^+$.

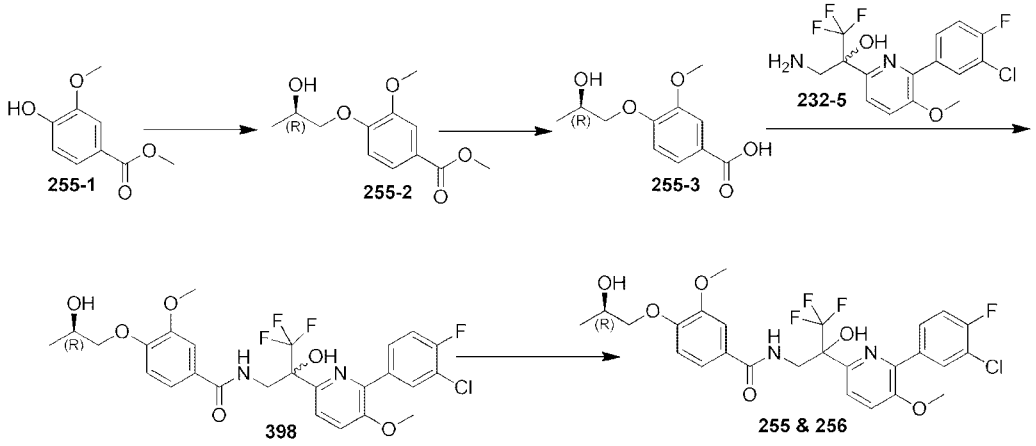
EXAMPLE 113
Preparation of Compound 254



254

[0525] Compound **254** was prepared essentially as described in the preparation of **232** by using benzo[d]thiazole-6-carboxylic acid and **232-5**. Compound **254** was obtained as a white solid (38 mg, 33%). +ESI-MS:m/z 525.9 $[M+H]^+$.

EXAMPLE 114
Preparation of Compounds 255, 256 and 398

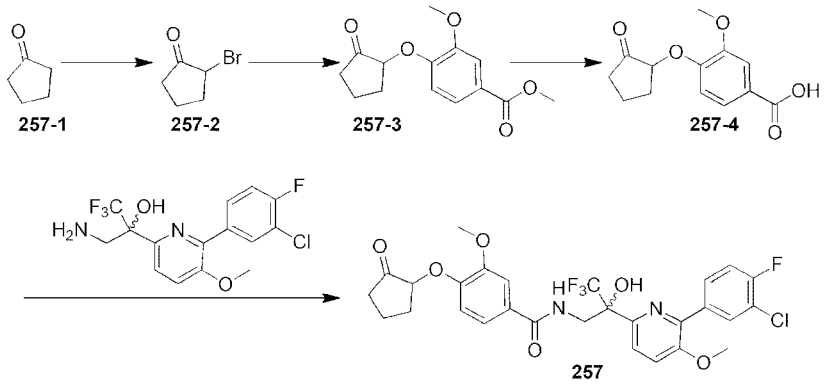


[0526] To a solution of **255-1** (5 g, 27 mmol) and (R)-2-methyloxirane (4.7 g, 82 mmol) in DMF (100 mL) was added K_2CO_3 (7.4 g, 54 mmol). The mixture was stirred at 80 ^oC for 3 h. The reaction was quenched with water and extracted by EA (3 x 50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography on silica gel to give **255-2** (6.5 g, 95%).

[0527] Compound **255-3** was prepared essentially as described in the preparation of **233**. Compound **398** was prepared essentially as described in the preparation of **232** by using **255-3** and **232-5**. Compound **398** was obtained as a white solid (687 mg, 68%).

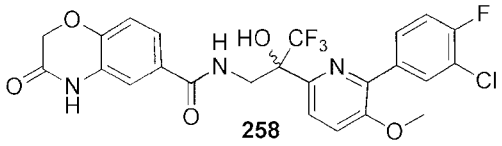
[0528] Compound **398** (350 mg, 1.14 mmol) was separated via SFC to give two diastereomers: **255** (113 mg) and **256** (107 mg). **255**: +ESI-MS:m/z 573.1 $[M+H]^+$. **256**: +ESI-MS:m/z 573.1 $[M+H]^+$.

EXAMPLE 115
Preparation of Compound 257



[0529] Compound **257-2** was prepared according to the procedure provided in Xu et al., *Angew. Chem. Int. Ed.* (2011) 50(51):12249-12252. Compound **257** was prepared essentially as described in the preparation of **234** by using **257-2** and **232-5**. Compound **257** was obtained as a white solid (51 mg, 23.8%). +ESI-MS:m/z 597.1 $[M+H]^+$.

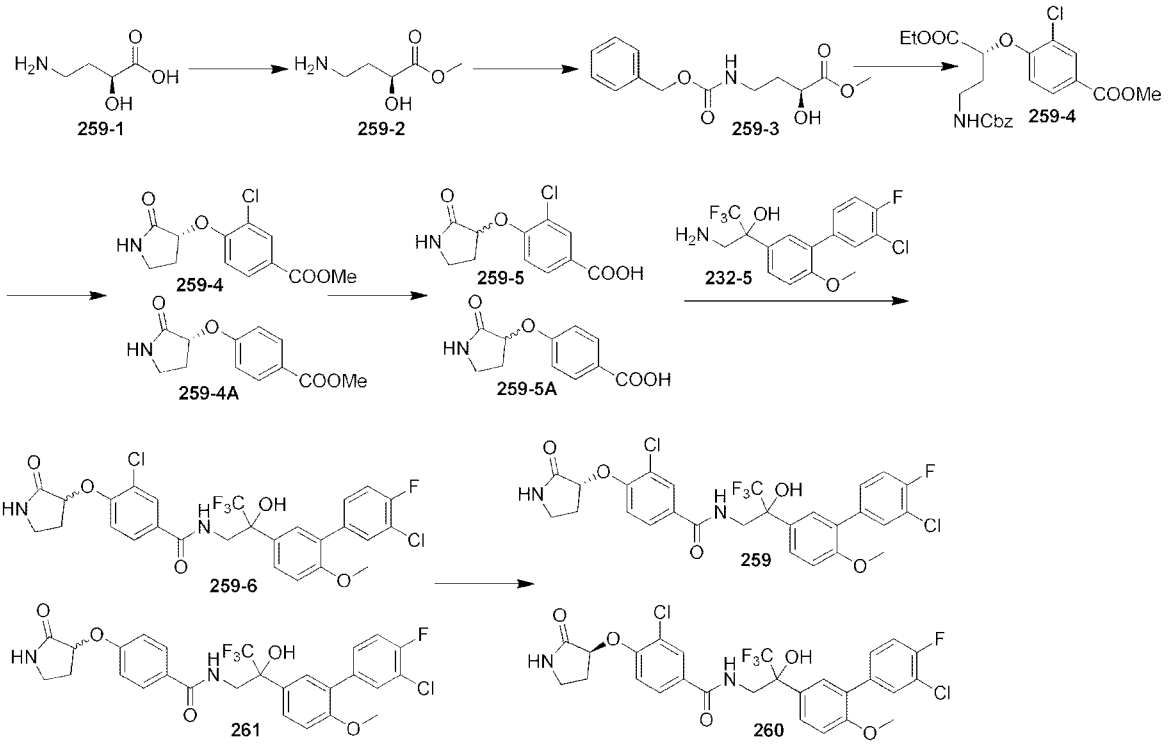
EXAMPLE 116
Preparation of Compound 258



[0530] Compound **258** was prepared essentially as described in the preparation of **232** by using 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxylic acid and **232-5**. Compound **258** was obtained as a white solid (80 mg, 41%). +ESI-MS:m/z 540.0 $[M+H]^+$.

EXAMPLE 117

Preparation of Compounds 259, 260 and 261



[0531] Compound **259-2** was prepared according to the procedure provided in Chinese Patent No. CN 1869008, published Nov. 29, 2006, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **259-2**. Compound **259-3** was prepared according to the procedure provided in Barbayianni et al., *J. Org. Chem.* (2005) 70(22):8730-8733, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **259-3**. Compound **259-4** was prepared essentially as described in the preparation of **235** by using **259-3** and methyl 3-chloro-4-hydroxybenzoate. Compound **259-4** was obtained as a white solid (4 g, 90%).

[0532] Under H_2 atmosphere, a mixture of **259-4** (4g, 9 mmol) and Pd/C (200 mg) in MeOH (45 mL) was stirred at 30 ^{0}C for 10 h. Purification by column chromatography on silica gel provided **259-4** (2 g, 80%). +ESI-MS:m/z 269.8$[M+H]^+$.

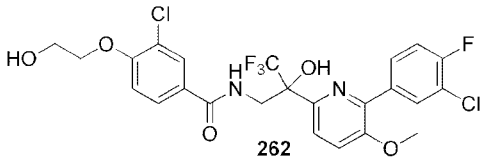
[0533] To a solution of **259-4** and **259-4A** (2 g, 7.4 mmol) in THF/H_2O (10 mL/1 mL) was added NaOH (400 mg, 10 mmol) in portions until the starting material was consumed completely. The mixture was neutralized by addition of 2 N HCl solution. The

mixture was extracted with EA (3 x 40 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated at low pressure to give **259-5** and **259-5A**.

[0534] Compound **259-6** and **261** were prepared essentially as described in the preparation of **232** by using **259-5** and **232-5**. Compound **259-6** (100 mg) and **261** (30 mg) were each obtained as a white solid. **261**: +ESI-MS:m/z 568.1 $[M+H]^+$.

[0535] Compound **259-6** (100 mg, 0.16 mmol) was separated by SFC to give **259** (80 mg, 80%) and **260** (20 mg, 20%). **259**: +ESI-MS:m/z 602.1 $[M+H]^+$. **260**: +ESI-MS:m/z 602.1 $[M+H]^+$.

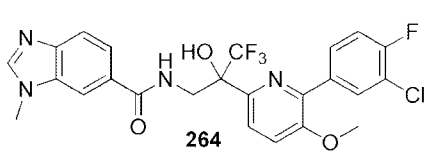
EXAMPLE 118
Preparation of Compound 262



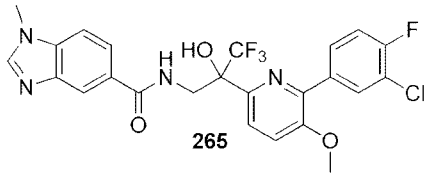
262

[0536] Compound **262** was prepared essentially as described in the preparation of **237** by using 2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylic acid and **232-5**. Compound **262** was obtained as a white solid (58 mg, 24.5%). +ESI-MS:m/z 563.0 $[M+H]^+$.

EXAMPLE 119
Preparation of Compounds 264 and 265



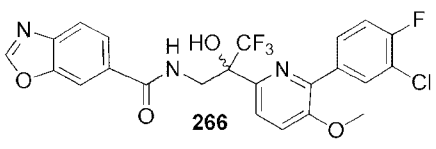
264



265

[0537] Compounds **264** and **265** were prepared essentially as described in the preparation of **232** by using 1-methyl-1H-benzo[d]imidazole-6-carboxylic acid or 1-methyl-1H-benzo[d]imidazole-5-carboxylic acid, and **232-5**, respectively. Compounds **264** (47 mg, 26%) and **265** (51 mg, 28%) were each obtained as a white solid. **264**: +ESI-MS:m/z 522.9 $[M+H]^+$. **265**: +ESI-MS:m/z 523.0 $[M+H]^+$.

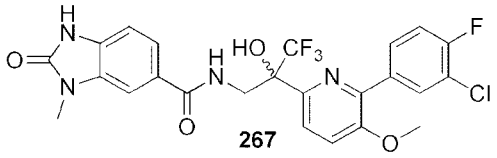
EXAMPLE 120
Preparation of Compound 266



266

[0538] Compound **266** was prepared essentially as described in the preparation of **232** by using benzo[d]oxazole-6-carboxylic acid and **232-5**. Compound **266** was obtained as a white solid (60 mg, 23%). +ESI-MS:m/z 509.9 $[M+H]^+$.

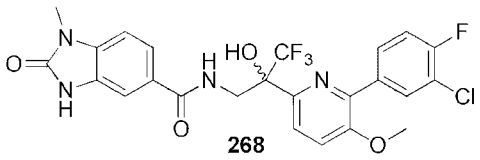
EXAMPLE 121
Preparation of Compound 267



267

[0539] Compound **267** was prepared essentially as described in the preparation of **232** by using 3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylic acid and **232-5** as start material. Compound **267** was obtained as a white solid (10.7 mg, 7.6%). +ESI-MS:m/z 539.0 $[M+H]^+$.

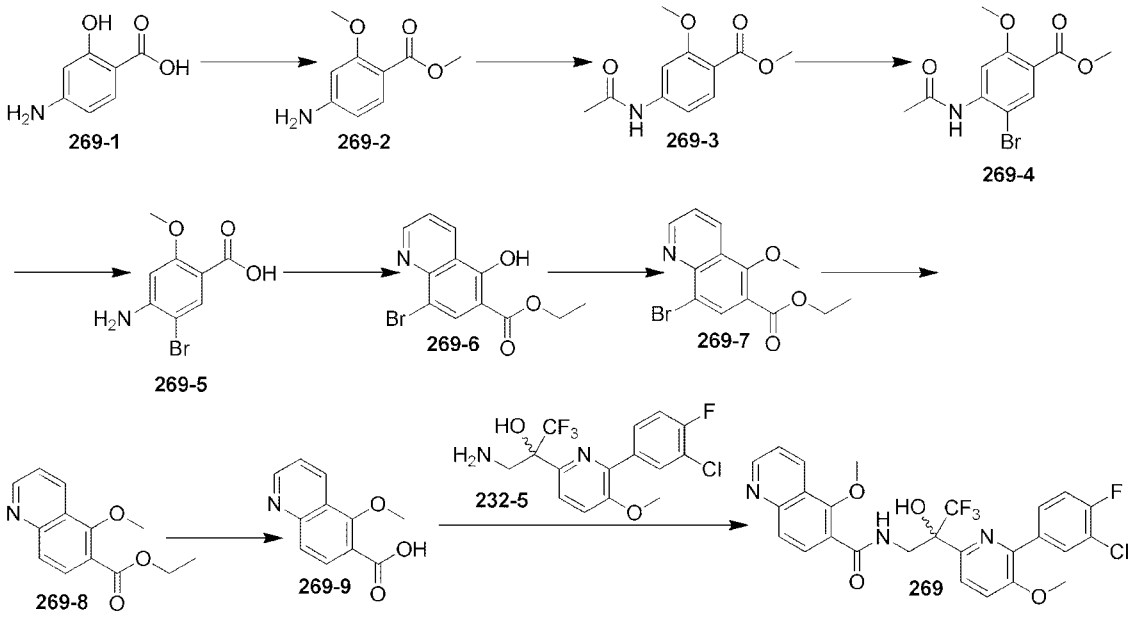
EXAMPLE 122
Preparation of Compound 268



268

[0540] Compound **268** was prepared essentially as described in the preparation of **232** by using 1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylic acid and **232-5**. Compound **268** was obtained as a white solid (14 mg, 8.4%). +ESI-MS:m/z 539.0 $[M+H]^+$.

EXAMPLE 123
Preparation of Compound 269



[0541] To a stirred solution of **269-1** (20.0 g, 130.68 mmol) in acetone (400 mL) was added KOH (18.4 g, 15 mmol) and $(CH_3)_2SO_4$ (29.4 mL, 318.9 mmol). The mixture was stirred at r.t. overnight. The solvent was evaporated at low pressure, and the residue was dissolved in hot water. The pH was adjusted to 9 with 1 N NaOH solution. After cooling to r.t., the precipitate was filtered off and thoroughly washed with cold EtOAc to give **269-2** as a light yellow powder (23.66 g, 63.4%). +ESI-MS:m/z 181.8 $[M+H]^+$.

[0542] To a solution of **269-2** (14.4 g, 8 mmol) in EtOH (120 mL) was added acetic anhydride (9.0 g, 88 mmol). The mixture was allowed to stir at 50 °C for 2 h. The mixture was cooled to r.t., and neutralized with aqueous $NaHCO_3$ solution. The mixture was extracted with EA (3 x 60 mL). The organic phase was dried over anhydrous sodium sulfate, and concentrated at low pressure. The residue was purified by flash column chromatography on silica gel (PE:EA 1:1) to give **269-3** (15.0 g, 84.1%). +ESI-MS:m/z 223.9 $[M+H]^+$.

[0543] To a solution of **269-3** (4.46 g, 20 mmol), PdOAc (0.45 g, 2 mmol) and $Cu(OAc)_2$ (7.26 g, 40 mmol) in 1,2-dichloroethane (150 mL) was added anhydrous $CuBr_2$ (8.93 g, 40 mmol) under N_2 atmosphere. The mixture was stirred at 90 °C for 72 h. After cooling to r.t., the reaction was quenched by water, and filtered through a celite pad. The solution was washed with brine, dried by anhydrous Na_2SO_4 and concentrated at low

pressure. The residue was purified by flash column chromatography on silica gel (PE:EA 1:1) to give **269-4** (6.04 g, 51.3%). +ESI-MS:m/z 303.7 $[M+H]^+$.

[0544] To a solution of **269-4** (4.53 g, 15 mmol) in ethanol (60 mL) and water (60 mL) was added NaOH (6.0 g, 150 mmol), and the mixture was stirred at 70 °C overnight. After cooling to 0°C, the mixture was neutralized with 5% aqueous HCl. The precipitate was filtered and concentrated to give **269-5** as a light yellow powder (3.1 g, 82.0%), which was used without further purification. +ESI-MS:m/z 247.6$[M+H]^+$.

[0545] A mixture of **269-5** (2.44 g, 10 mmol), glycerol (1.5 mL, 20 mmol), and 3-nitrobenzensulfonate (10 g, 45 mmol) were treated with conc. H_2SO_4 (25 mL) and H_2O (8.3 mL). The mixture was heated at 100 °C for 3 h., and then stirred at 140 °C for 1 h. The mixture was slowly cooled to 60 °C. Ethanol (15 mL) was added, and the mixture was stirred overnight. The mixture was neutralized with ammonia water, and extracted with EA (3 x 50 mL). The solution was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by flash column chromatography on silica gel (PE:EA 10:1) to give **269-6** (0.50 g, 16.9%). +ESI-MS:m/z 295.9 $[M+H]^+$.

[0546] To a stirred solution of **269-6** (0.295 g, 1 mmol) in DMF (3 mL) was added K_2CO_3 (145 mg, 1.05 mmol) and CH_3I (149 mg, 1.05 mmol). The mixture was stirred at r.t. overnight, and then concentrated at low pressure. The residue was dissolved in EA (20 mL). The solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography on silica gel (PE:EA= 5:1) to give **269-7** (216 mg, 70.0%) as a white solid. +ESI-MS:m/z 311.9 $[M+H]^+$.

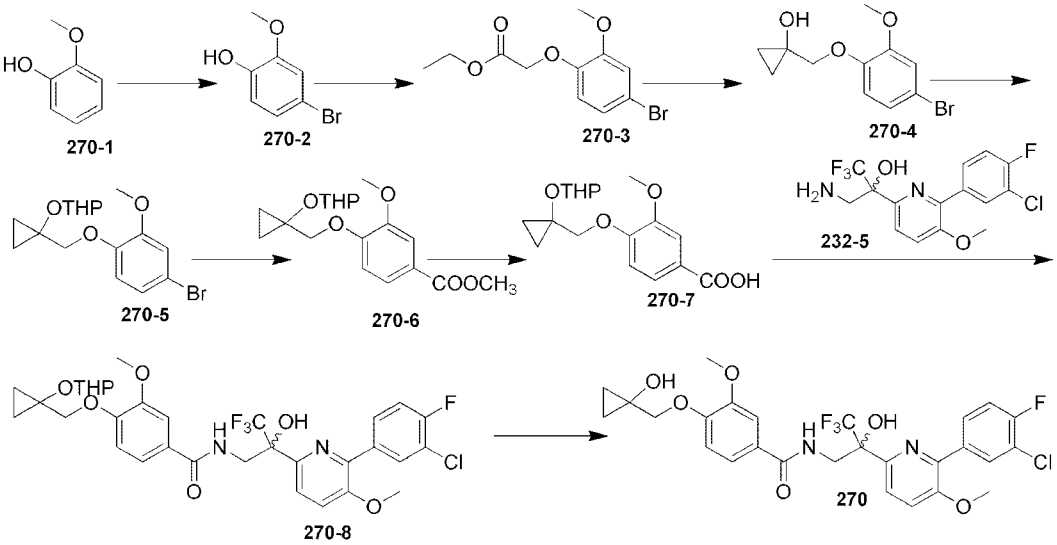
[0547] To a stirred solution of **269-7** (240 g, 0.77 mmol) in methanol (30 mL) was added Pd/C (15 mg). The mixture was stirred at r.t. under H_2 (balloon) for 1 h. The mixture was filtered, and the filtrate was concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA= 5:1) to give **269-8** (101 mg, 56.0%) as a white solid. +ESI-MS:m/z 231.9 $[M+H]^+$.

[0548] To a solution of **269-8** (0.1 g, 0.44 mmol) in CH_3OH (2 mL) and water (2mL) was added NaOH (80 mg, 2 mmol), and the mixture was stirred at 50 °C for 0.5 h. The mixture was cooled to 0 °C, and the pH was adjusted to 5 using 5% HCl solution. The mixture was extracted with EA (3 x 20 mL). The organic layer was dried over anhydrous

sodium sulfate, and concentrated at low pressure to give crude **269-9** (66 mg, 75.8%) as a white solid, which was used without further purification.

[0549] To a solution of **269-9** (66 mg, 0.325 mmol) in DCM (5 mL) were added DMF (1 drop) and $(COCl)_2$ (0.23 mL, 1.3 mmol). The mixture was stirred at r.t. for 2 h, and then concentrated at low pressure. The residue was treated with a solution of **232-5** (117 mg, 0.325 mmol) and TEA (0.28 mL) in DCM (5 mL) at 50 °C. The mixture was allowed to stir at r.t. overnight. The mixture was diluted with water, and extracted with EA (3 x 20 mL). The organic layer was dried over anhydrous sodium sulfate, and concentrated in vacuum. The residue was purified by HPLC to give **269** as a white solid (25 mg, 14.0%). +ESI-MS:m/z 550.0 $[M+H]^+$.

EXAMPLE 124
Preparation of Compound 270



[0550] Compound **270-2** was prepared according to the procedure provided in Rye et al., *Eur. J. Med. Chem.* (2013) 60:240-248, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **270-2**. To a stirred solution of **270-2** (18.0 g, 89.1 mmol) in acetone (200 mL) were added ethyl 2-bromoacetate (29.6 g, 178.2 mmol) and K_2CO_3 (36.9 g, 270 mmol). The mixture was stirred at 80 °C for 12 h. The mixture was diluted with water and extracted with EA. The organic layers were dried over anhydrous sodium sulfate, and concentrated in vacuum. The residue was purified by column chromatography on silica gel to give crude **270-3** (25 g yield: 98%).

[0551] To a solution of **270-3** (11 g, 38.2 mmol) in anhydrous THF (100 mL) was added $Ti(i\text{-}PrO)_4$ (10.85 g, 38.2 mmol) under N_2 at 0 °C, and then EtMgBr (34.4 mL, 103.14 mmol) was added dropwise. The mixture was stirred at r.t. overnight. The reaction was quenched with water, and extracted with EA (3 x 60 mL). The organic layer was dried over anhydrous sodium sulfate, and concentrated at low pressure. The residue was purified by column chromatography on silica gel to give **270-4** (4.2 g, 40.4%).

[0552] To a solution of **270-4** (2.5 g, 9.19 mmol) in DCM (20 mL) were added DHP (1.54 g, 18.38 mmol) and TsOH (158.2 mg, 0.92 mmol). The mixture was stirred at r.t. overnight. The reaction was quenched with water, and extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel to give **270-5** as a white solid (2.6 g, yield: 74.0%).

[0553] To a solution of **270-5** (1.5 g, 4.21 mmol) in anhydrous THF (15 mL) was added *n*-BuLi (2.0 mL, 5.0 mmol) at -78 °C dropwise. After the mixture was stirred at -78 °C for 0.5 h, $ClCOOCH_3$ (2.39 g, 25.28 mmol) was added in one portion. The mixture was stirred at -78 °C for 1 h, and then diluted with EA (50 mL) and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by chromatography to generate **270-6** as a white solid (820 mg, yield: 58%).

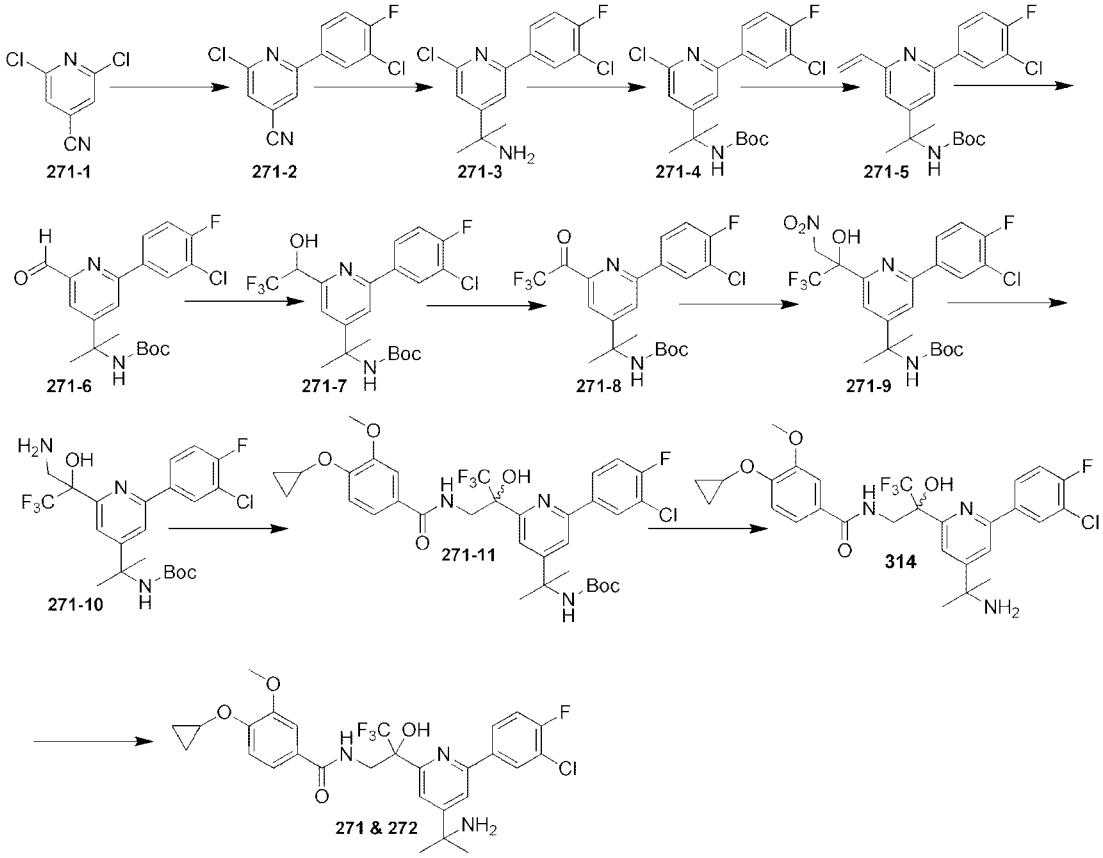
[0554] To a stirred solution of **270-6** (410 mg, 1.22 mmol) in $EtOH/H_2O$ (3:1, 10 mL) was added NaOH (195 mg, 4.88 mmol), and the mixture was stirred at 50 °C for 1 h. The mixture was diluted with water and extracted with EA. The pH of aqueous layers was adjusted to 4.0 by adding 5% HCl solution. The aqueous phase was extracted with EA. The organic layers were dried over anhydrous sodium sulfate and concentrated in vacuum to give crude **270-7** (198 mg).

[0555] To a solution of **270-7** (200 mg, 0.62 mmol) in DMF (15 mL) were added DIPEA (240 mg, 1.86 mmol) and HATU (236 mg, 0.62 mmol). The mixture was stirred at r.t. for 30 mins, and then **232-5** (226 mg, 0.62 mmol) was added. The mixture was stirred at r.t. for 2 h, and then diluted with water and extracted with EA (3 x 20 mL). The organic layer

was dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel to give **270-8** (250 mg, 60.4%).

[0556] To a solution of **270-8** (250 mg, 0.37 mmol) in EtOH (10 mL) was added PPTS (19.4 mg, 0.075 mmol). The mixture was stirred at 70 °C for 2 h, and then diluted with EA (50 mL) and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by prep-HPLC to give **270** as a white solid (80 mg, 37.0%). +ESI-MS:m/z 585.1 $[M+H]^+$.

EXAMPLE 125
Preparation of Compounds 271, 272 and 314



[0557] A 1 L round bottom flask was charged with a mixture of **271-1** (15 g, 86.71 mmol), (3-chloro-4-fluorophenyl) boronic acid (15 g, 86.03 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.0 g, 1.37 mmol) and K_2CO_3 (23.7g, 172 mmol) in dioxane/H_2O (450 mL/50 mL) under N_2 atmosphere. The mixture was heated to 100 °C for 2 h. The mixture was cooled to r.t. and dioxane was evaporated under reduced pressure. The residue was diluted with EA and water. The organic layer was dried

over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue (PE:EtOAc 100:1 to 40:1) afforded **271-2** as a white solid (11 g, 47.8%).

[0558] To a solution of **271-2** (7.2 g, 26.9 mmol) in toluene (200 mL) was added MeMgBr (27 mL, 81mmol) in 5 mins. The solution was stirred for 30 mins at r.t. $Ti(OiPr)_4$ (8 mL, 27.3 mmol) was added slowly at r.t. The solution was bathed in 100 °C oil and stirred for 20 mins. The mixture was cooled to r.t., and the reaction was quenched with a sat. aq. Na_2CO_3 solution. The mixture was separated by filtration, and the cake was washed with EA. The organic phase was concentrated to dryness, and crude **271-3** (7.0 g, brown oil) was used directly in the next step.

[0559] To a solution of **271-3** (7.0 g, 23.4 mmol) in toluene (100 mL), Et_3N (7.09 g, 70.2 mmol) and Boc_2O (5.6 g, 25.7 mmol) were added at r.t. The solution was bathed in 100 °C oil and stirred for 3 h. The solution was cooled to r.t., and separated between EA (300 mL) and water (200 mL). The organic phase was washed with brine and dried over Na_2SO_4. The organic phase was concentrated, and the residue was purified by chromatography on silica gel (PE:EA 20:1-10:1) to give **271-4** as a yellow solid (7.05 g, 75.5%). +ESI-MS: m/z 398.9 $[M+H]^+$.

[0560] To a solution of **271-4** (7.0 g, 17.5 mmol) in EtOH (70 mL) were added K_2CO_3 (3.62 g, 26.2 mmol) and potassium trifluoro(vinyl)borate (2.8 g, 21.0 mmol) at r.t. $Pd(dppf)Cl_2$ (256 g, 0.35 mmol) was added under N_2 atmosphere. The mixture was bathed in 100 °C oil and stirred for 3 h. The solution was concentrated at low pressure, and the residue was separated between EA (100 mL) and water (50 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by chromatography on silica gel (PE:EA 20:1-10:1) to give **271-5** as a yellow oil (6.1 g, 89.3%). +ESI-MS: m/z 391.0 $[M+H]^+$.

[0561] A solution of **271-5** (6.1 g, 15.6 mmol) in DCM (150 mL) was bubbled with O_3 at -78 °C until the solution turned blue. The solution was then bubbled with N_2 until the blue colour disappeared. PPh_3 (4.9 g, 18.72 mmol) was added at -78 °C, and stirred for 2 h at -78 °C. The mixture was concentrated at low pressure, and the residue was purified by chromatography on silica gel (PE:EA 10:1-5:1) to give **271-6** as a white solid (4.8 g, 78.4%).

[0562] To a solution of **271-6** (4.86 g, 12.38 mmol) in dry DMF (25 mL) was added $TMSCF_3$ (4.4 g, 31.0 mmol). The mixture was cooled down to -78 °C, and TBAF (1M in THF, 7.3 mL, 7.3 mmol) was added dropwise. The mixture was allowed to gradually warm to r.t., and stirred for 0.5 h. The mixture was diluted with water and EtOAc. The organic layers was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue (PE:EtOAc 100:0 to 80:20) afforded **271-7** (4.1 g, 72%).

[0563] To a stirred solution of **271-7** (4.1 g, 8.86 mmol) in dry DCM (45 mL) was added Dess-Martin periodinane (4.96 g, 17.7 mmol). The mixture was stirred at r.t. for 10 h. The mixture was concentrated under reduced pressure and chromatography of the residue (PE:EtOAc 100:0 to 70:30) afforded **271-8** (3.8 g, 93%).

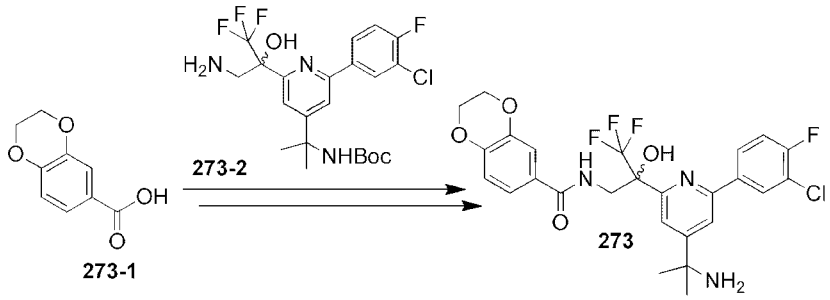
[0564] To a solution of **271-8** (3.8 g, 8.25 mmol) in $MeNO_2$ (10 mL) was added Et_3N (2 mL, 14mmol), and the mixture was stirred at r.t. for 30 mins. The mixture was concentrated under reduced pressure, and the residue was dissolved in co-solvent of EtOH:H_2O(50 mL:5 mL). The mixture was treated with iron powder (1.85 g, 33mmol) and NH_4Cl (1.8 g, 33mmol), and then heated to 80 °C for 2 h. After filtration, the solution was concentrated under reduced pressure. The residue was purified by chromatography to give **271-10** (2.5 g, 61.7%). +ESI-MS: m/z 491.9 $[M+H]^+$.

[0565] A 100 mL round bottom flask was charged with a solution of 4-cyclopropoxy-3-methoxybenzoic acid (208 mg, 1.0 mmol), DIPEA (193 mg, 1.5 mmol) and HATU (380 mg, 1.0 mmol) in anhydrous DMF (10 mL). The mixture was stirred at r.t. for 30 mins. Compound **271-10** (490 mg, 1.0 mmol) was added in one portion, and the mixture was stirred at r.t. for 2~3 h. The mixture was diluted with EA and water, and the organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA 1:1) to give **271-11** as a pale yellow oil (610 mg, 88%).

[0566] A 50 mL round bottom flask was charged with a solution of **271-11** (610 mg, 0.88 mmol) in EA (10 mL). The solution was treated with HCl in EA (10 mL, 4.0 M). The mixture was stirred at r.t. for 1~2 h. The mixture was concentrated at low pressure to give crude **314** (550 mg).

[0567] Compound **314** (550 mg) was separated via SFC separation to give two enantiomers. The two enantiomers were treated with 2 M HCl in EA and then concentrated to give **271** (120 mg) and **272** (124 mg). **271**: +ESI-MS:m/z 582.1 $[M+H]^+$. **272**: +ESI-MS:m/z 582.1 $[M+H]^+$.

EXAMPLE 126
Preparation of Compound 273

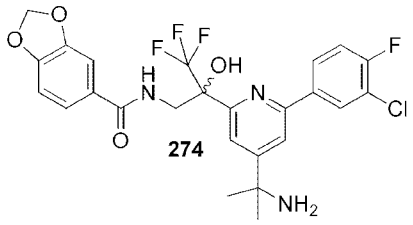


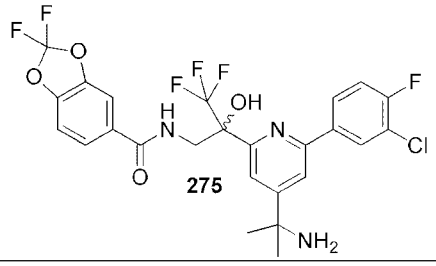
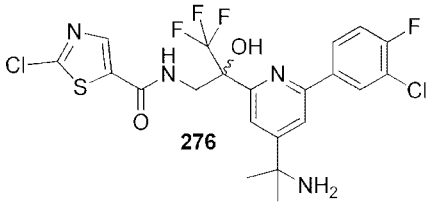
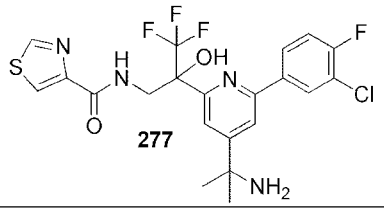
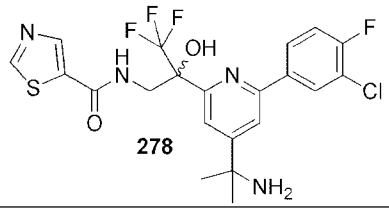
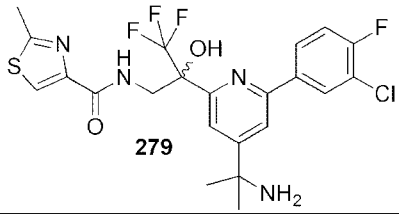
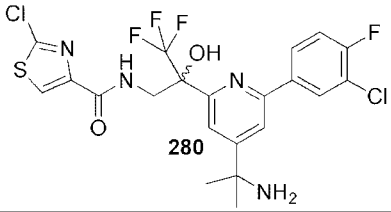
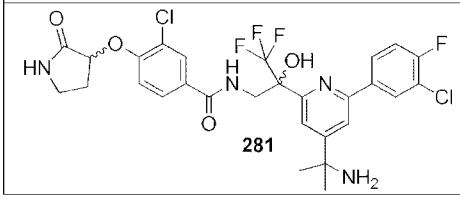
[0568] Compound **273** was prepared essentially as described in the preparation of compound **272** by **273-1** and **273-2**. Compound **273** was obtained as a white solid (41 mg, 52.2%). +ESI-MS:m/z 554.0 $[M+H]^+$.

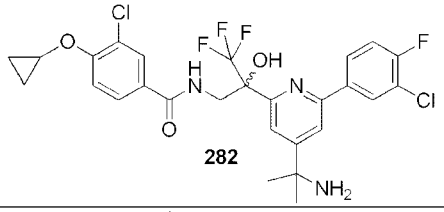
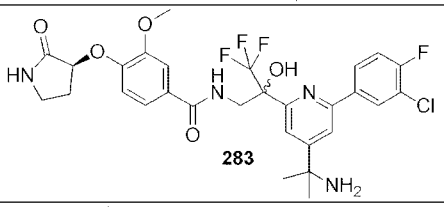
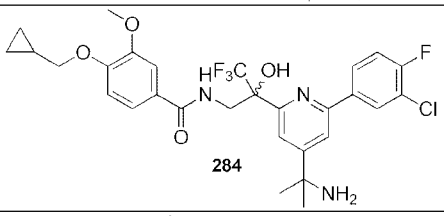
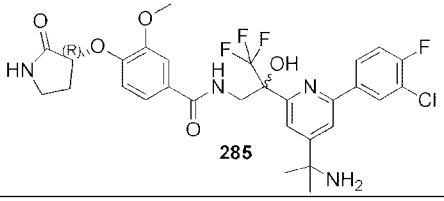
EXAMPLE 127
Preparation of Compounds 274-285

[0569] The following compounds in Table 1 were prepared essentially as described in the preparation of **272** by using the listed acid and amine.

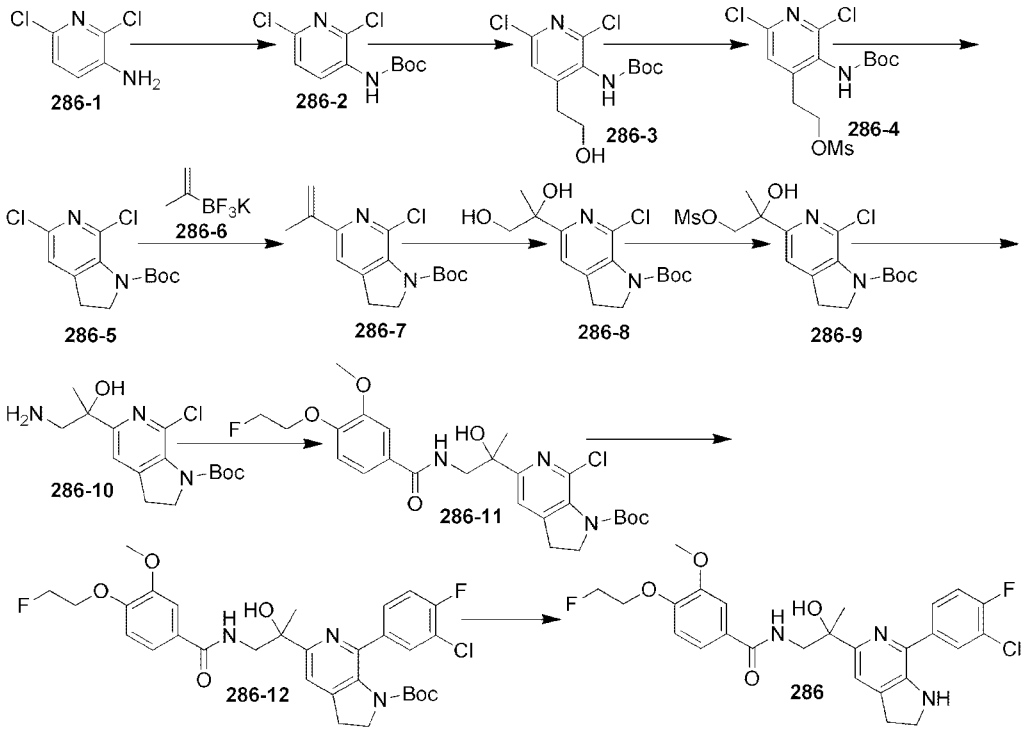
Table 1

Compound	Acid	Amine	Yield and +ESI-MS:m/z
	benzo[d][1,3]dioxole-5-carboxylic acid	273-2	32 mg, 58.8% 539.9 $[M+H]^+$

Compound	Acid	Amine	Yield and +ESI-MS:m/z
 275	2,2-difluorobenzo[d][1,3]dioxole-5-carboxylic acid	273-2	38 mg, 46.5% 576.0 $[M+H]^+$
 276	2-chlorothiazole-5-carboxylic acid	273-2	30 mg, 54.5% 536.9 $[M+H]^+$
 277	thiazole-4-carboxylic acid	273-2	32 mg, 64.0% 502.9 $[M+H]^+$
 278	thiazole-5-carboxylic acid	273-2	18 mg, 36.0% 502.9 $[M+H]^+$
 279	2-methylthiazole-4-carboxylic acid	273-2	23 mg, 45 % 517.0 $[M+H]^+$
 280	2-chlorothiazole-4-carboxylic acid	273-2	24 mg, 45 % 537.0 $[M+H]^+$
 281	3-chloro-4-((2-oxopyrrolidin-3-yl)oxy)benzoic acid	273-2	28 mg, 45 % 629.0 $[M+H]^+$

Compound	Acid	Amine	Yield and +ESI-MS:m/z
 282	3-chloro-4-cyclopropoxybenzoic acid	273-2	20 mg, 34 % 585.9 $[M+H]^+$
 283	*(S)*-3-methoxy-4-((2-oxopyrrolidin-3-yl)oxy)benzoic acid	273-2	28 mg, 45 % 625.1 $[M+H]^+$
 284	4-(cyclopropylmethoxy)-3-methoxybenzoic acid	273-2	30 mg, 68.2% 596.1 $[M+H]^+$
 285	*(R)*-3-methoxy-4-((2-oxopyrrolidin-3-yl)oxy)benzoic acid	273-2	28 mg, 45 % 625.0 $[M+H]^+$

EXAMPLE 128
Preparation of Compound 286



[0570] Compound **286-2** was prepared according to the procedure provided in PCT Publication No. WO 2009/005638, published Jan. 8, 2009, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **286-2**.

[0571] To a solution of **286-2** (1.83 g, 7 mmol) in THF (15 mL) was added n-BuLi (7 mL, 2.5 M in THF) at -78 °C. After 5 mins, TMEDA (1.624g, 14 mmol) was added at -78 °C. The solution was warmed slowly to -30 °C, and stirred for 30 mins at -30 °C. The solution was cooled to -78 °C and oxirane (0.7 mL, 14 mmol) was added. The solution was stirred at -78 °C for 2 h., and stirred overnight at r.t. The reaction was quenched with H_2O and extracted with EA (2 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (PE:EA 10:1) to give **286-3** (0.7 g, 32.7 %).

[0572] To a solution of **286-3** (4.5 g, 14.7 mmol) in DCM (100 mL) was added TEA (4.45 g, 44.1 mmol). After cooled to 0 °C, MsCl (3.36 g, 29.4 mmol) was added slowly. The solution was stirred for 30 mins. The reaction was quenched with H_2O, and extracted with DCM (3 x 100 mL). The organic phase was washed with brine, dried over

anhydrate sodium sulfate and concentrated at low pressure to give crude **286-4** (5.6 g, 99.2%). +ESI-MS:m/z 384.8 $[M+H]^+$.

[0573] To a solution of **286-4** (5.6 g, 14.5 mmol) in DMF (50 mL) was added K_2CO_3 (4.02 g, 29.2 mmol). The mixture was heated up to 50-60 ^oC, and stirred for 1 h. The solution was cooled to r.t., poured into cold water and extracted with EA (2 x 100 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by chromatography (PE:EA 10:1) to give **286-5** (3.1g, 74.3%).

[0574] To a solution of **286-5** (1.68 g, 5.83 mmol), **286-6** (860 mg, 5.83 mmol) and K_2CO_3 (1.61 g, 11.66 mmol) in MeOH (50 mL) was added $Pd(dppf)Cl_2$ (426 mg, 0.583 mmol). The mixture was degassed and then refilled with N_2 (3 times). The mixture was stirred under nitrogen at 70 °C for 15 h, and then cooled to r.t., and extracted with EA (3 x 50 mL). The organic phase was washed by brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (PE:EA 5:1) to give **286-7** as a white solid (1.2 g, 70%).

[0575] To a solution of **286-7** (2.94 g, 10 mmol) in DCM (50 mL) were added NMO (2.4 g, 20 mmol) and OsO_4 (500 mg, 0.2 mmol) at r.t. The mixture was stirred at r.t. for 1 h. The reaction was quenched with sat. aq. Na_2SO_3, and stirred for 2 h. The mixture was extracted with DCM (2 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (PE:EA 3:1) to give **286-8** (2.94 g, 89.6%). +ESI-MS:m/z 328.9 $[M+H]^+$.

[0576] To a solution of **286-8** (3.28 g, 10 mmol) and TEA (4.45 g, 44.1 mmol) in DCM (20 mL) was added MsCl (2.2 g, 20 mmol) slowly at 0^oC. The solution was stirred for 30 mins, and then diluted with DCM (20 mL). The solution was washed with brine and dried over anhydrous sodium sulfate. The organic phase was concentrated at low pressure to give crude **286-9** (4.06 g, 100.0%).

[0577] A solution of **286-9** (4.0 g, 10 mmol) in ammonia water and ethanol (10 mL:10 mL) in a seal tube was stirred for 1 h at r.t. The solution was heated to 40 °C for 15 h.

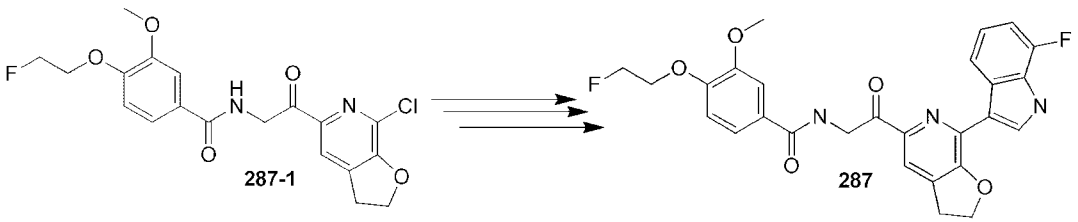
The mixture was concentrated to dryness under reduced pressure to give crude **286-10** (1.6 g, 50%), which was used without purification. +ESI-MS:m/z 327.9 $[M+H]^+$.

[0578] To a solution of 4-(2-fluoroethoxy)-3-methoxybenzoic acid (214 mg, 1 mmol), HATU (456 mg, 1.2 mmol) and DIPEA (258 mg, 2 mmol) in anhydrous DMF (5 mL) was added **286-10** (327 mg, 1 mmol) at 25 °C. The solution was stirred for 2 h at 25 °C. The reaction was quenched by a sat. aq. $NaHCO_3$ solution (40 mL), and then extracted with EA (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA 3:1) to give **286-11** (201 mg, 38.2%). +ESI-MS:m/z 524.0 $[M+H]^+$.

[0579] To a solution of **286-11** (150 mg, 0.3 mmol), (3-chloro-4-fluorophenyl)boronic acid (105 mg, 0.6 mmol) and K_2CO_3 (84 mg, 0.6 mmol) in dioxane (6 mL) was added $Pd(dppf)Cl_2$ (22 mg, 0.03 mmol). The mixture was degassed and then refilled with N_2 (3 times). The mixture was heated to 120 °C by microwave under N_2 for 2 h. The solution was cooled to r.t. and diluted with EA (20 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (PE:EA 1:1) to give **286-12** (123 mg, 65%).

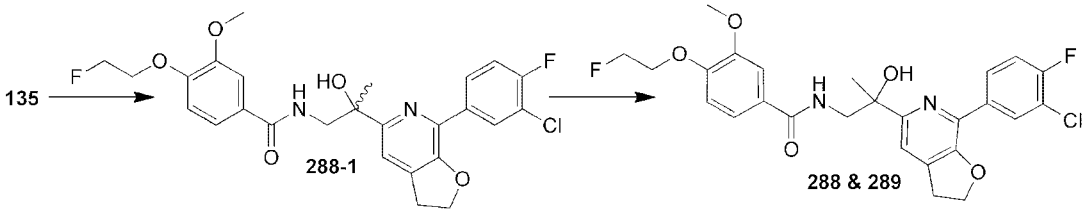
[0580] To a solution of **286-12** (123 mg, 0.2 mmol) in DCM (2 mL) was added TFA (4 mL) at r.t. The mixture was stirred for 30 mins, concentrated to dryness and dissolved in EA (20 mL). The solution was washed with a sat. $NaHCO_3$ solution. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by prep-HPLC to give **286** (80 mg, 77.6%) as a yellow solid. +ESI-MS:m/z 518.1 $[M+H]^+$.

EXAMPLE 129
Preparation of Compound 287



[0581] Compound **287** was prepared essentially as described in the preparation of **286** by using 7-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole and **287-1**. Compound **287** was obtained as white solid. +ESI-MS:m/z 507.9 $[M+H]^+$.

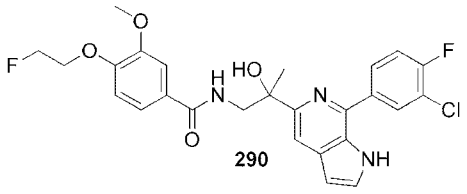
EXAMPLE 130
Preparation of Compounds 288 and 289



[0582] To a solution of **135** (400 mg, 0.80 mmol) in THF (10 mL) was added MeMgBr (3 mL, 1.3 N in THF) under N_2. The mixture was stirred at r.t. for 1 h under N_2. The reaction was quenched with sat. aq. NH_4Cl and extracted with EA (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by prep-HPLC to give **288-1** (150 mg).

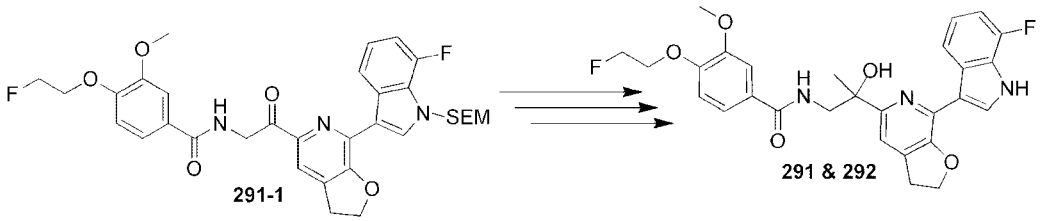
[0583] Compounds **288** (39 mg) and **289** (41 mg) were obtained by SFC separation of **288-1**. **288**: +ESI-MS:m/z 519.3 $[M+H]^+$. **289**: +ESI-MS: m/z 519.3 $[M+H]^+$.

EXAMPLE 131
Preparation of Compound 290



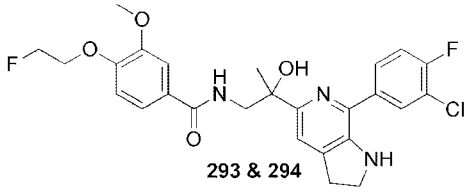
[0584] To a solution of **286** (400 mg, 0.77 mmol) in DCM (20 mL) was added MnO_2 (336 mg, 3.86 mmol) at r.t. The mixture was stirred for 2 h. The precipitate was removed by filtration, and the filtrate was concentrated at low pressure. The residue was purified by prep-HPLC to give **290** (150 mg, 37.5%) as a yellow solid. +ESI-MS:m/z 515.9 $[M+H]^+$.

EXAMPLE 132
Preparation of Compounds 291 and 292



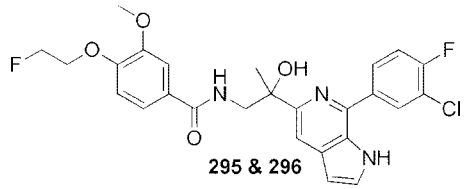
[0585] Compounds **291** and **292** were prepared essentially as described in the preparation of **288** and **289** by using **291-1**. Compound **291** (31 mg) and **292** (30 mg) were obtained as white solids. **291**: +ESI-MS:m/z 524.1 $[M+H]^+$. **292**: +ESI-MS:m/z 524.1 $[M+H]^+$.

EXAMPLE 133
Preparation of Compounds 293 and 294



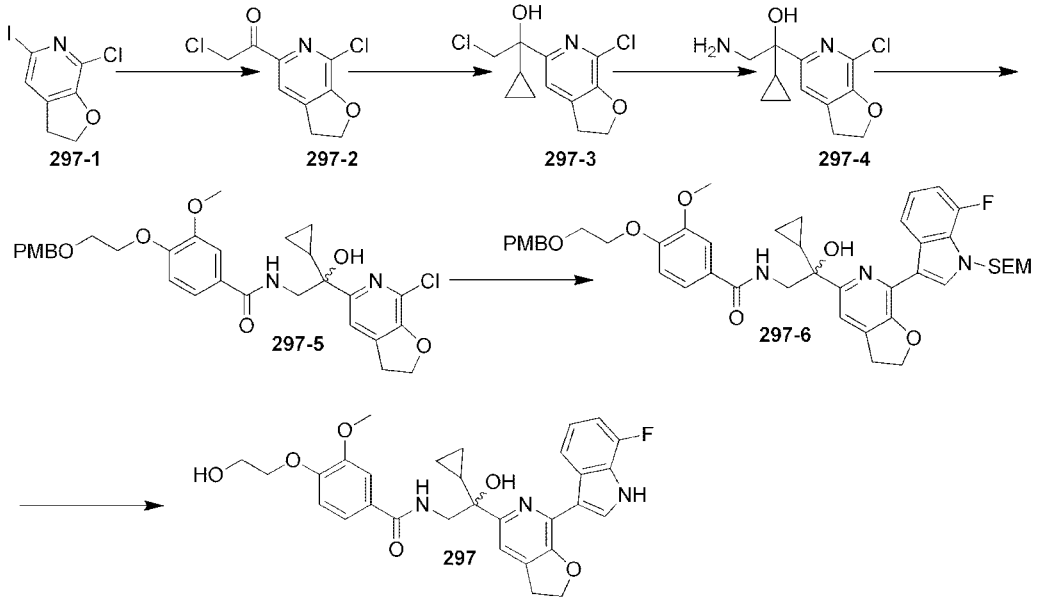
[0586] Compound **286** (60 mg) was separated via SFC separation to obtain two enantiomers: **293** (24 mg) and **294** (22 mg). **293**: +ESI-MS:m/z 517.9 $[M+H]^+$. **294**: +ESI-MS:m/z 517.9 $[M+H]^+$.

EXAMPLE 134
Preparation of Compounds 295 and 296



[0587] Compound **290** (65 mg) was separated via SFC separation to obtain two enantiomers: **295** (21 mg) and **296** (18 mg). **295**: +ESI-MS:m/z 515.9 $[M+H]^+$. **296**: +ESI-MS:m/z 515.9 $[M+H]^+$.

EXAMPLE 135
Preparation of Compound 297

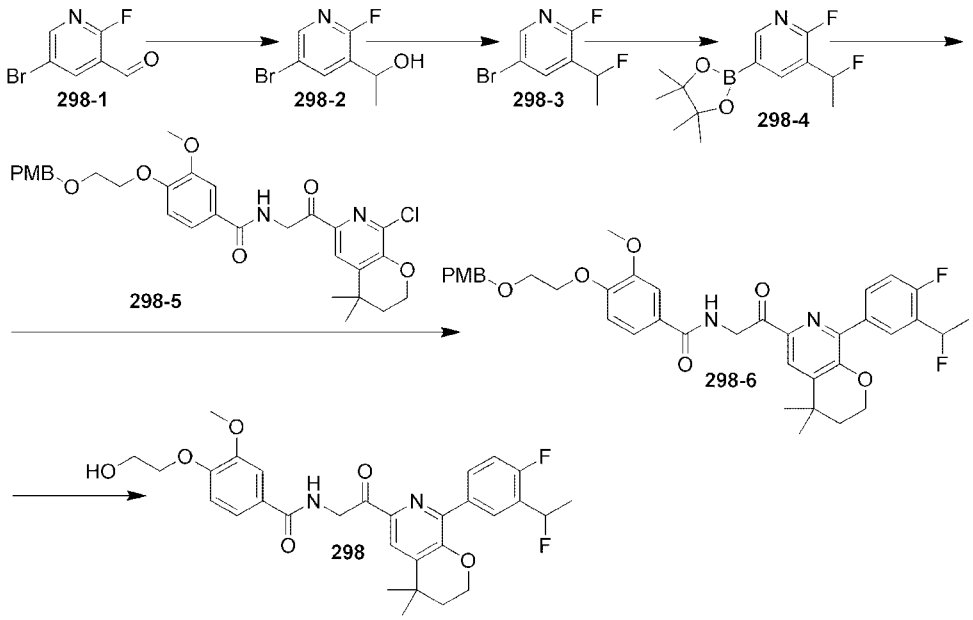


[0588] To a solution of **297-1** (1.4 g, 5.0 mmol) and 2-chloro-N-methoxy-N-methylacetamidein (700 mg, 5.0 mmol) in THF (20 mL) was added *i*-PrMgCl (3 mL, 2.0 M in THF) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with water, and extrcted with EA (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography on silical gel to give **297-2** (1.0 g, 87%). +ESI-MS:m/z 232.0 $[M+H]^+$.

[0589] To a solution of **297-2** (460 mg, 2.0 mmol) in THF (4 mL) was added cyclopropylmagnesium bromide (4 mL, 0.5 M in THF) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with water, and extracted with EA (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Compound **297-3** was used without furthur purification.

[0590] Compound **297** was prepared essentially as described in the preparation of **286** by using **297-3**. Compound **297** was obtained as white solid (98 mg). +ESI-MS:m/z 548.3 $[M+H]^+$.

EXAMPLE 136
Preparation of Compound 298

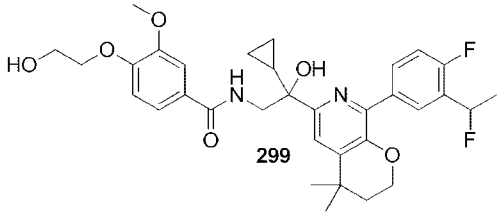


[0591] Compound **298-2** was prepared according to the procedure provided in PCT Publication No. WO 2009/016460, published Feb. 5, 2009, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **298-2**. To a solution of **298-2** (1.8 g, 8.3 mmol) in DCM (10 mL) was added DAST (2 mL) dropwise at 0°C. The mixture was stirred at r.t. for 30 mins. The reaction was quenched with sat. $NaHCO_3$ solution at 0 °C and extracted with EA (3 x 30 mL). The combined organic layers were washed by brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography on silica gel column (PE:EA 30:1) to give **298-3** as a white solid (1.4 g, 77.8%).

[0592] To a solution of **298-3** (1.4 g, 6.4 mmol) in THF (10 mL) was added n-BuLi (3.3 mL, 2.5 N in hexane) dropwise at -78 °C under N_2. The mixture was stirred at -78 °C for 30 mins. 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.6 g, 9.4 mmol) was added at -78 °C, and the mixture was allowed to warm to r.t., and stirred 10 mins. The reaction was quenched with sat. NH_4Cl solution and extracted with EA. The combined organic solutions were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA 50:1) to give **298-4** as an oil (1.0 g, 58.9%).

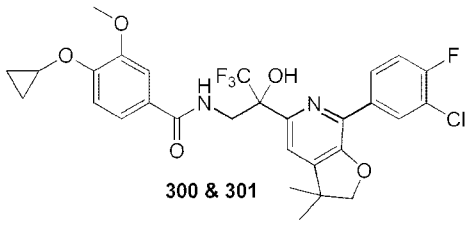
[0593] Compound **298** was prepared essentially as described in the preparation of **286** by using **298-4**. Compound **298** was obtained as a white solid (70 mg). +ESI-MS:m/z 555.1 $[M+H]^+$.

EXAMPLE 137
Preparation of Compound 299



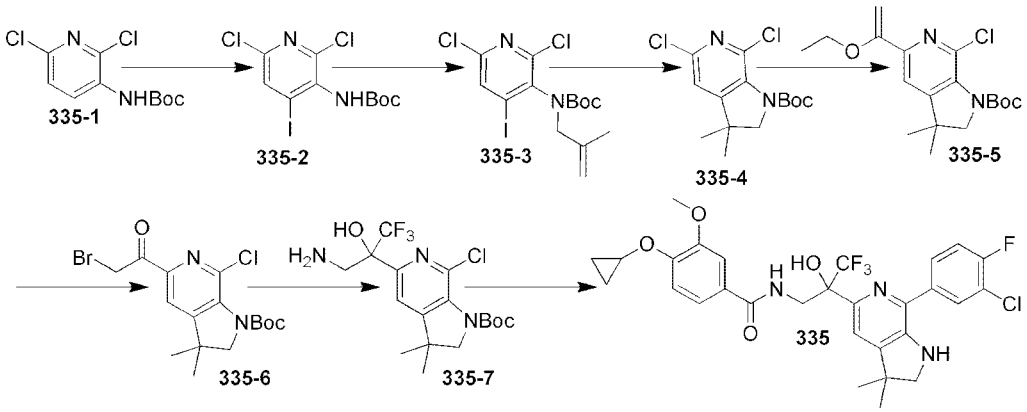
[0594] Compound **299** was prepared essentially as described in the preparation of **288** and **289** by using **298** and cyclopropylmagnesium bromide. Compound **299** (30 mg) was obtained as a white solid. +ESI-MS:m/z 597.2 $[M+H]^+$.

EXAMPLE 138
Preparation of Compounds 300 and 301



[0595] Compound **229** (28 mg, 0.047 mmol) was separated via SFC separation to give two enantiomers: **300** (3.8 mg) and **301** (4.5 mg) as white solids. **300**: +ESI-MS:m/z 595.0 $[M+H]^+$. **301**: +ESI-MS:m/z 595.0 $[M+H]^+$.

EXAMPLE 139
Preparation of Compound 335



[0596] To a solution of **335-1** (5.2 g, 20 mmol) in THF (50 mL) was added *n*-BuLi (16 mL, 20mmol, 2.5M) at -78 °C under N_2. After stirred at -78°C for 0.5 h, a solution of I_2 (5.1g 20 mmol) in THF (25 mL) was added slowly. The mixture was stirred at -78 °C for 1 h. The reaction was quenched with water and extracted with EA (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA 10:1) to give **335-2** (7.5 g, 95 %). +ESI-MS: m/z 388.9 $[M+H]^+$.

[0597] To a solution of **335-2** (3.88 g, 10.0 mmol) in DMF (50 mL) was added sodium hydride (480 mg, 10 mmol, 60% in the mineral oil) at r.t. The mixture was stirred for 0.5 h and 3-chloro-2-methylprop-1-ene (1.0 g, 11 mmol) was added dropwise. The mixture was stirred for 2 h. The reaction was quenched with water and extracted with EA (2 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure to give crude **335-3** (4.4 g, 99%), which was used without further purification.

[0598] Under N_2 atmosphere, a mixture of **335-3** (4.4 g, 10 mmol), LiCl (420 mg, 10 mmol), sodium formate (1.36 g, 20 mmol) and $Pd(OAc)_2$ (111 mg, 0.1 mmol) in DMF (95 mL) was stirred at 100 °C for 2 h. After cooling to r.t, the mixture was diluted with EA (50 mL). The solution was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA 10:1) to give **335-4** (1.5 g, 50%). +ESI-MS: m/z 316.9 $[M+H]^+$.

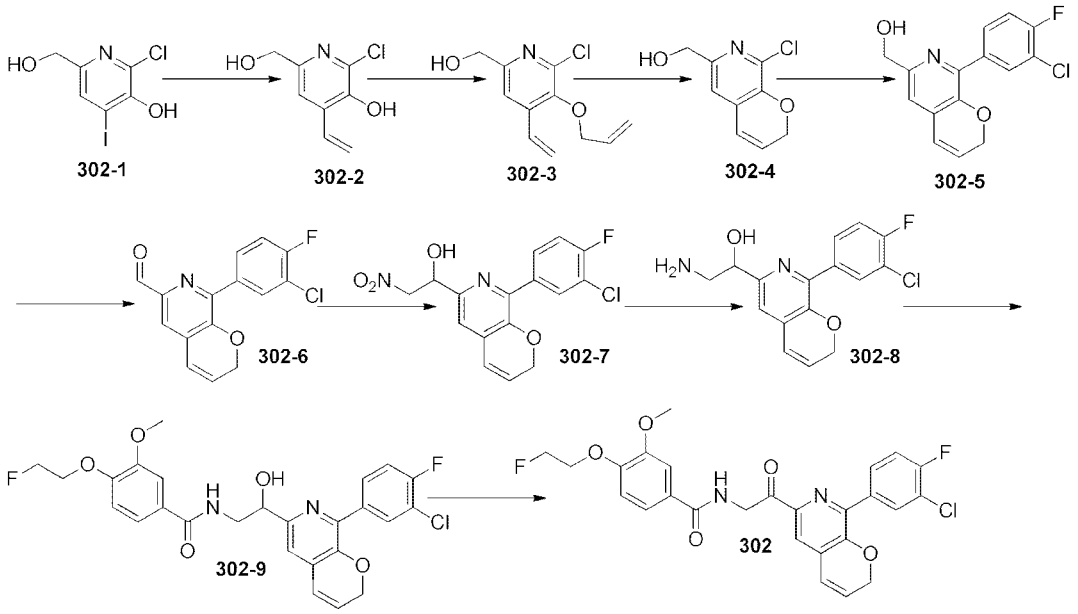
[0599] Under N_2 atmosphere, a mixture of **335-4** (1.5 g, 5 mmol), tributyl(1-ethoxyvinyl)stannane (3.6 g, 10 mmol) and $Pd(dppf)Cl_2$ (180 mg, 0.25 mmol) in toluene (15 mL) was stirred at 140 °C for 0.5 h. After cooling to r.t., the mixture was concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA 10:1) to give **335-5** (1.5 g, 88%). +ESI-MS:m/z 352.9 $[M+H]^+$.

[0600] To a solution of **335-5** (1.5 g, 1.35 mmol) in THF/H_2O (30mL/1mL) was added NBS (2.70 g, 15 mmol) in portions. The mixture was diluted with water and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA 10:1) to give **335-6** (1.5 g, 75 %).

[0601] To a solution of **335-6** (400 mg, 1.0 mmol) in DMF (5mL) was added CF_3TMS (1 mL) and LiOAc (10 mg 0.02 eq.). After addition, the mixture was stirred at r.t. until **335-6** was consumed. The mixture was treated with ammonia water (5 mL), and then stirred at r.t. for 0.5 h. The mixture was diluted with EA (50 mL). The solution was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA 1:1) to give **335-7** (205 mg, 50%). +ESI-MS:m/z 410.0 $[M+H]^+$.

[0602] Compound **335** was prepared essentially as described in the preparation of **286** by using 4-cyclopropoxy-3-methoxybenzoic acid and **335-7**. Compound **335** was obtained as a white solid (25 mg). +ESI-MS:m/z 594.1 $[M+H]^+$.

EXAMPLE 140
Preparation of Compound 302



[0603] To a stirring mixture of **302-1** (460 mg, 1.6 mmol) in DMF (2 mL, deoxygenated prior to use) were added $PdCl_2(PPh_3)_2$ (114 mg, 0.16 mmol) and tributyl(vinyl)stannane (500 mg, 1.6 mmol). The reaction was carried out under microwave irradiation at 80 ^oC for 2 h. The mixture was cooled to r.t. and diluted with EtOAc. The mixture was washed with brine:water:$NaHCO_3$. The mixture was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Crude **302-2** was purified via a silica gel column. LCMS: m/z 186.05 $[M+H]^+$.

[0604] To a stirring mixture of **302-2** (170 mg, 0.915 mmol) in DMF (3mL) was added NaI I (37 mg, 0.915 mmol). The mixture was stirred for 10 mins before allyl bromide (96 μL, 1.09 mmol) was added. The mixture was stirred for 1 h at r.t., and then diluted with EtOAc and a 10% $NaHCO_3$ aq. solution. The mixture was worked-up with EtOAc. The crude was purified via a silica gel column to afford **302-3** as a yellow oil. LCMS: m/z 226.05 $[M+H]^+$.

[0605] To a stirring mixture of **302-3** (100 mg, 0.44 mmol) in CH_2Cl_2 at r.t. (3.5 mL) was added benzylidene-bis(tricyclohexylphosphine) dichlororuthenium (12 mg, 0.014 mmol). The mixture was stirred for 3 h and then concentrated under reduced pressure. The crude was purified via a silica gel column to afford **302-4** as a tan solid. LCMS: m/z 198.0 $[M+H]^+$.

[0606] To a stirring mixture of **302-4** (70 mg, 0.35 mmol) in DME (2 mL, deoxygenated prior to use) were added (3-chloro-4-fluorophenyl)boronic acid (74 mg, 0.43 mmol), $PdCl_2(PPh_3)_2$, a solution of Cs_2CO_3 (0.4 mL, 2.65 M). The mixture was carried out under microwave irradition at 110 °C for 1 h and then diluted with EtOAc and water. A normal aqueous workup was followed. The crude was purified via a silica gel column to afford **302-5** as a white solid. LCMS: m/z 292.0 $[M+H]^+$.

[0607] To a stirring mixture of **302-5** (70 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) at r.t. were added $NaHCO_3$ (114 mg, 1.7 mmol) and Dess–Martin periodinane (509 mg, 1.2 mmol). The mixture was stirred at r.t. until the alcohol was consumed. The reaction was quenched with 5% $NaHSO_3$ and sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **302-6**. LCMS: m/z 290.0 $[M+H]^+$.

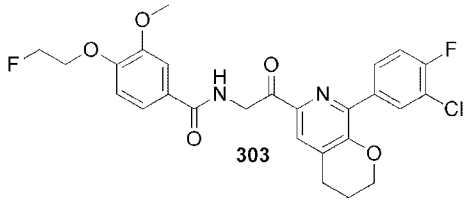
[0608] To a stirring mixture of **302-6** (40 mg, 0.138 mmol) in THF (2 mL) were added K_2CO_3 and nitromethane (25 mg, 0.42 mmol). The mixture was stirred overnight at r.t. The reaction was diluted with EtOAc and quenched with water and brine. The aqueous layer was extracted with EtOAc (2 x 25mL). The crude was purified via a silica gel chromatography to afford **302-7** as a white solid; LCMS: m/z 351.0 $[M+H]^+$.

[0609] To a stirring mixture of **302-7** (55 mg, 0.158 mmol) in EtOAc (0.5 mL) was added $SnCl_2$. $2H_2O$ (106 mg, 0.47 mmol). The mixture was heated at reflux for 1 h. The mixture was cooled and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **302-8** as a colorless oil. LCMS: m/z 321.0 $[M+H]^+$.

[0610] To a stirring mixture of 4-(2-fluoroethoxy)-3-methoxybenzoic acid (33.8 mg, 0.156 mmol) in DMF (0.5 mL) were added HATU (59.3 mg, 0.156 mmol) and DIPEA (40 mg, 0.26 mmol). The mixture was stirred at r.t. for 10 mins. Compound **302-8** (50 mg, 0.156 mmol) in DMF (0.5 mL) was added, and then the mixture was stirred for 10 mins. The reaction was quenched with a 10% aq. solution of $NaHCO_3$ (10 mL). The mixture was diluted with DCM and a normal aqueous work up with DCM was followed. The crude was purified via prep-HPLC to afford **302-9** as a white solid. LCMS: m/z 517.10 [M+H].

[0611] To a stirring mixture of **302-9** (30 mg, 0.058 mmol) in DCM (1 mL) at r.t. was added Dess–Martin periodinane (172 mg, 0.41 mmol). The mixture was stirred at r.t. for 1 h and the reaction quenched with 5% $NaHSO_3$ and a sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified via HPLC to afford **302** as a white solid. LCMS: m/z 515.05 [M+H].

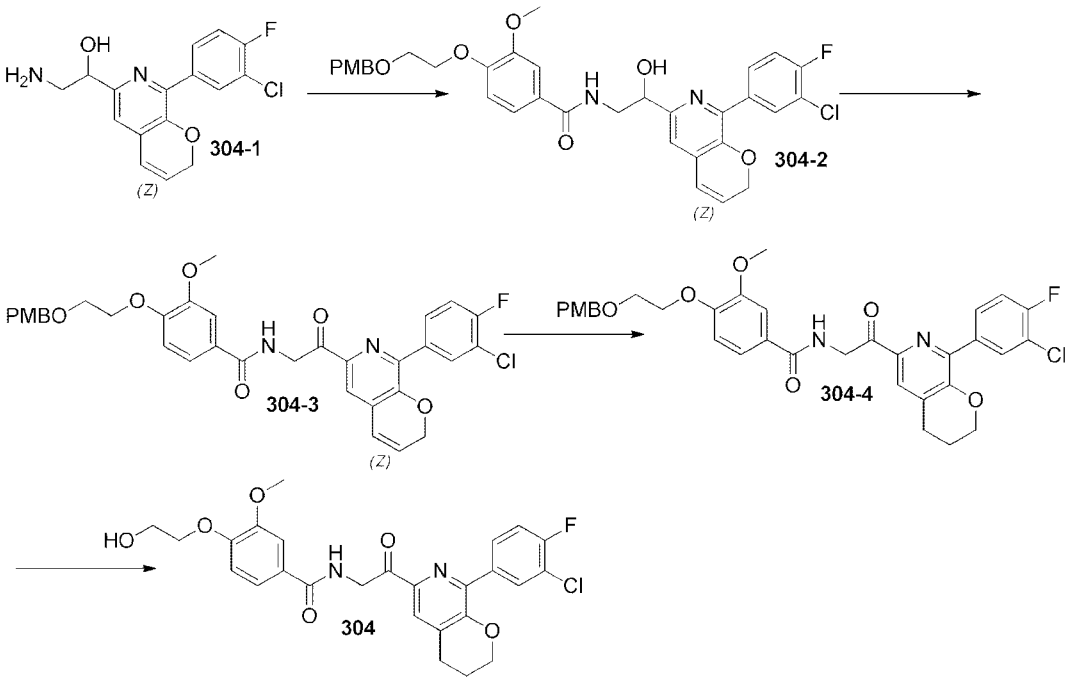
EXAMPLE 141
Preparation of Compound 303



303

[0612] Compound **303** was synthesized by reacting **302** under hydrogenation reaction conditions using Pd/C in EtOAc/EtOH. LCMS: m/z 517.1 [M+H].

EXAMPLE 142
Preparation of Compound 304



[0613] To a stirring mixture of 3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzoic acid (40 mg, 0.12 mmol) in DMF (0.5 mL) were added HATU (36 mg, 0.096 mmol) and DIPEA (25 mg, 0.192 mmol). The mixture was stirred at r.t. for 10 mins. Compound **304-1** (31 mg, 0.096 mmol) in DMF (0.5 mL) was added, the mixture was stirred for 10 mins. The reaction was quenched with 10% $NaHCO_3$ (3 mL). The mixture was diluted with DCM and a normal aqueous workup with DCM was followed. The crude was purified via prep- HPLC to afford **304-2** as a white solid. LCMS: m/z 635.1 [M+H].

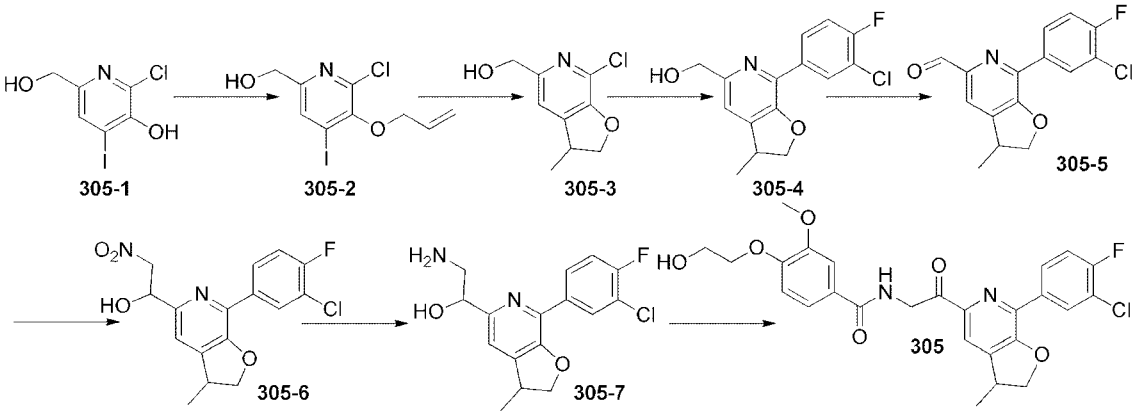
[0614] To a stirring mixture of **304-2** (30 mg, 0.047 mmol) in DCM (1 mL) at r.t. was added Dess–Martin periodinane (200 mg, 0.47 mmol). The mixture was stirred at r.t. for 1 h, and the reaction was quenched with 5% $NaHSO_3$ and a sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified via HPLC to afford **304-3** as a white solid; LCMS: m/z 633.15 $[M+H]^+$.

[0615] To a stirring mixture of **304-3** (20 mg, 0.031 mmol) in EtOH/EtOAc (1:1, 10 mL) was added Pd/C (10 mg). The mixture was reacted under H_2 balloon. The mixture

was filtered through a plug of celite, and the filtrate was concentrated under reduced pressure. Crude **304-4** was used without further purification; LCMS: m/z 635.15 $[M+H]^+$.

[0616] To a stirring mixture of **304-4** in DCM (1 mL) at 0 °C was added TFA (0.3 mL) dropwise. The mixture was stirred at r.t. for 10 mins and then diluted with EtOAc. The reaction was quenched sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified via prep-HPLC to afford **304** as a white solid. LCMS: m/z 515.10 $[M+H]^+$.

EXAMPLE 143
Preparation of Compound 305



[0617] To a stirring mixture of **305-1** (500 mg, 1.75 mmol) in DMF (8.8 mL) at 0 °C was added NaH (144 mg, 3.6 mmol). The mixture was stirred at 0 °C for 5 mins. Allyl bromide (222 mg, 1.75 mmol) was added, and the mixture was stirred at 0 °C for 20 mins. The mixture was warmed to r.t. and stirred for 5 mins. The mixture was diluted with EtOAc and quenched with water. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via a silica gel chromatography to afford **305-2**. LCMS: m/z 325.9 $[M+H]^+$.

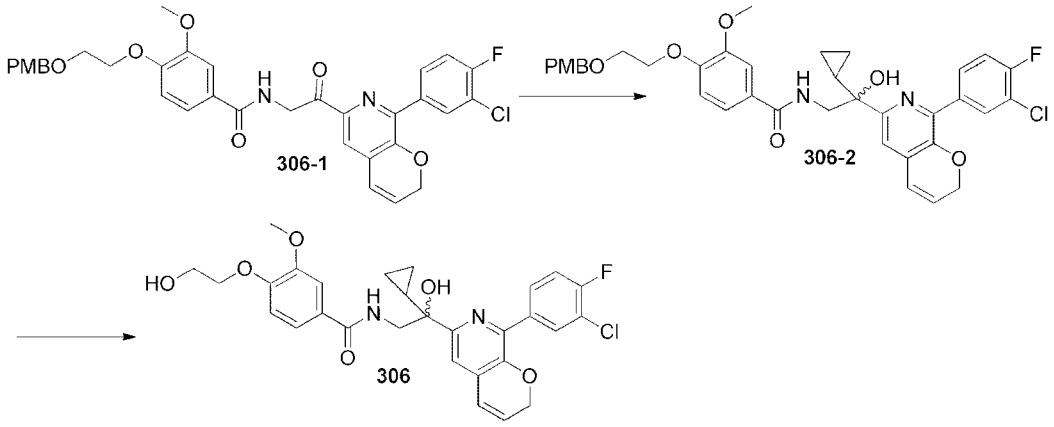
[0618] To a stirring mixture of **305-2** (280 mg, 1.4 mmol) and AIBN (23 mg, 0.14 mmol) in toluene (3.5 mL) under Ar at reflux was added a solution of tributyltin hydride (407 mg, 1.4 mmol) in toluene (1 mL) dropwise over 5 mins. The mixture was stirred at reflux for 2 h. and then concentrated under reduced pressure. The crude was purified via a silica gel column to afford **305-3** as a colorless oil. LCMS: m/z 200.05 $[M+H]^+$.

[0619] To a stirring mixture of **305-3** (170 mg, 0.85 mmol) in DME (2.4 mL, deoxygenated prior to use) were added (3-chloro-4-fluorophenyl)boronic acid (163 mg, 0.94

mmol), $PdCl_2(PPh_3)_2$ (93 mg, 0.13 mmol) and a solution of Cs_2CO_3 (0.6 mL, 4.25 M). The reaction was carried out under microwave irradition at 110 °C for 1 h. The mixture was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **305-4** as a white solid. LCMS: m/z 294.0 [M+H].

[0620] Compound **305-7** was prepared in three steps similarly to the methods described for the synthesis of **302**. Coupling of **305-7** with 3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzoic acid followed by alcohol oxidation and deprotection afforded **305**. LCMS: m/z 515.10 $[M+H]^+$.

EXAMPLE 144
Preparation of Compound 306

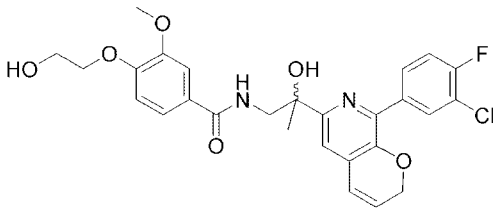
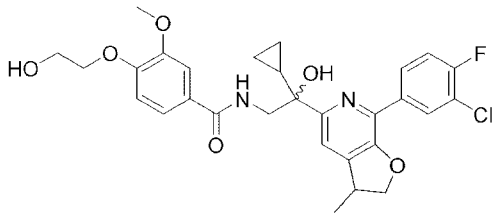
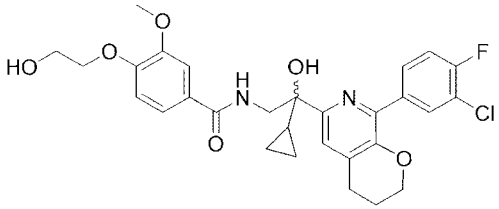
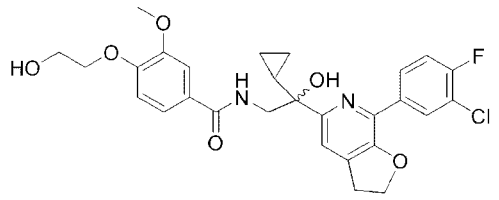
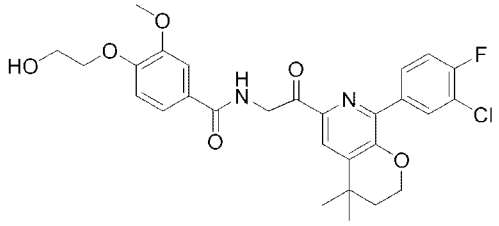
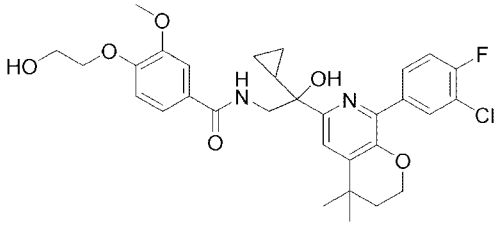


[0621] To a stirring mixture of **306-1** (30 mg, 0.047 mmol) in THF (0.45 mL) at r.t. under Ar was added cyclopropyl magnesium bromide (1.9 mL, 0.95 mmol). The mixture was stirred for 30 mins and then diluted with EtOAc. The reaction was quenched with a sat. NH_4Cl solution. A normal aqueous workup with EtOAc was followed. The crude was purified via a silica gel column to afford **306-2**. LCMS: m/z 675.20 $[M+H]^+$.

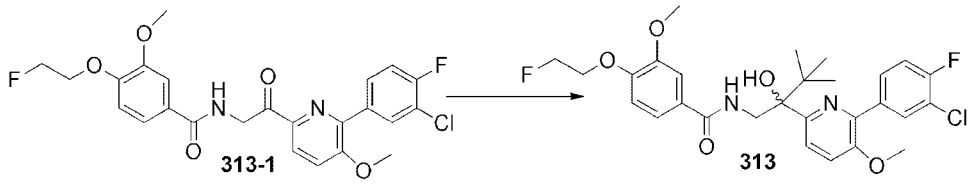
[0622] To a stirring mixture of **306-2** (30 mg, 0.052 mmol) in DCM (1 mL) was added TFA (0.2 mL) at r.t. The mixture was stirred for 10 mins, and then quenched with a cold sat. $NaHCO_3$ solution. The aqueous solution was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude was purified via prep-HPLC to afford **306** as a white solid. LCMS: m/z 555.10 $[M+H]^+$.

EXAMPLE 145
Preparation of Compounds 307-312

Table 2

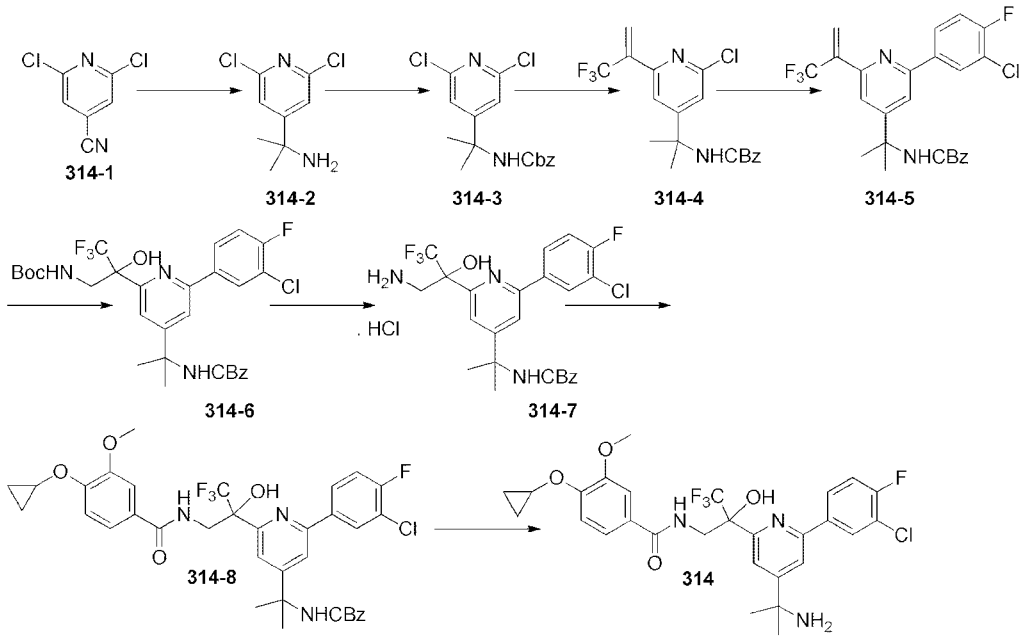
Example Method	No.	Structure	LCMS:m/z
Compound 306	307		529.10 $[M+H]^+$
Compound 306	308		557.15 $[M+H]^+$
Compound 306	309		557.15 $[M+H]^+$
Compound 306	310		543.15 $[M+H]^+$
Compound 298	311		543.15 $[M+H]^+$
Compound 306	312		585.15 $[M+H]^+$

EXAMPLE 146
Preparation of Compound 313



[0623] To a stirring mixture of **313-1** (45 mg, 0.092 mmol) in THF(1 mL) at r.t. under Ar was added a solution of *t*-BuMgCl in THF (0.91 mL, 0.91 mmol). The mixture was cooled to r.t., diluted with EtOAc and quenched with a sat. NH_4Cl solution. The mixture was stirred at r.t. for 20 mins and the layers were separated. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified via silica gel column and further purified via prep-HPLC to afford **313** as a white solid. LCMS: m/z 549.15 $[M+H]^+$.

EXAMPLE 147
Preparation of Compound 314



[0624] Methylmagnesium bromide (27 mL, 3.2 M in THF, 87 mmol) was added to a solution of **314-1** (5.0 g, 29 mmol) in Et_2O (80 mL) at 0 °C. After 1 h of stirring, titanium isopropoxide (8.2 mL, 29 mmol) was added, and the reaction was heated at 50 °C for 2 h. Copious quantities of celite were added to the mixture which was cooled to r.t. The

mixture was basified with 2N NaOH and filtered through celite and washing with CH_2Cl_2. The layers were separated, and the organic layer was concentrated. The mixture was re-dissolved in CH_2Cl_2 and extracted with 1N HCl (3x). The aqueous extracts were basified with solid K_2CO_3 and back-extracted with EA. The combined organic layers were washed with brine, dried and concentrated to provide crude **314-2** (3.25 g).

[0625] Crude **314-2** (3.28 g, 16 mmol) was dissolved in CH_2Cl_2. Benzyl chloroformate (2.3 mL, 16 mmol) and DIPEA (3.0 mL, 18 mmol) were added, and the reaction was stirred at r.t. for 3 h. The mixture was washed with 1N HCl, brine, dried (Na_2SO_4) and concentrated. The crude was purified via a silica gel chromatography to afford **314-3** as a white solid.

[0626] To a stirring mixture of **314-3** (2 g, 5.9 mmol) in DME (10 mL, deoxygenated prior to using) were added 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (1.32 g, 5.9 mmol) and a solution of Cs_2CO_3 (6M, 3 mL), $PdCl_2$(dppf) (461 mg, 0.59 mmol). The mixture was stirred at 110 ^oC under microwave reaction conditions for 1 h. The mixture was diluted with EtOAc and water. A normal aqueous workup with EtOAc was followed. The crude was purified via a silica gel chromatography (EtOAc:hex 0-20%) to afford **314-4** (1.3 g), which was used without further purification.

[0627] To a stirring mixture of **314-4** (1.3 g, 3.2 mmol) in DME (5 mL, deoxygenated prior to using) were added 3-chloro-4-fluorophenylboronic acid (550 mg, 3.2 mmol), a solution of Cs_2CO_3 (6M, 1.5 mL), and $PdCl_2$(dppf) (230 mg, 0.32 mmol). The mixture was stirred at 110 ^oC under microwave reaction conditions for 1 h. The mixture was diluted with EtOAc and water. A normal aqueous workup with EtOAc was followed. The crude was purified via a silica gel chromatography (EtOAc:hex 0-20%) to afford **314-5**. LCMS: m/z 493.05 $[M+H]^+$.

[0628] To a stirring mixture of tert-butyl hydroxycarbamate (2 g, 15 mmol) in THF (10 mL) at 0 ^oC was added TsCl (2.8 g, 15 mmol) and TEA (2.2 mL, 15.8 mmol). The mixture was stirred at 0 ^oC for 20 mins, and then warmed to r.t. for 5 mins. The mixture was diluted with DCM and washed with water. A normal aqueous workup with DCM was followed. The crude was purified via a silica gel to afford tert-butyl tosyloxycarbamate as a white solid.

[0629] To a stirring mixture of **314-5** (950 mg, 1.9 mmol) in t-BuOH:water (3:1, 3 mL total volume) at r.t. were added potassium osmate dihydrate (105 mg, 0.3 mmol) and tert-butyl tosyloxycarbamate (1 g, 3.8 mmol). The mixture was stirred at r.t. overnight, and then diluted with water and DCM. A normal aqueous work up with DCM was followed. The crude was purified via a silica gel chromatography to afford **314-6** (1.3 g, 80% pure). LCMS: m/z 626.20 $[M+H]^+$.

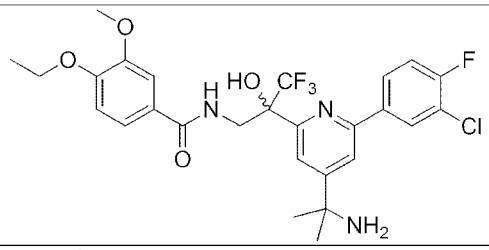
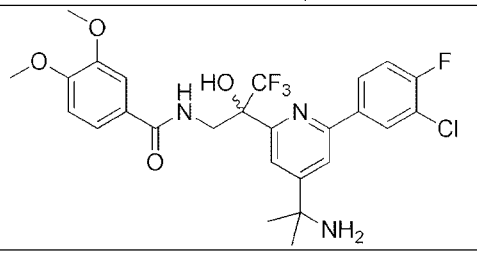
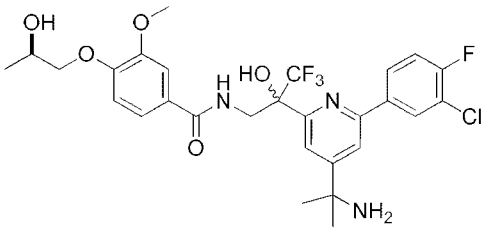
[0630] Compound **314-6** was dissolved in a solution of HCl (4N) in dioxane (10 mL) at r.t. The mixture was stirred at r.t. The mixture was concentrated under reduced pressure to afford crude **314-7**, which was used without further purification. LCMS: m/z 526.05 $[M+H]^+$.

[0631] To a stirring mixture of 4-cyclopropoxy-3-methoxybenzoic acid (350 mg, 1.69 mmol) in DMF (1.5 mL) were added HATU (642 mg, 1.69 mmol) and DIPEA (735 mL, 4.2 mmol). The mixture was stirred at r.t. for 10 mins. Compound **314-7** in DMF (2 mL) was added, and then stirred for 10 mins. The reaction was quenched with a 10% aqueous solution of $NaHCO_3$ (10 mL), and then diluted with DCM. A normal aqueous work up with DCM was followed. The crude was purified via prep-HPLC to afford **314-8** as a white solid. LCMS: m/z 716.2 $[M+H]^+$.

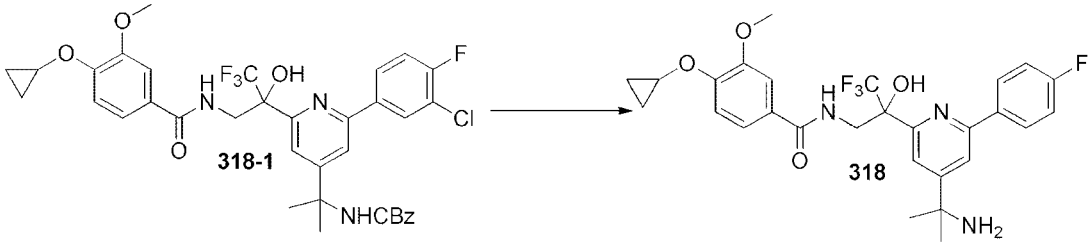
[0632] To a stirring mixture of **314-8** (602 mg, 0.84 mmol) in AcCN (3 mL) at r.t. were added NaI (630 mg, 4.2 mmol) and TMSCl (453 mg, 4.2 mmol). The mixture was warmed to 60 ^oC until the starting material disappeared. The mixture was cooled to r.t. and purified by silica gel chromatography (EtOAc:hex 0-50% and then MeOH:DCM 0-20%). The product was further purified via prep-HPLC and then converted to the HCl salt to afford **314**. LCMS: m/z 582.2 $[M+H]^+$.

EXAMPLE 148
Preparation of Compounds 315-317

Table 3

Example Method	No.	Structure	LCMS: m/z
Compound 314	315		570.10 $[M+H]^+$
Compound 314	316		556.10 $[M+H]^+$
Compound 314	317		600.15 $[M+H]^+$

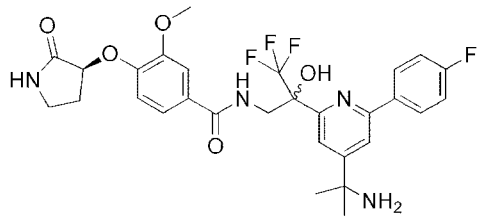
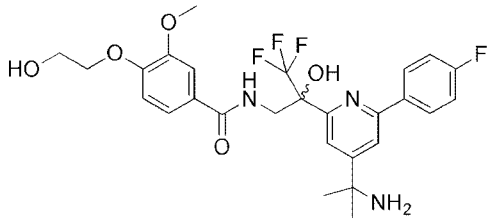
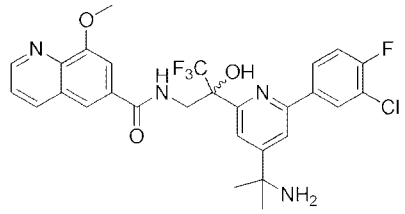
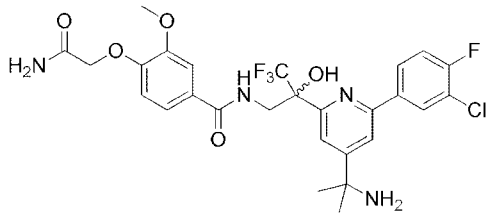
EXAMPLE 149
Preparation of Compound 318



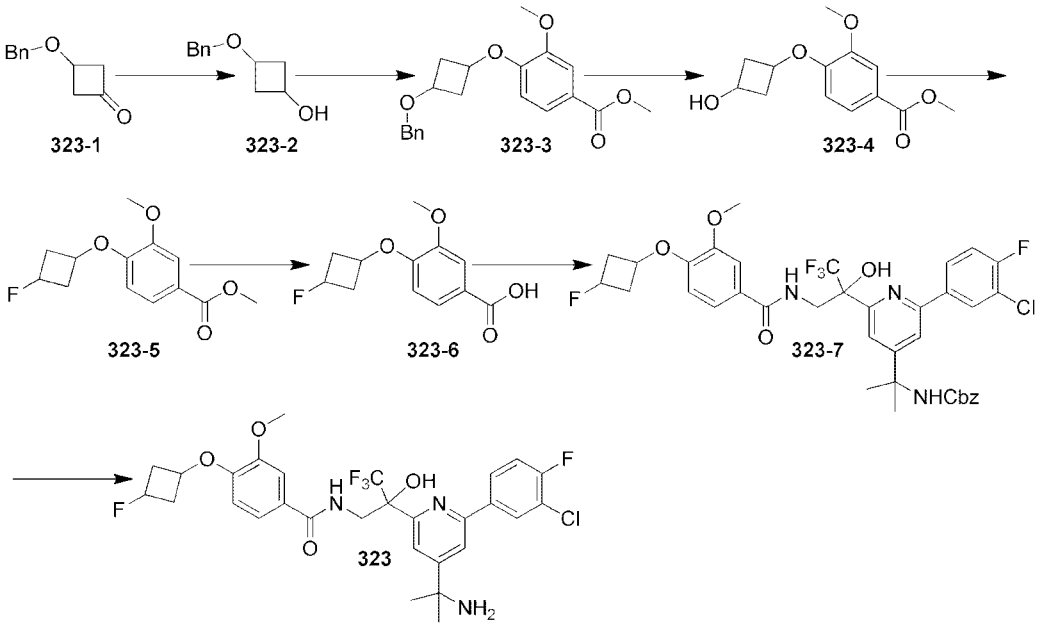
[0633] To a stirring solution of **318-1** (40 mg, 0.028 mmol) in EtOAc:EtOH:HOAc (5 mL:1.0 mL:0.1 mL) was added Pd/C (20 mg). The mixture was placed under a H_2 balloon. The mixture was stirred for several hours until the starting material was consumed. The mixture was filtered through a plug of celite, and the plug was washed with EtOAc (2 x 10 mL). The mixture was concentrated under reduced pressure and purified via prep-HPLC to afford **318** as a white solid. LCMS: m/z 548.15 $[M+H]^+$.

EXAMPLE 150
Preparation of Compounds 319-322

Table 4

Example Method	No.	Structure	LCMS: m/z
Compound 318	319		591.15 $[M+H]^+$
Compound 318	320		522.15 $[M+H]^+$
Compound 318	321		577.15 $[M+H]^+$
Compound 318	322		599.10 $[M+H]^+$

EXAMPLE 151
Preparation of Compound 323



[0634] To a solution of **323-1** (2.5 g, 14.2 mmol) in THF (10 mL) and MeOH (10 mL) was added $NaBH_4$ (1.6 g, 42.1 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 mins. The reaction was quenched with 1.0 N HCl and extracted with EtOAc. The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified on a silica gel column (PE:EA 5:1) to give **323-2** as a colorless oil (2.0 g, 79.1%).

[0635] A solution of **323-2** (2.0 g, 11.2 mmol), methyl 4-hydroxy-3-methoxybenzoate (2.1 g, 11.5 mmol) and PPh_3 (4.5 g, 17.3 mmol) was stirred in dry THF (40 mL) at 0 °C under a N_2 atmosphere. DIAD (3.5 g, 17.5 mmol) added dropwise over a period of 5 mins, and the solution was allowed to stir at 50°C for 3 h. After disappearance of the starting material, the solvent was evaporated under reduced pressure. The residue was purified on by column chromatography on silica gel (PE:EA 10:1) to give **323-3** as a white solid (2.8 g, 73.7%); ^{1}H-NMR ($CDCl_3$, 400 MHz), δ = 7.62-7.60 (dd, J = 1.6 Hz, J = 10.0 Hz, 1H), 7.53 (s, 1H), 7.34-7.25 (m, 5H), 6.66 (d, J = 8.4 Hz, 1H), 4.96-4.93 (m, 1H), 4.44 (s, 2H), 4.36-4.32 (m, 1H), 3.93 (s, 3H), 3.87 (s, 3H),2.59-2.54 (m, 4H).

[0636] To a mixture of **323-3** (2.8 g, 8.2 mmol) in MeOH (15 mL) was added $Pd(OH)_2$ on carbon (10%, 500 mg) under N_2. The suspension was degassed under vacuum

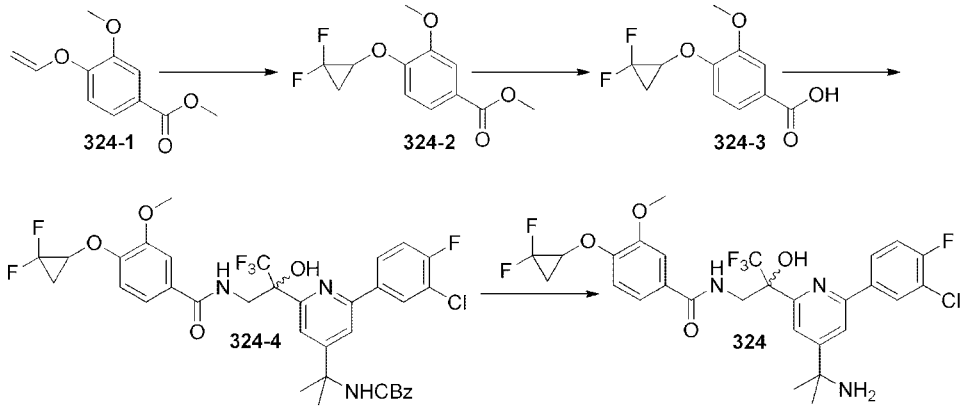
and purged with H_2 (3x). The mixture was stirred under H_2 (40 psi) at r.t. for 3 h. The suspension was filtered through a pad of Celite, and the cake was washed with MeOH. The combined filtrates were concentrated to give crude **323-4** (1.7 g, 84.5%) which was used without purification.

[0637] To a mixture of **323-4** (1.7 g, 6.7 mmol) in DCM (10 mL) was added DAST (3 mL) at 0 °C. The mixture was stirred at 0 °C for 30 mins. The reaction was quenched by sat. aq. $NaHCO_3$ at 0 °C and then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE:EA 15:1) to give **323-5** as a white solid (800 mg, 47.1%).

[0638] A solution of **323-5** (254 mg, 1.0 mmol) and aq. lithium hydroxide (2 N, 1 mL) in THF (5 mL) was stirred at r.t. for 1 h. The mixture was neutralized by using 2N HCl and extracted with EtOAc. The combined organic solutions were dried ($MgSO_4$), and evaporated under reduced pressure to give **323-6** as a white solid (100 mg, 41.6%).

[0639] Compound **323** was prepared similarly to the preparation of **314**. LCMS: m/z 614.15 $[M+H]^+$.

EXAMPLE 152
Preparation of Compound 324

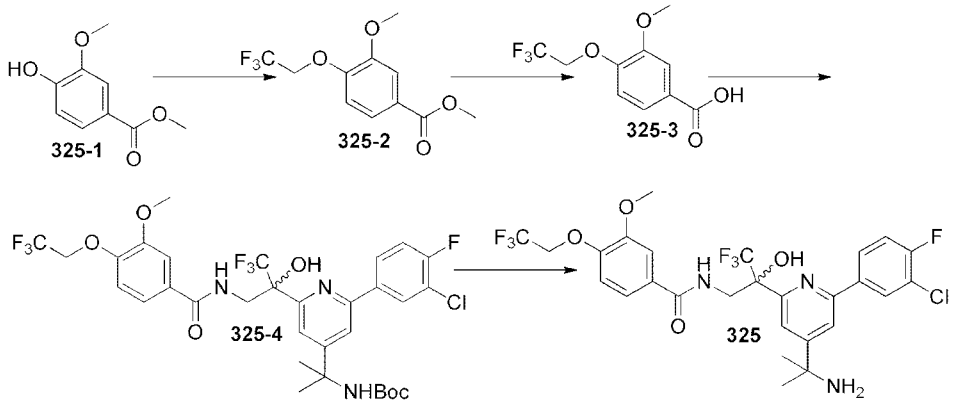


[0640] To a stirring mixture of **324-1** (360 mg, 1.73 mmol) and NaF (7.3 mg, 0.173 mmol) in toluene (2 mL) at reflux was added trimethylsilyl-2,2-difluoro-2-(fluorosulphonyl)acetate dropwise over 1 h. The mixture was heated at reflux for 1 h and then cooled to r.t. The mixture was concentrated under reduced pressure and loaded into a silica gel column to afford **324-2**. LCMS: m/z 259.05 $[M+H]^+$.

[0641] To a stirring mixture of **324-2** (320 mg, 1.24 mmol) in THF:water (1.0 mL:0.2 mL) at r.t. was added aq. LiOH (155 mg, 3.7 mmol). The mixture was stirred for 2 d. The mixture was diluted with EtOAc and acidified with 10% aqueous HCl solution. A normal aqueous work up with EtOAc was followed. Crude **324-3** was used without further purification.

[0642] Compound **324** was prepared similarly to the preparation of **314**. LCMS: m/z 618.15 $[M+H]^+$.

EXAMPLE 153
Preparation of Compound 325

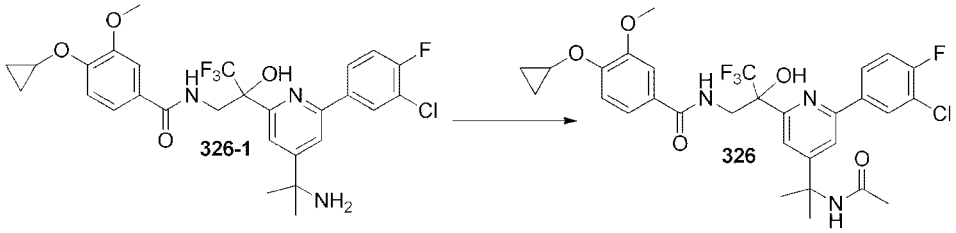


[0643] To a stirring mixture of **325-1** (0.5 g, 2.75 mmol) in DMF (7 mL) were added Cs_2CO_3 (1.35 g, 4.12 mmol), and 2,2,2-trifluoroethyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (837 mg, 2.2 mmol). The mixture was heated at 55 °C overnight, and then diluted with EtOAc, and washed with water. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **325-2** as a white solid; LCMS: m/z 265.05 $[M+H]^+$.

[0644] To a stirring mixture of **325-2** (300 mg, 1.13 mmol) in THF:water (1 mL:0.1 mL) was added aq. LiOH. The mixture was stirred at r.t. overnight. The mixture was diluted with EtOAc and acidified with a 1N HCl aqueous solution. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude **325-3** was used without further purification.

[0645] Compound **325** was prepared similarly to the preparation of **314**. LCMS: m/z 624.1 $[M+H]^+$.

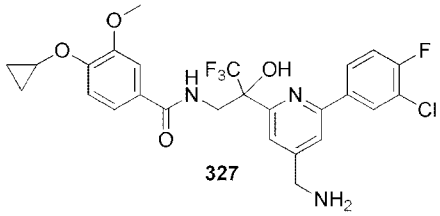
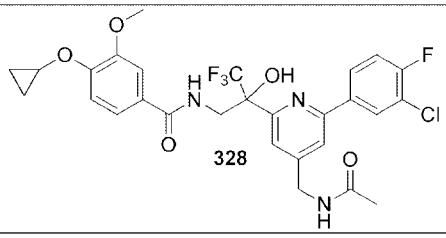
EXAMPLE 154
Preparation of Compound 326

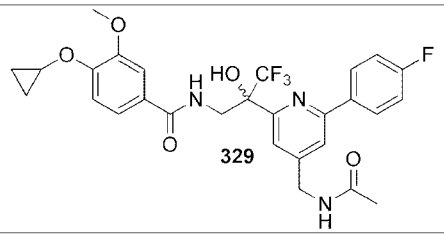
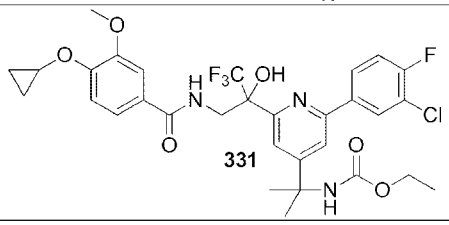
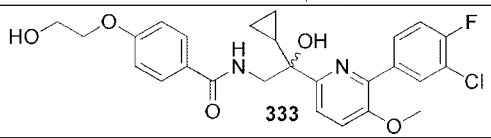
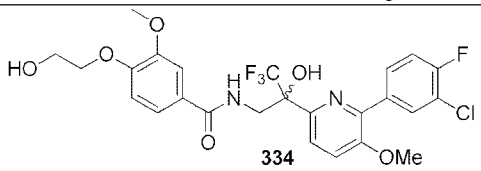
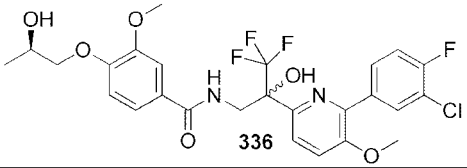
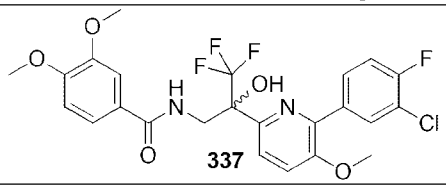
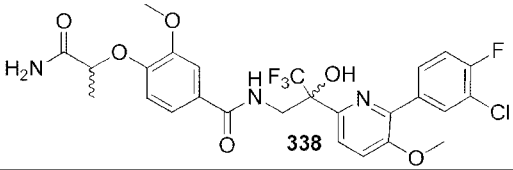
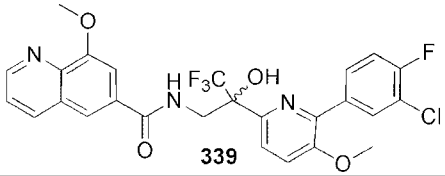


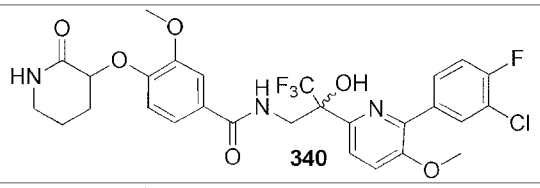
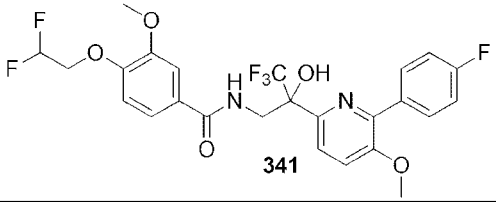
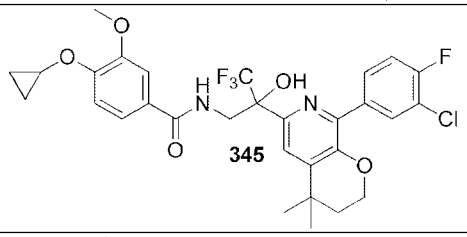
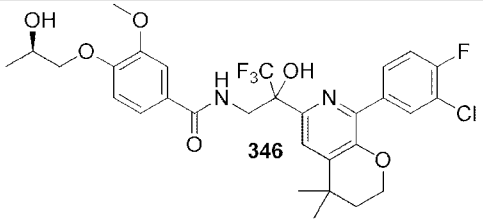
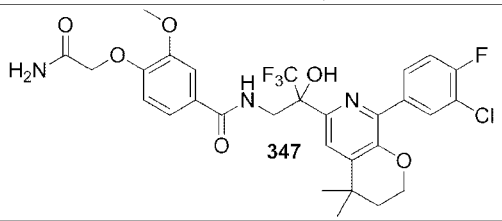
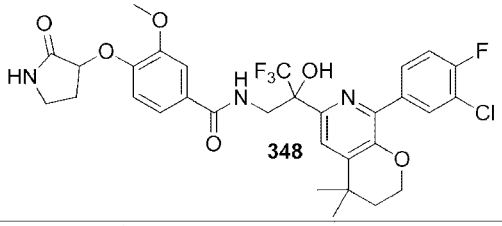
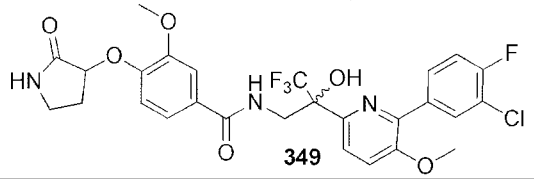
[0646] To a stirring mixture of acetic acid (5 mg, 0.083 mmol) in DMF (0.2 mL) were added HATU (3.1 mg, 0.083) and DIPEA (17 mg, 0.13 mmol). The mixture was stirred at r.t. for 5 mins. A solution of **326-1** in DMF (0.8 mL) was added, and the mixture was stirred for 10 mins. The reaction was quenched with a 10% aq. solution of $NaHCO_3$ (10 mL). The mixture was diluted with DCM, and a normal aqueous work up with DCM was followed. Crude product was purified via prep-HPLC to afford **326** as a white solid. LCMS: m/z 624.15 $[M+H]^+$.

EXAMPLE 155
Preparation of Compounds 327-329

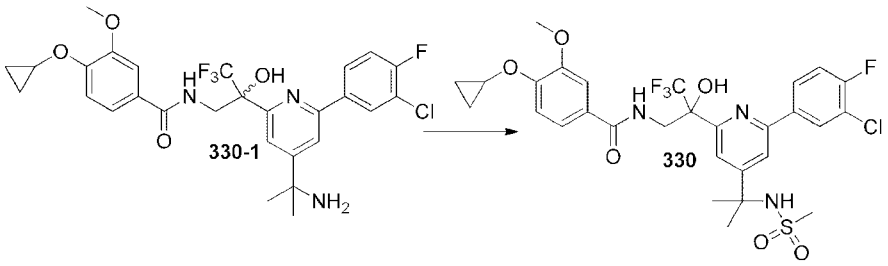
Table 5

Example Method	Structure	LCMS: m/z
Compound 314		554.10 $[M+H]^+$
Compound 326		596.1 $[M+H]^+$

Example Method	Structure	LCMS: m/z
Compound 326	 329	562.15 $[M+H]^+$
Compound 330	 331	654.15 $[M+H]^+$
Compound 306	 333	501.10 $[M+H]^+$
Compound 314	 334	559.10 $[M+H]^+$
Compound 334	 336	573.15 $[M+H]^+$
Compound 334	 337	529.1 $[M+H]^+$
Compound 334	 338	586.05 $[M+H]^+$
Compound 334	 339	550.05 $[M+H]^+$

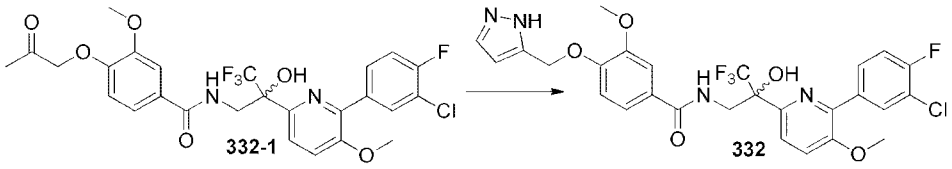
Example Method	Structure	LCMS: m/z
Compound 334	 340	612.1 $[M+H]^+$
Compound 334	 341	545.15 $[M+H]^+$
Compound 334	 345	609.10 $[M+H]^+$
Compound 334	 346	627.15 $[M+H]^+$
Compound 334	 347	626.15 $[M+H]^+$
Compound 334	 348	652.2 $[M+H]^+$
Compound 334	 349	598.1 $[M+H]^+$

EXAMPLE 156
Preparation of Compound 330



[0647] To a stirring mixture of **330-1** (20 mg, 0.034 mmol) in DCM (0.4 mL) were added TEA (7 mg, 0.069 mmol) and MsCl (1 drop). The mixture was stirred for 20 mins and slowly warmed to r.t. The mixture was diluted with DCM, and the reaction was quenched with a sat. $NaHCO_3$ solution. The aqueous layer was extracted with DCM. The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Crude product was purified via prep-HPLC to afford **330** as a white solid. LCMS: m/z 660.10 $[M+H]^+$.

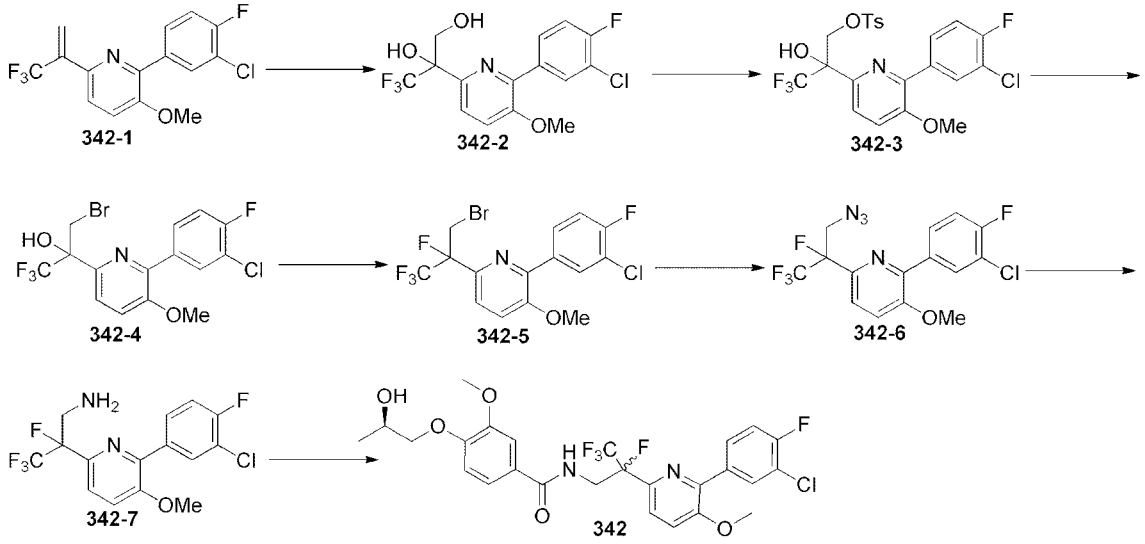
EXAMPLE 157
Preparation of Compound 332



[0648] To a stirring mixture of **332-1** (8 mg, 0.014 mmol) in DMF (0.2 mL) was added DMF.DMA (0.2 mL). The mixture was stirred at 90 °C until the starting material was consumed. The crude mixture was concentrated under reduced pressure and used without further purification.

[0649] To a stirring mixture of crude product from the previous step in DCM (0.5 mL) at 0 °C were added hydrazine monohydrate (0.1 mL) and HOAc (0.05 mL). The mixture was warmed to r.t. and then reflux for 30 mins. The mixture was cooled to r.t., and the reaction was quenched with a sat. $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced product. Crude product was purified via prep-HPLC to afford **332** as a white solid. LCMS: m/z 595.1 $[M+H]^+$.

EXAMPLE 158
Preparation of Compound 342



[0650] To a stirring mixture of **342-1** (50 mg, 0.15 mmol) in t-BuOH:water (3:1, 1.3 mL) at 0 °C were added NMO (26 mg, 0.23 mmol) and potassium osmate dehydrate (5.5 mg, 0.016 mmol). The mixture was warmed to r.t. overnight, and then diluted with DCM and water. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified on a silica gel column to afford **342-2** as a brownish oil (50 mg, 91% yield). LCMS: m/z 366.0 $[M+H]^+$.

[0651] To a stirring mixture of **342-2** (50 mg, 0.136 mmol) in DCM (1 mL) at 0 °C were added TsCl (52 mg, 0.273 mmol), TEA (60 μL, 0.41 mmol) and DMAP (2 crystals). The mixture was warmed to r.t. for 1 h and then diluted with DCM. The reactino was quenched with sat. $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **342-3** (65 mg, 92% yield). LCMS: m/z 520.0 $[M+H]^+$.

[0652] To a stirring mixture of **342-3** (128 mg, 0.246 mmol) in acetone (1 mL) was added LiBr (64 mg, 0.74 mmol). The mixture was stirred at reflux for 2 h and loaded into a silica gel column to afford **342-4** as a colorless oil (75 mg, 71% yield). LCMS: m/z 427.95 $[M+H]^+$.

[0653] To a stirring mixture of **342-4** in DCM (1 mL) at 0 °C was added DAST (58 mL, 0.44 mmol). The mixture was stirred at 0 °C for 30 mins and then warmed to r.t. for

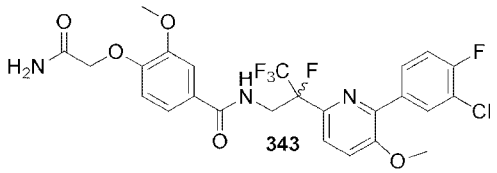
5 mins. The reaction was quenched with a cold aq. $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **342-5** (56 mg, 74% yield). LCMS: m/z 429.95 $[M+H]^+$.

[0654] To a stirring mixture of **342-5** (50 mg, 0.116 mmol) in DMF (2 mL) were added tetrabutylammonium azide (330 mg, 1.2 mmol) and tetrabutylammonium iodide (5 mg). The mixture was stirred at 95 °C for 4 h. The mixture was loaded onto a silica gel column, eluting with hexane:EtOAc to afford **342-6** as a colorless oil. LCMS: m/z 393.0 $[M+H]^+$.

[0655] To a stirring mixture of **342-6** (25 mg, 0.064 mmol) in THF:water (10:1, 1.1 mL) was added triphenylphosphine (polymer-bound, 167 mg, 0.64 mmol). The mixture was stirred at 70 °C for 30 mins, cooled to r.t. and filtered through a plug of celite. The plug was washed several times with EtOAc. The mixture was concentrated under reduced pressure and **342-7** used without further purification. LCMS: m/z 367.0 $[M+H]^+$.

[0656] To a stirring mixture of (R)-4-(2-hydroxypropoxy)-3-methoxybenzoic acid (18 mg, 0.079 mmol) in DMF (0.5 mL) were added HATU (36 mg, 0.095 mmol) and DIPEA (35 μL, 0.191 mmol). The mixture was stirred at r.t. for 10 mins. A solution of **342-7** in DMF (0.5 mL) was added, and the mixture was stirred at for 10 mins. The reaction was quenched with a 10% aq. solution of $NaHCO_3$ (10 mL). The mixture was diluted with DCM and a normal aqueous work up with DCM was followed. The crude was purified via prep-HPLC to afford **342** as a white solid. LCMS: m/z 575.15 $[M+H]^+$.

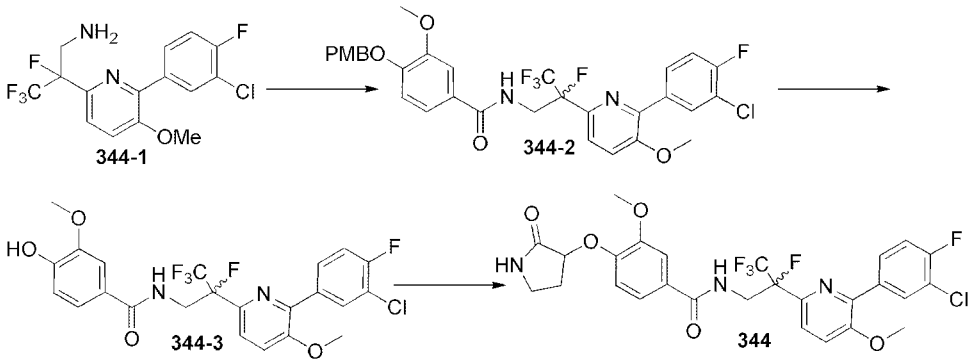
EXAMPLE 159
Preparation of Compound 343



343

[0657] Compound **343** was prepared according to the method described for **342**. LCMS: m/z 574.10 $[M+H]^+$.

EXAMPLE 160
Preparation of Compound 344

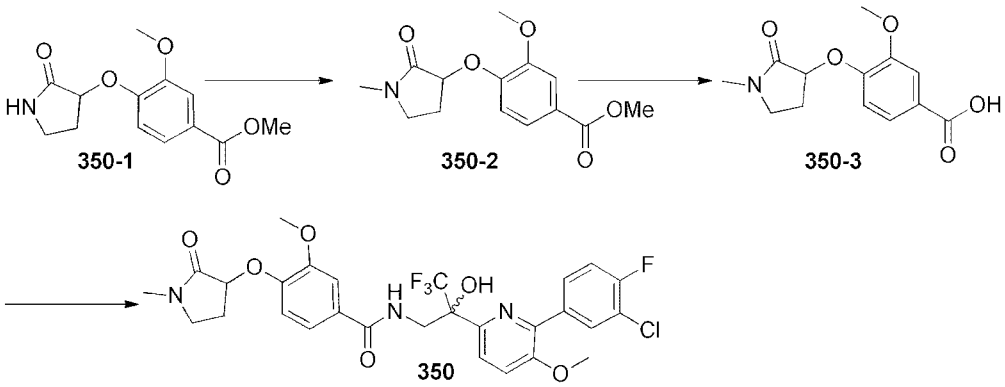


[0658] To a stirring mixture of 3-methoxy-4-((4-methoxybenzyl)oxy)benzoic acid (35 mg, 0.095 mmol) in DMF (0.5 mL) were added HATU (45 mg, 0.114 mmol) and DIPEA (35 μL, 0.19 mmol). The mixture was stirred at r.t. for 10 mins. A solution of **344-1** in DMF (0.5 mL) was added, and the mixture was stirred for 10 mins. The reaction was quenched with a 10% aq. solution of $NaHCO_3$ (5 mL). The mixture was diluted with DCM and a normal aqueous work up with DCM was followed. The crude was purified via a silica gel column to afford **344-2** as a colorless oil. LCMS: m/z 637.15 $[M+H]^+$.

[0659] To a stirring mixture of **344-2** in DCM (1 mL) was added TFA (0.4 mL). The mixture was stirred at r.t. until **344-2** was consumed. The reaction was quenched with a cold sat. $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to give **344-3** as a colorless oil. LCMS: m/z 517.1 $[M+H]^+$.

[0660] To a stirring mixture of **344-3** (30 mg, 0.058 mmol) in DCM was added Cs_2CO_3 (47 mg, 0.145 mmol) and 3-bromopyrrolidin-2-one (11.4 mg, 0.07 mmol). The mixture was heated under microwave irradiation at 70 °C for 1 h. The mixture was filtered through a plug of celite and washed several times with DCM. The mixture was concentrated under reduced pressure and further purified via HPLC to afford **344** as a white solid. LCMS: m/z 600.15 $[M+H]^+$.

EXAMPLE 161
Preparation of Compound 350

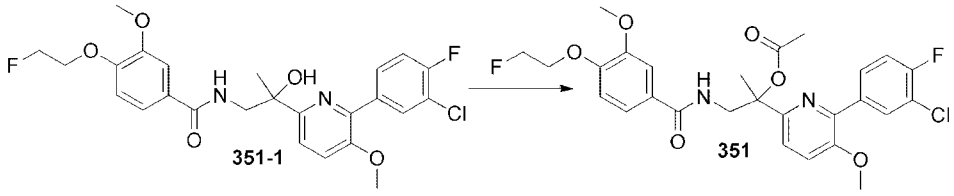


[0661] To a stirring mixture of **350-1** (57 mg, 0.21 mmol) in THF (1 mL) at 0 °C was added NaH (17 mg, 0.43 mmol). The mixture was stirred at 0 °C for 5 mins, and then methyl iodide (61 mg, 0.43 mmol) was added. The mixture was warmed to r.t. and then diluted with EtOAc. The reaction was quenched with a sat. NH_4Cl solution. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to give **350-2**. LCMS: m/z 280.05 $[M+H]^+$.

[0662] To a stirring mixture of **350-2** (50 mg, 0.17 mmol) in THF:MeOH:water (1:0.4:0.1) at r.t. was added aq. LiOH (36 mg, 0.86 mmol). The mixture was stirred overnight at r.t. The mixture was diluted with EtOAc and acidified with a 1N HCl solution. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude **350-3** was used without further purification. LCMS: m/z 266.05 $[M+H]^+$.

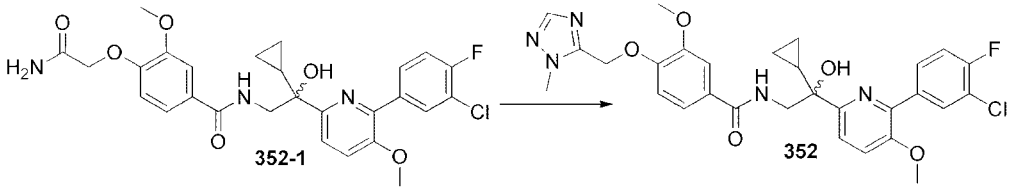
[0663] Compound **350** was prepared similarly according to the methods for **349**. LCMS: m/z 612.1 $[M+H]^+$.

EXAMPLE 162
Preparation of Compound 351



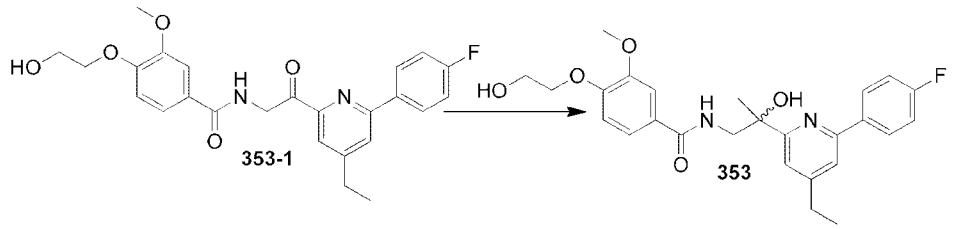
[0664] To a stirring mixture of **351-1** (15 mg, 0.0295 mmol) in DCM (1 mL) at 0 °C were added acetic anhydride (10 mg, 0.09 mmol), TEA (20 µl) and DMAP (1 crystal). The mixture was stirred at r.t. until the alcohol was consumed. The reaction was quenched with a sat. $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via HPLC to afford **352** as a white solid. LCMS: m/z 549.10 $[M+H]^+$.

EXAMPLE 163
Preparation of Compound 352



[0665] To a stirring mixture of **352-1** (25 mg, 0.047 mmol) in DMF (0.1 mL) was added DMF. DMA (0.1 mL). The mixture was stirred at 60 °C until the starting material was consumed. The mixture was cooled to r.t. and concentrated under reduced pressure. The crude used was without further purification. To the stirring crude in DCM at 0 °C were added HOAc (3 drops) and methyl hydrazine (3 drops). The mixture was warmed to r.t. for 20 mins and heated to reflux. The mixture was cooled to r.t., diluted with DCM and quenched with a cold sat. $NaHCO_3$ solution. The aqueous layer was extracted with DCM (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via prep-HPLC to afford **352** as a white solid. LCMS: m/z 582.15 $[M+H]^+$.

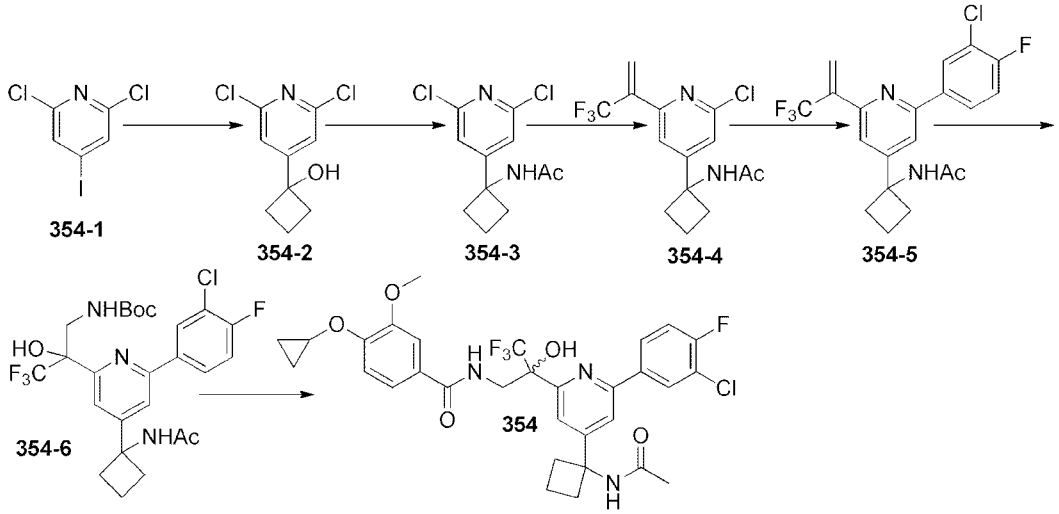
EXAMPLE 164
Preparation of Compound 353



[0666] To a solution of **353-1** (53 mg, 0.11 mmol) in THF (4 mL) was added MeMgCl (1 mL). The mixture was stirred at 0 °C for 1 h. The reaction was quenched with a sat. NH_4Cl solution. The organic layers was washed with brine, dried over Na_2SO_4 and

concentrated. The crude was purified by prep-HPLC to give **353** (20 mg, 40%) as a white solid. LCMS: m/z 469.3 $[M+H]^+$.

EXAMPLE 165
Preparation of Compound 354

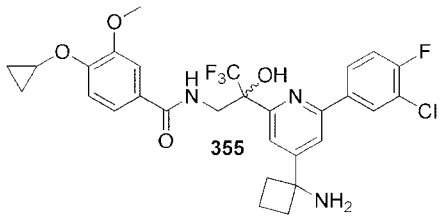


[0667] A solution of i-PrMgCl (2.75 mL, 3.84 mmol) in THF was added dropwise to a stirring mixture of **354-1** (1 g, 3.66 mmol) at -45 °C over 5 mins. The mixture was stirred for 1 h, and then cyclobutanone (256 mg, 3.66 mmol) in THF (1 mL) was added. The mixture was warmed to r.t. and stirred overnight. The mixture was diluted with EtOAc, and the reaction quenched with a sat. NH_4Cl solution. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **354-2** as a colorless oil. LCMS: m/z 218 $[M+H]^+$.

[0668] To a stirring mixture of **354-2** (0.4 g, 1.83) in CH_3CN (4 mL) at 0 °C was added dropwise H_2SO_4 (conc.) (490 μL, 9.2 mmol) over 5 mins. The mixture was warmed to r.t. for 1 h and then warmed to 80 °C for 30 mins. The mixture was cooled to r.t., and then diluted with EtOAc. The reaction was quenched with a sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **354-3** as a white solid. LCMS: m/z 258.95 $[M+H]^+$.

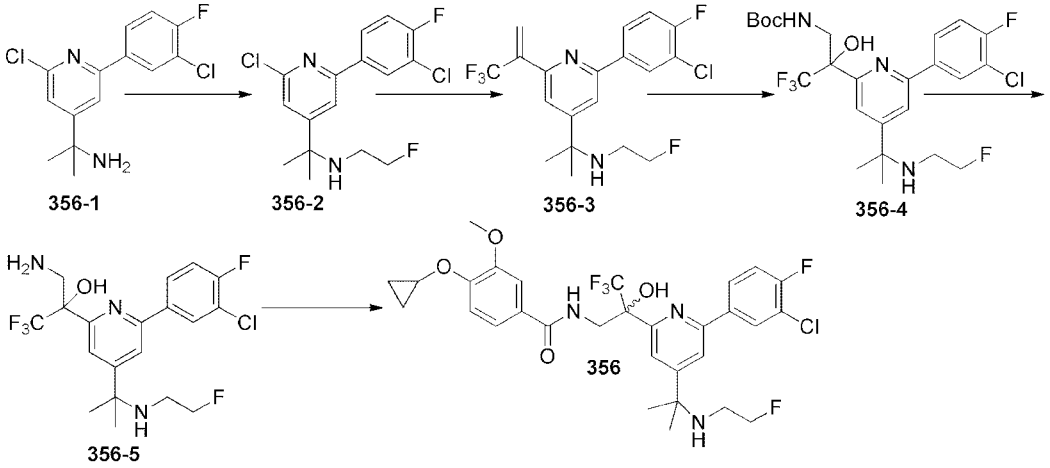
[0669] Steps 3-6 were conducted in a similar manner as **314** to provide **354**. LCMS: m/z 636.15 $[M+H]^+$.

EXAMPLE 166
Preparation of Compound 355



[0670] To a stirring mixture of **354** (16 mg, 0.025 mmol) in 4N HCl in dioxane (2 mL) was added a 6N HCl aqueous solution. The mixture was heated under microwave irradiation at 120 °C for 1 h. The mixture was cooled to r.t., diluted with DCM and neutralized with a cold sat. $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified via prep-HPLC to afford **355** as a white solid. LCMS: m/z 594.10 $[M+H]^+$.

EXAMPLE 167
Preparation of Compound 356

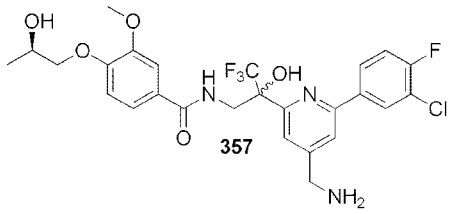
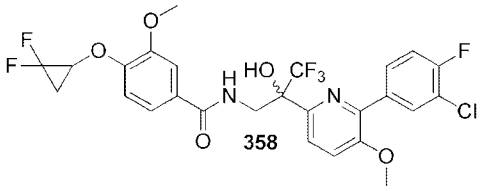
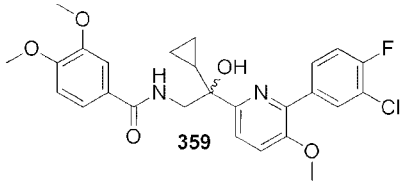
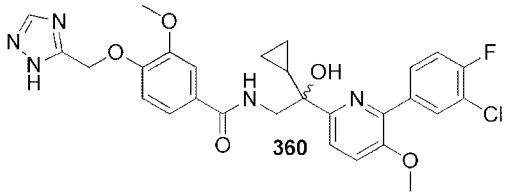
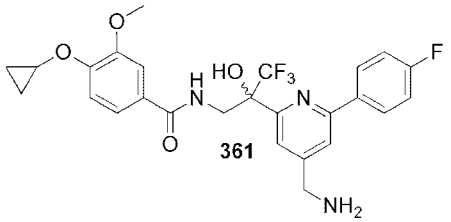
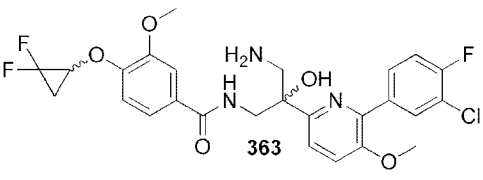


[0671] To a stirring mixture of **356-1** (0.3 g, 1 mmol) in DMF at r.t. were added Cs_2CO_3 (488 mg, 1.5 mmol), NaI (15 mg) and 1-bromo-2-fluoroethane (127 mg, 1 mmol). The mixture was heated to 45 °C overnight. The mixture was diluted with EtOAc and quenched with water. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **356-2**. LCMS: m/z 345.1 $[M+H]^+$.

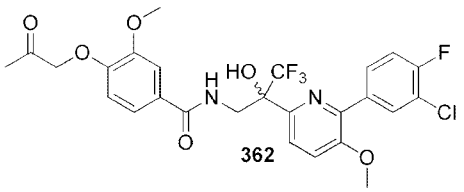
[0672] Compound **356** was prepared in 4 steps using the similar methods as **314**. LCMS: m/z 628.15 $[M+H]^+$.

EXAMPLE 168
Preparation of Compounds 357-361 and 363

Table 6

Example Method	Structure	LCMS: m/z
Compound 327	 357	572.15 $[M+H]^+$
Compound 334	 358	591.10 $[M+H]^+$
Compound 306	 359	501.10 $[M+H]^+$
Compound 352	 360	568.15 $[M+H]^+$
Compound 327	 361	520.15 $[M+H]^+$
Compound 383	 363	553.10 $[M+H]^+$

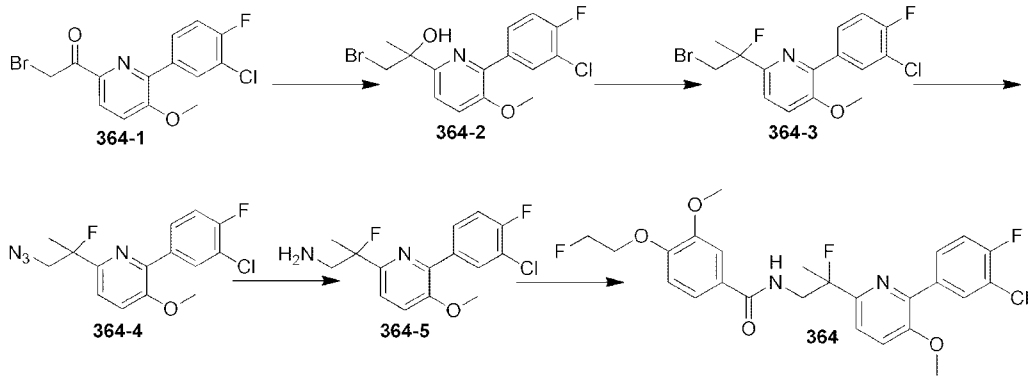
EXAMPLE 169
Preparation of Compound 362



362

[0673] To a stirring mixture of **336** (20 mg, 0.035 mmol) in DCM (1 mL) at r.t. was added Dess–Martin periodinane (150 mg, 0.175 mmol). The mixture was stirred at r.t. for 1 h and then quenched with 5% $NaHSO_3$ and a sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified via HPLC to afford **362** as a white solid. LCMS: m/z 571.1 $[M+H]^+$.

EXAMPLE 170
Preparation of Compound 364



[0674] Methylmagnesium bromide (1.4 M in THF, 0.50 mL, 0.68 mmol) was added to a solution of bromoketone (0.163g, 0.45 mmol) in THF (2 mL) at 0 °C. After 30 mins, the reaction was quenched with NH_4Cl and extracted with EA, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **364-2** (0.115 g, 68%). LCMS: m/z 375.95 $[M+H]^+$.

[0675] To a solution of **364-2** (0.115 g, 0.31 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added DAST (81uL, 0.61 mmol). The solution was stirred for 1 h. The mixture was diluted with sat. $NaHCO_3$ and extracted with EA. The combined organic phase was dried over

anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **364-3** (0.071 g, 61%). LCMS: m/z 377.95 $[M+H]^+$.

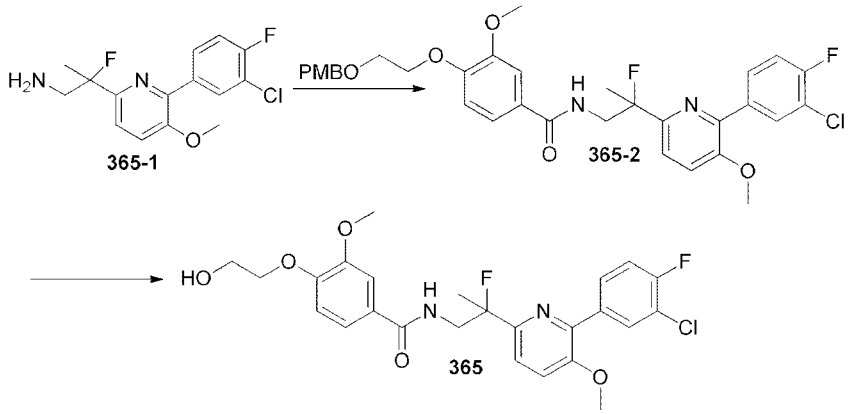
[0676] To a solution of **364-3** (0.071 g, 0.19 mmol) in DMF (1 mL) was added tetrabutylammonium azide (0.7 g, 0.94 mmol). The solution was stirred for 3 h at 90 °C and then diluted with EA. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **364-4** (0.054 g, 84%). LCMS: m/z 339.05 $[M+H]^+$.

[0677] To a solution of **364-4** (0.054 g, 0.16 mmol) in THF (1 mL) and water (1 drop) was added polymer supported triphenylphosphine (0.5 g, 1.5 mmol). The solution was stirred for 2 h at 60 °C. The mixture was diluted with EA and filtered to remove resin. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to provide crude **364-5** (0.032g, 63%), which was used without further purification. LCMS: m/z 313.00 $[M+H]^+$.

[0678] Diisopropylethylamine (52 uL, 0.31 mmol) was added to a solution of 4-(2-fluoroethoxy)-3-methoxybenzoic acid (33 mg, 0.15 mmol), **364-5** (32 mg, 0.10 mmol) HBTU (62 mg, 0.16 mmol) in DMF (1 mL). The solution was stirred at r.t. for 3 h. The mixture was diluted with EtOAc, and washed with 1N HCl, sat. Na_2CO_3 and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by reverse phase HPLC to give **364** (10.4 mg, 20%). LCMS: m/z 509.05 $[M+H]^+$.

EXAMPLE 171

Preparation of Compound 365

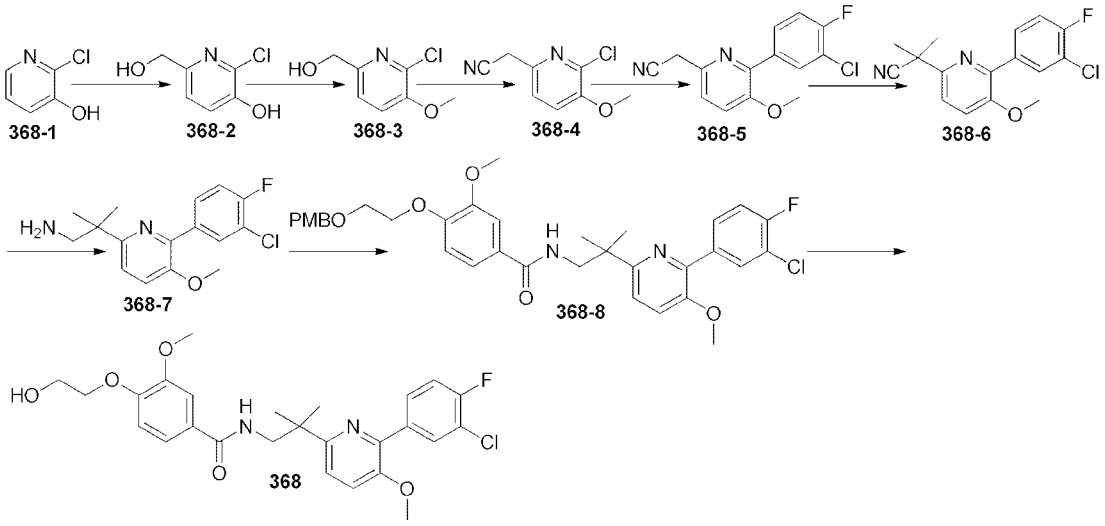


[0679] Diisopropylethylamine (0.13mL, 0.75 mmol) was added to a solution of 3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzoic acid (33 mg, 0.15 mmol), **365-1** (78

mg, 0.25 mmol) HATU (0.15 g, 0.40 mmol) in DMF (1 mL). The solution was stirred at r.t. for 3 h. The mixture was diluted with EtOAc, and washed with 1N HCl, sat. Na_2CO_3 and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (EA:hexane) to give **365-2**. LCMS: m/z 627.20 $[M+H]^+$.

[0680] Compound **365-2** was deprotected using TFA (0.25 mL) in CH_2Cl_2 (1.0 mL) at r.t. for 8 mins. The reaction was quenched with cold $NaHCO_3$ and extracted with CH_2Cl_2. The crude was purified by reverse phase HPLC to give **365** (10.4 mg, 8%). LCMS: m/z 507.01 $[M+H]^+$.

EXAMPLE 172
Preparation of Compound 368



[0681] Compound **368-1** (5.0 g, 39 mmol) and solid $NaHCO_3$ (5.0 g, 60 mmol) were suspended in water (40 mL) and heated to 90 °C. Formaldehyde (10 mL) was added portionwise over 8 h and the reaction was heated at 90 °C overnight. The mixture was cooled to 0 °C and acidified to pH 1 with 6N HCl. The solution was stirred at 0 °C for 1 h. The reaction was filtered, and the filtrate extracted with EA to provide **368-2** (4.9 g, 79%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, J = 4.6, 1H), 7.20 (d, J = 4.6, 1H), 4.4 (s, 2H).

[0682] Iodomethane (4.5 mL, 72 mmol) was added to a solution of **368-2** (7.7 g, 48 mmol) and potassium carbonate (13 g, 144 mmol) in DMF (60 mL). The mixture was stirred at 50 °C for 1 h. The mixture was diluted with EA, washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica

gel (EA:hexane) to give **368-3** (2.57 g, 31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 2H), 4.6 (d, J = 6.0, 2H).

[0683] Methanesulfonyl chloride (1.4 mL, 0.18 mmol) was added to a solution of **368-3** (2.57 g, 15 mmol) and diisopropylethyl amine (3.9 mL, 22 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After 30 mins, the mixture was diluted with CH_2Cl_2, washed with 1N HCl and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was dissolved in DMF (10 mL) and treated with sodium cyanide (2.2 g, 44 mmol) at 80 °C for 3 h. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **368-4** (1.13 g, 41%). LCMS: m/z 183.03 $[M+H]^+$.

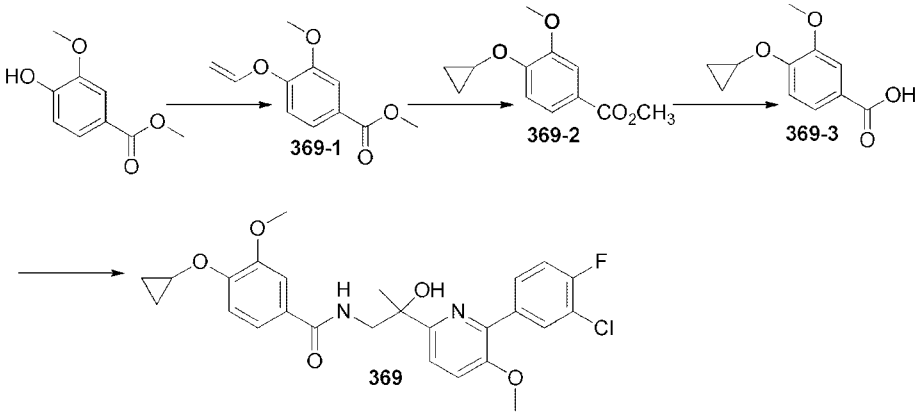
[0684] $Pd(dppf)Cl_2$ (0.45 g, 0.61 mmol) was added to a solution of **368-4** (0.56g, 3.1mmol), 3-chloro-4-fluorophenyl boronic acid (0.80g, 4.6 mmol) in CH_3CN (10 mL) and 1M K_2CO_3 (5 mL). The reaction vessel was heated under microwave irradiation for 3 h at 120 °C. The mixture was diluted with EA. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **368-5** (0.70 g, 81%). LCMS: m/z 277.05 $[M+H]^+$.

[0685] Sodium hydride (76 mg, 1.9 mmol) was added to a solution of **368-5** (0.21 g, 0.76 mmol) in DMF (1 mL). After 5 mins, iodomethane (0.14 mL, 2.3 mmol) was added, and the mixture was stirred for 30 mins. The reaction was quenched with NH_4Cl, diluted with EA. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **368-6** (0.19 g, 81%). LCMS: m/z 305.00 $[M+H]^+$.

[0686] Lithium aluminum hydride (1.8 mL, 1M in THF, 1.8 mmol) was added to a solution of **368-6** (0.19 g, 0.61 mmol) in THF (5 mL), and the mixture was stirred at r.t. for 2 h. The reaction was quenched by the addition of solid sodium sulfate decahydrate and stirred for 10 mins. The solids were filtered, and the filtrate was concentrated to yield **368-7** (0.16 g, 85%). LCMS: m/z 309.05 $[M+H]^+$.

[0687] Compounds **368-8** and **368** were prepared in the same manner as **365**. Compound **368-8**: LCMS: m/z 624.3 $[M+H]^+$. Compound **368**: LCMS: m/z 503.15 $[M+H]^+$.

EXAMPLE 173
Preparation of Compound 369



[0688] Methyl vanillate (0.25g, 1.4 mmol) and vinyl acetate (0.25 mL, 2.7 mmol) were added to $[IrCl(cod)]_2$ (9 mg, 0.014) and sodium carbonate (52 mg, 0.49 mmol) in toluene (1 mL). The mixture was flushed with Ar and stirred at 110 °C for 1.5 h and then diluted with EA. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **369-1** (0.159 g, 55%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, J = 1.6, 8.0, 1H), 7.0 (d, J = 8.4, 1H), 6.63 (dd, J = 6.0, 14, 1H), 4.87 (dd, J = 2.4, 14, 1H), 4.55 (dd, J = 2.0, 6.0, 1H), 2.92 (s, 2H), 3.91 (s, 3H).

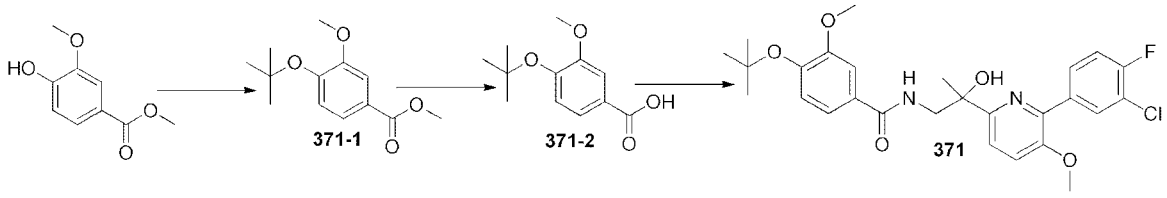
[0689] Diethylzinc (9 mL, 9.0 mmol) was added dropwise to a solution of **369-1** (0.234 g, 1.1 mmol) and diiodoethane (0.72 mL, 9.0 mmol) in dichloroethane (3 mL) at 0 °C. The mixture was stirred at r.t. overnight, and then diluted with EA. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **369-2** (0.121 g, 55%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, J = 1.6, 8.0, 1H), 7.0 (d, J = 8.4, 1H), 6.63 (dd, J = 6.0, 14, 1H), 4.87 (dd, J = 2.4, 14, 1H), 4.55 (dd, J = 2.0, 6.0, 1H), 3.92 (s, 3H).

[0690] 2N Sodium hydroxide (1 mL) was added to a solution of **369-2** (58 mg) in methanol (3 mL), and the mixture was stirred at r.t. overnight. The mixture was acidified with 1N HCl and extracted with EA to give **369-3** (50 mg, 86%). ^1H NMR (400 MHz,

$CDCl_3$): δ 7.78 (d, J = 1.95, 1H), 7.58 (s, 1H), 7.30 (d, J = 1.95, 1H), 3.91 (s, 3H), 3.80-3.83 (m, 1H), 0.85-0.89 (m, 4H).

[0691] Compound **369** was prepared in a similar manner as **364**. LCMS: m/z 501.1 $[M+H]^+$.

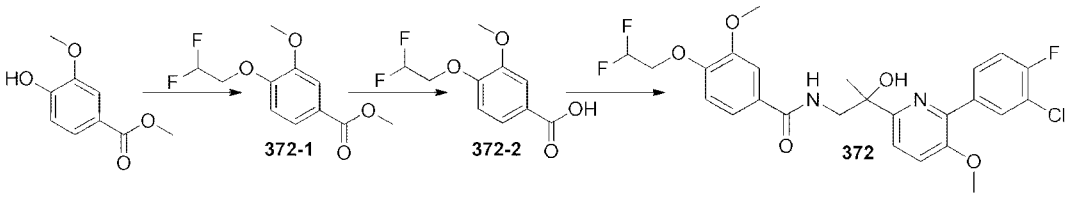
EXAMPLE 174
Preparation of Compound 371



[0692] Isobutylene (10 mL, 105 mmol) was added to a solution of methyl vanillate (1 g, 5.5 mmol) and H_2SO_4 (3 drops) in CH_2Cl_2 (15 mL) in a sealed vessel at -40 °C. The mixture was warmed to r.t. and stirred over 2-3 d. The mixture was diluted with EA. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **371-2** (0.161 g, 12%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 6.26, 1H), 7.63 (d, J = 1.96, 1H), 7.09 (d, J = 8.26, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 1.41 (s, 9H).

[0693] Compound **371** prepared in a similar manner as **364**. LCMS: m/z 517.2 $[M+H]^+$.

EXAMPLE 175
Preparation of Compound 372

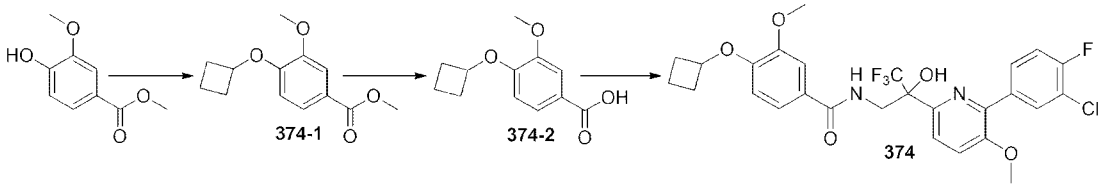


[0694] Potassium fluoride (0.10 g, 1.7 mmol) and methyl vanillate (0.31 g, 1.7 mmol) were mixed in methanol (5 mL) for 15 mins. The mixture was concentrated, co-evaporating with diethyl ether (2x). The residue was dissolved in DMSO (2.0 mL) and added to difluoroiodoethane (0.36 g, 1.9 mmol) in a vial. The vial was flushed with Ar, sealed, and heated at 120 °C overnight. The mixture was diluted with EA. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue

was purified by chromatography on silica gel (EA:hexane) to give **372-1** (0.060 g, 14%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 766 (dd, J = 1.95, 8.41, 1H), 7.59 (d, J = 1.95, 1H), 6.92 (d, J = 8.41, 1H), 6.00-6.30 (m, 1H), 4.24-4.31 (m, 2H), 3.91 (s, 3H), 3.91 (s, 3H).

[0695] Compound **372** was prepared in a similar manner as **364**. LCMS: m/z 525.10 $[M+H]^+$.

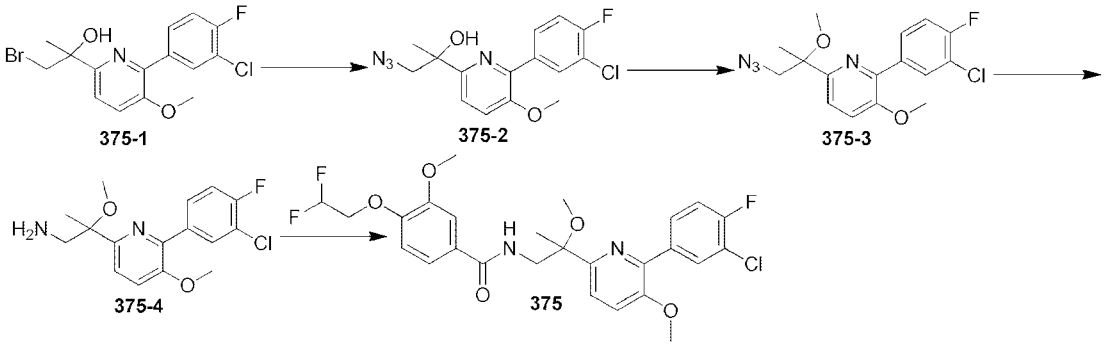
EXAMPLE 176
Preparation of Compound 374



[0696] Sodium iodide (1 mg) was added to a solution of methyl vanillate (0.26 g, 1.4 mmol), bromocyclobutane (0.40 mL, 4.3 mmol), potassium carbonate (0.98 g, 4.3 mmol) in NMP (1.5 mL). The mixture was heated under microwave irradiation at 180 °C for 1.5 h and then diluted with EA. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **374-1** (0.18 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.3 (d, J = 8.41, 1H), 7.53 (s, 1H), 6.74 (d, J = 8.41, 1H), 4.4-4.7 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H).

[0697] Compound **372-2** was hydrolyzed in a similar manner as **369**, and **372** was prepared in a similar manner as **364**. LCMS: m/z 568.9 $[M+H]^+$.

EXAMPLE 177
Preparation of Compound 375



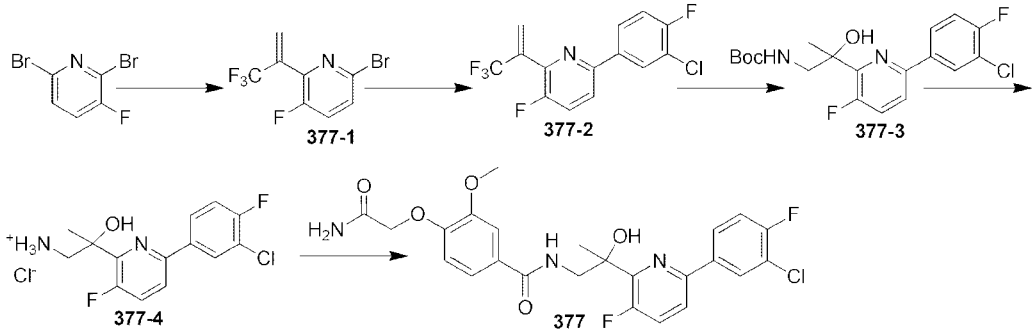
[0698] Tetrabutylammonium azide (0.33 g, 0.57 mmol) was added to **375-1** (60 mg, 0.16 mmol) in DMF (1 mL), and the mixture was heated at 80 °C for 5h. The mixture was diluted with EA. The organic phase was washed with water and brine, dried over

anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **375-2** (0.052 g, 96%). LCMS: m/z 337.05 $[M+H]^+$.

[0699] NaH (12 mg, 0.31 mmol) was added to **375-2** (52 mg, 0.15 mmol) in DMF (1 mL). The mixture was stirred at r.t. for 15 mins. Iodomethane (30 uL, 0.46 mmol) was added, and the mixture reaction was stirred for 2 h. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **375-3** (0.052 g, 98%). LCMS: m/z 351.05 $[M+H]^+$.

[0700] Compound **375** was prepared in a similar manner as **364**. LCMS: m/z 539.15 $[M+H]^+$.

EXAMPLE 178
Preparation of Compound 377



[0701] $Pd(dppf)Cl_2$ (20 mg, 0.02 mmol) was added to a solution of 2,6-dichloro-3-fluoropyridine (0.20 g, 0.78 mmol) and 1-(trifluoromethyl)vinylboronic acid hexylene glycol ester (0.18 g, 0.86 mmol) in CH_3CN (0.5 mL) and 1M K_2CO_3 (0.25 mL). The mixture was heated under microwave irradiation for 1 h at 110 °C. The reaction was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **377-1** (0.10 g, 47%). LCMS: m/z 271.90 $[M+H]^+$.

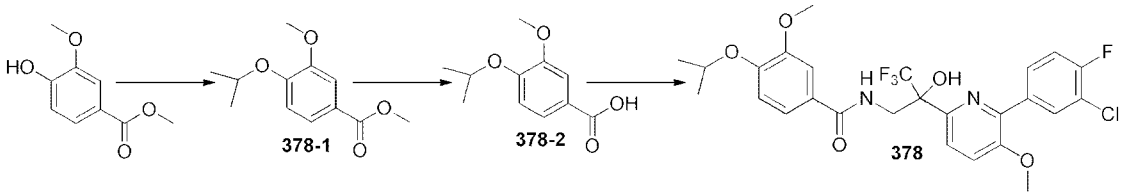
[0702] $Pd(dppf)Cl_2$ (75 mg, 0.091 mmol) was added to **377-1** (0.493 g, 1.8 mmol) and 3-chloro-4-fluorophenyl boronic acid (0.38 g, 2.7 mmol) in CH_3CN (2 mL) and 1M K_2CO_3 (0.5 mL). The mixture was heated under microwave irradiation at 110 °C for 30 mins. The mixture was heated under microwave irradiation for 1 h at 110 °C. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over

anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **377-2** (0.286 g, 33%). LCMS: m/z 319.95 $[M+H]^+$.

[0703] Potassium osmate (50 mg, 0.13 mmol) was added to a suspension of **377-2** (0.286g, 0.89 mmol) and tert-butyl (tosyloxy)carbamate (0.36 g, 1.3 mmol) in t-butanol (2 mL) and water (0.6 mL), and the mixture was stirred overnight at r.t. The crude was poured directly onto a silica gel column and chromatographed (EA:hexane) to give **377-3**. (0.162 g, 40%). LCMS: m/z 398.83 $[M+H]^+$.

[0704] 4N HCl in dioxane (2 mL) was added to **377-3** (0.16 g), and the mixture was stirred at r.t. for 1 h. The mixture was concentrated to give **377-4**, which was used without further purification. Compound **377** was prepared in a similar manner as **364**. LCMS: m/z 506.20 $[M+H]^+$.

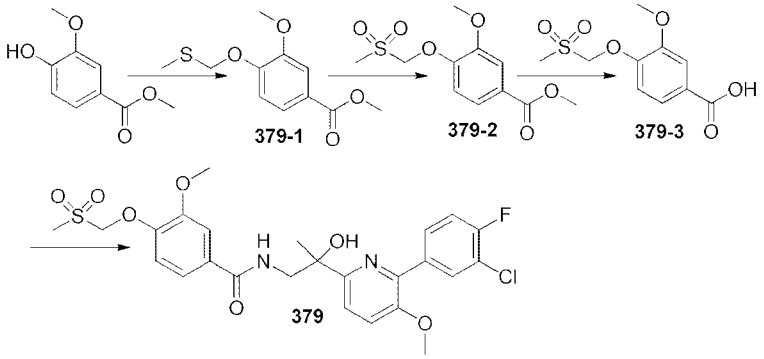
EXAMPLE 179
Preparation of Compound 378



[0705] NaH (0.13 g, 3.1 mmol) was added to a solution of methyl vanillate (0.44 g, 2.4 mmol) and 2-iodopropane (1.2 mL, 12 mmol) in DMF (3.0 mL), and the mixture was heated at 65 °C for 1 h. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **378-1** (0.50 g, 93%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, J = 1.95, 8.6, 1H), 7.55 (d, J = 1.96, 1H), 6.90 (d, J = 8.6, 1H), 4.61-4.66 (m, 1H), 3.91 (s, 3H), 3.58 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H).

[0706] Compound **378-1** was hydrolyzed in a similar manner as **369** to give **378-2**. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, J = 1.95, 8.6, 1H), 7.60 (d, J = 1.96, 1H), 6.92 (d, J = 8.6, 1H), 4.65-4.68 (m, 1H), 3.92 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H). Compound **378** was prepared in a similar manner as **364**. LCMS: m/z 557.10 $[M+H]^+$.

EXAMPLE 180
Preparation of Compound 379

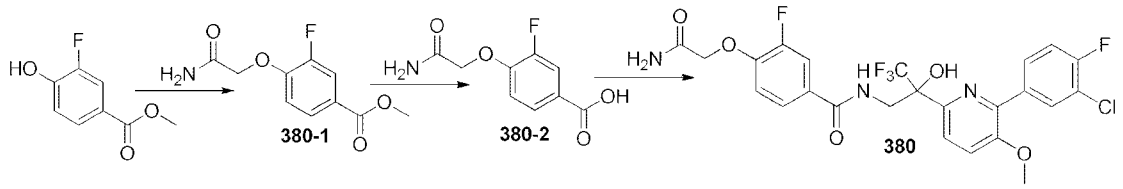


[0707] NaH (0.13 g, 3.1 mmol) was added to a solution of methyl vanillate (0.44 g, 2.4 mmol) and chloromethylmethyl sulfide (0.24 mL, 2.8 mmol) in DMF (3.0 mL), and the mixture was stirred for 1 h. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **379-1** (0.57 g, 92%).

[0708] MCPBA (0.9 g, 5.2 mmol) was added to **379-1** (0.576 g, 2.4 mmol) in CH_2Cl_2 (3 mL), and the mixture was stirred at r.t. for 1 h. The mixture was washed with Na_2CO_3, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **379-2** (0.40 g, 70%).

[0709] Compound **379-2** was hydrolyzed in a similar manner as **369** to give **379-3**. Compound **379** was prepared in a similar manner as **364**. LCMS: m/z 553.10 $[M+H]^+$.

EXAMPLE 181
Preparation of Compound 380

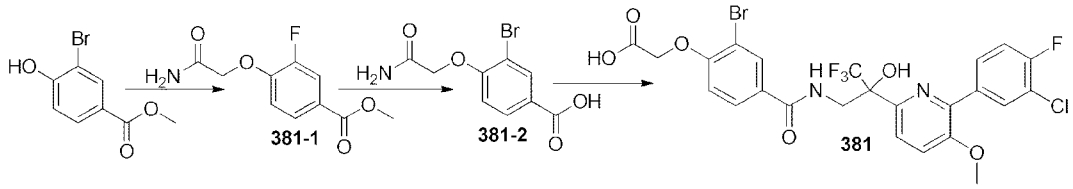


[0710] 2-Bromoacetamide (0.46 g, 3.4 mmol) was added to methyl 3-fluoro-4-hydroxybenzoate (0.29 g, 1.7 mmol) and potassium carbonate (0.70 g, 5.0 mmol) in DMF (1 mL), and the mixture was heated to 65 °C for 1h. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. Compound **380-1** was crystallized from EA and collected by filtration (0.27 g,

71%). ^{1}H NMR (400 MHz, dmso-d_6): δ 7.67-7.42 (m, 2H), 7.50 (br. s, 1H), 7.38 (br. s, 1H), 7.11 (t, J = 8.62, 1H), 4.62 (s, 2H), 3.79 (s, 3H).

[0711] Compound **380-1** was hydrolyzed in a similar manner as **369** to give **380-2**. ^{1}H NMR (400 MHz, dmso-d_6): δ 7.63-7.69 (m, 2H), 7.49 (br. s, 1H), 7.38 (br. s, 1H), 7.08-7.11 (m, 1H), 4.61 (s, 2H). Compound **380** was prepared in a similar manner as **364**. LCMS: m/z 560.05 $[M+H]^+$.

EXAMPLE 182
Preparation of Compound 381

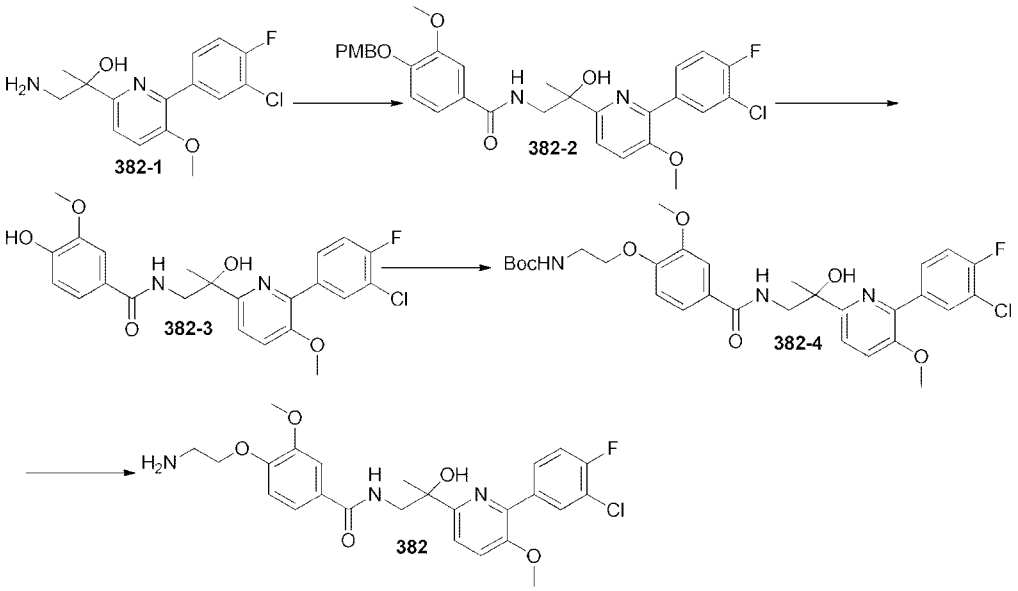


[0712] 2-Bromoacetamide (0.46 g, 3.4 mmol) was added to methyl 3-bromo-4-hydroxybenzoate (0.46 g, 1.7 mmol) and potassium carbonate (0.70 g, 5.0 mmol) in DMF (1 mL), and the mixture was heated to 65 °C for 1 h. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give 381-1 (0.091 g, 24%). ^{1}H NMR (400 MHz, dmso-d_6): δ 7.95 (d, J = 2.34, 1H), 7.90 (dd, J = 2.34, 8.61, 1H), 7.45 (br. s, 1H), 7.34 (br. s, 1H), 7.06 (d, J = 8.61, 1H), 4.65 (s, 2H), 3.78 (s, 3H).

[0713] **381-1** was hydrolyzed in a similar manner as **369-2** to give **381-2**. ^{1}H NMR (400 MHz, dmso-d_6): δ 8.12 (d, J = 2.34, 1H), 7.87 (dd, J = 2.35, 6.0, 1H), 7.15 (d, J = 6.0, 1H), 4.87 (s, 2H).

[0714] Compound **381** was prepared in a similar manner as **364**. LCMS: m/z 621.76 $[M+H]^+$.

EXAMPLE 183
Preparation of Compound 382



[0715] Diisopropylethylamine (0.15 mL, 0.84 mmol) was added to a solution of **382-1** (0.10 g, 0.34 mmol), 3-methoxy-4-(2-((methosybenzyl)oxy)ethoxy)benzoic acid (0.15 g, 0.51 mmol) and HATU (0.25 g, 0.67 mmol) in DMF (1 mL). The mixture was stirred at r.t. for 2 h. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **382-2** (0.15 g, 76%). LCMS: m/z 581.15 $[M+H]^+$.

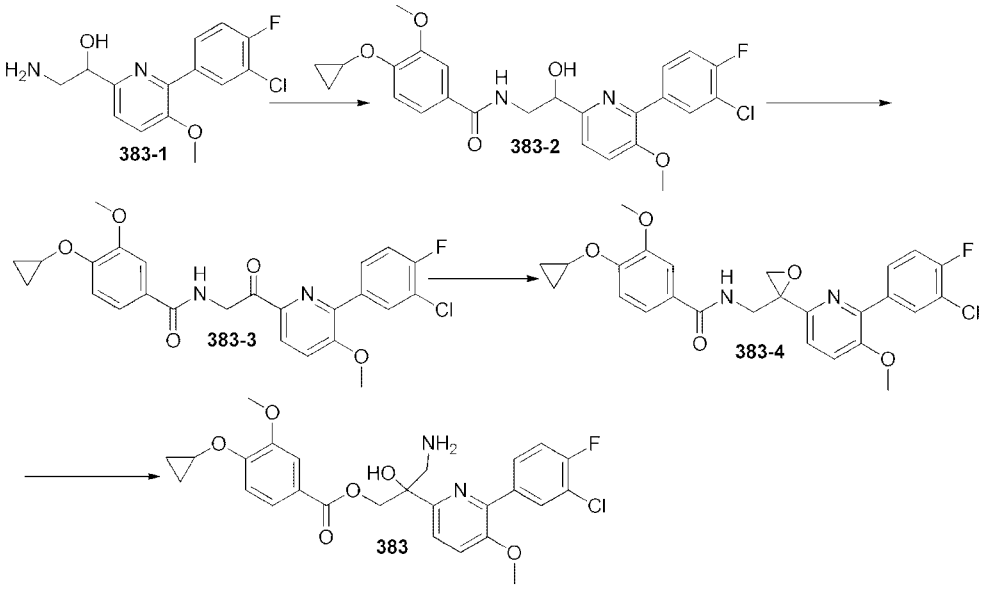
[0716] Compound **382-2** was deprotected in a similar manner as **368** to give **382-3** LCMS: m/z 461.10 $[M+H]^+$.

[0717] Cesium carbonate (0.11 g, 0.33 mmol) was added to a solution of **382-3** (0.050 g, 0.11 mmol) and 2-(Boc-amino)ethyl bromide (0.048 g, 0.22 mmol) in DMF (1 mL). The mixture was heated under microwave irradiation at 70 °C for 1 h. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **382-4** (39 mg, 60%). LCMS: m/z 604.20 $[M+H]^+$.

[0718] Hydrochloric acid in dioxane (1.5 mL, 4N) was added to **382-4** (39 mg, 0.077 mmol). The mixture was stirred at r.t. for 1 h and then concentrated under reduced

pressure. The crude was purified by reverse phase HPLC to give **382** (8 mg, 25%). LCMS: m/z 503.95 $[M+H]^+$.

EXAMPLE 184
Preparation of Compound 383



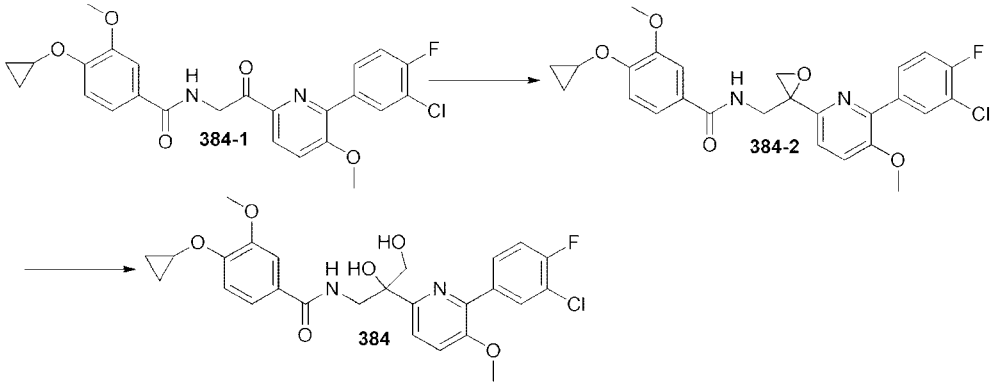
[0719] Compound **383-1** was prepared in a similar manner as **364** to give **383-2**. LCMS: m/z 487.10 $[M+H]^+$.

[0720] Dess-Martin periodinane (0.58 g, 1.4 mmol) was added to **383-2** (0.337 g, 0.69 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred at r.t. for 1 h. The mixture was diluted with CH_2Cl_2, washed with Na_2CO_3 and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude was purified by chromatography on silica gel (EA:hexane) to provide **383-3** (0.144 g, 43%). LCMS: m/z 485.10 $[M+H]^+$.

[0721] Potassium tert-butoxide (40 mg, 0.36 mmol) was added to trimethylsulfoxonium iodide (65 mg, 0.30 mmol) in DMSO (1 mL), and the mixture was stirred at r.t. for 30 mins. Compound **383-3** (0.144 g, 0.30 mmol) in DMSO (0.5 mL) was added, and the mixture was stirred for 1 h. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **383-4** (0.050 g, 33%). LCMS: m/z 499.15 $[M+H]^+$.

[0722] Compound **383-4** (0.050 g, 0.10 mmol) was dissolved in 6N HCl (1 mL) and MeOH (1 mL) and heated at 60 °C for 2 h. The mixture was concentrated, and the crude was purified by reverse phase HPLC to give **383** (14 mg, 28%). LCMS: m/z 517.10 $[M+H]^+$.

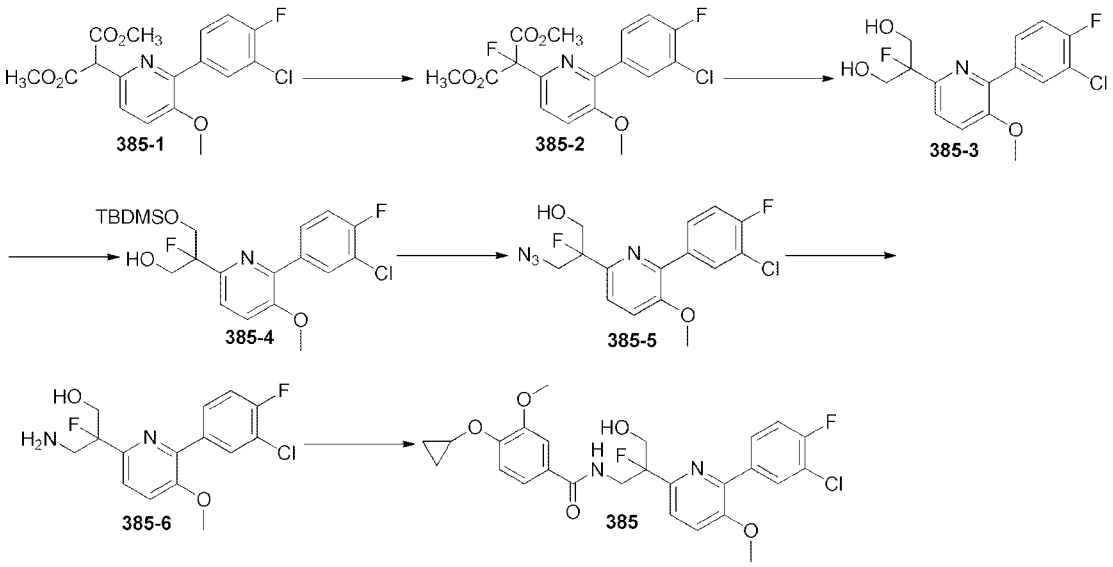
EXAMPLE 185
Preparation of Compound 384



[0723] Potassium tert-butoxide (81 mg, 0.72 mmol) was added to trimethylsulfoxonium iodide (0.13 g, 0.60 mmol) in DMSO (1 mL), and the mixture was stirred at r.t. for 30 mins. Compound **384-1** (0.329 g, 0.60 mmol) in DMSO (0.5 mL) was added, and the mixture was stirred for 1 h. The mixture was diluted with EA, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **384-2** (0.11 g, 37%). LCMS: m/z 499.15 $[M+H]^+$.

[0724] Compound **384-2** (0.11 g, 0.22 mmol) was dissolved in 6N HCl (1 mL) and MeOH (1 mL) and heated at 60 °C for 2 h. The mixture was concentrated and treated with 2N NaOH (2 mL) in MeOH (2 mL) for 2 h. The crude was purified by reverse phase HPLC to give **384** (17 mg, 5%). LCMS: m/z 517.10 $[M+H]^+$.

EXAMPLE 186
Preparation of Compound 385



[0725] LDA (2 M in THF, 1.4 mL, 2.8 mmol) was added dropwise to a solution of **385-1** (0.93 g, 2.5 mmol) in THF (10 mL) at -78 °C, and the mixture was stirred at -78 °C for 15 mins. N-fluorobenzenesulfonimide (1.2 g, 3.8 mmol) was added, and the mixture was stirred for 3 h. The mixture was warmed to r.t., and the reaction was quenched with 1N HCl. The mixture was extracted with EA, and the organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **385-2** (0.57 g, 59%). LCMS: m/z 386.10 $[M+H]^+$.

[0726] Sodium borohydride (0.12 g, 3.1 mmol) was added to a solution of **385-2** (0.14 g, 0.36 mmol) in EtOH. The mixture was stirred at r.t. for 2 h. The reaction was quenched with 1N HCl and extracted with EA. The organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **385-3** (0.040 g, 33%). LCMS: m/z 330.00 $[M+H]^+$.

[0727] Compound **385-3** (25 mg, 0.076 mmol) in THF (1 mL) was added to NaH (3.0 mg, 0.076 mmol) in THF (0.5 mL), and the mixture solution was stirred for 30 mins. TBDMSCl (11 mg, 0.076 mmol) was added, and the mixture was stirred at r.t. for 2 h. The reaction was quenched with 1N HCl and extracted with EA. The organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by

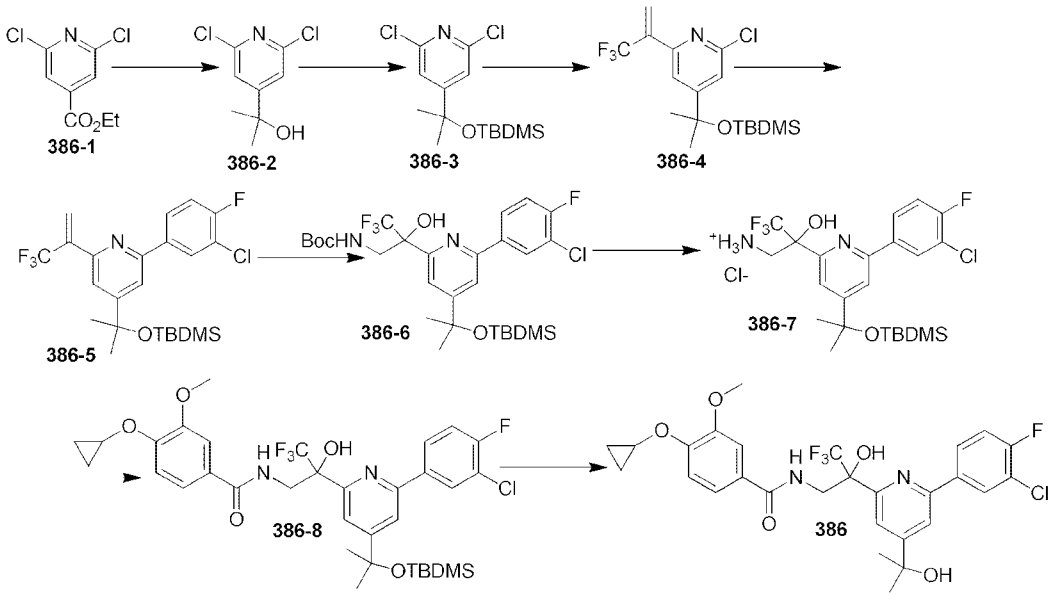
chromatography on silica gel (EA:hexane) to give **385-4** (0.014 g, 41%). LCMS: m/z 444.10 $[M+H]^+$.

[0728] Triflic anhydride (45 uL, 0.27 mmol) was added to a solution of **385-4** (60 mg, 0.14 mmol) and 2,6-lutidine (47 uL, 0.40 mmol) in CH_2Cl_2 (1 mL) at -78 °C. The mixture was warmed to r.t. The reaction was quenched with1N HCl and extracted with EA. The organic extracts were washed with brine, dried over sodium sulfate and concentrated. The crude triflate was immediately dissolved in NMP (0. 5 mL) and tetrabutylammonium azide (0.39 g, 1.4 mmol) was added, and the mixture was heated at 65 °C for 1 h. The mixture was diluted with EA, and organic extracts were washed with water and brine, dried over sodium sulfate and concentrated. The crude was purified by chromatography on silica gel (EA:hexane) to give **385-5** (0.057 g, 114%). LCMS: m/z 355.05 $[M+H]^+$.

[0729] Compound **385-5** was reduced in a similar manner as **364** to give **385-6**. LC/MS: [M+H] 329.00. Diisopropylethylamine (62 uL, 0.36 mmol) was added to a solution of **385-6** (54 mg, 0.12 mmol), 4-cyclopropoxy-3-methoxybenzoic acid (37 mg, 0.18 mmol) and HBTU (81 mg, 0.21 mmol) in DMF (1 mL), and the mixture was stirred at r.t. for 1 h. The mixture was diluted with EA and washed with 1 N HCl, sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated. The crude was purified by reverse phase HPLC to give **385** (14 mg, 22%). LCMS: m/z 520.15 $[M+H]^+$.

EXAMPLE 187

Preparation of Compound 386



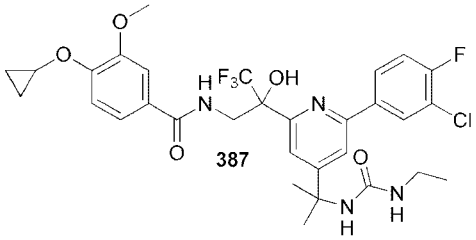
[0730] Methyl magnesium bromide (1.4 M in THF, 6.0 mL, 8.4 mmol) was added to a solution of ethyl 2,6-dichloroisonicotinate (0.74 g, 3.4 mmol) in THF (20 mL) at 0 °C. The mixture was stirred at r.t. for 2 h. The reaction was quenched with 1N HCl and extracted with EA. The organic extracts were washed with brine, dried over sodium sulfate and concentrated. The crude was purified by chromatography on silica gel (EA:hexane) to give **386-2** (0.63 g, 88%). LCMS: m/z 206.00 $[M+H]^+$.

[0731] TBDMSOTf (2.6 mL, 12 mmol) was added dropwise to a solution of **386-2** (0.80 g, 3.9 mmol) and 2,6-lutidine (2.3 mL, 19 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred at r.t. for 3 h. The reaction was quenched with 1N HCl and extracted with EA. The organic extracts were washed with brine, dried over sodium sulfate and concentrated. The crude was purified by chromatography on silica gel (EA:hexane) to give **386-3** (1.2 g, 96%). LCMS: m/z 320.05 $[M+H]^+$.

[0732] Compounds **386-4**, **386-5**, **386-6**, **386**-7 and **386-8** were prepared in a similar manner as **377**. **386**-4: LCMS: m/z 350.10 $[M+H]^+$. **386-5**: LCMS: m/z 474.15 $[M+H]^+$. **386-6**: LCMS: m/z 607.20 $[M+H]^+$. **386-7**: LCMS: m/z 507.15 $[M+H]^+$. **386-8**: LCMS: m/z 697.25 $[M+H]^+$.

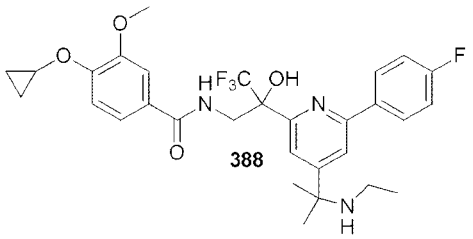
[0733] TBAF (1M in THF, 0.13 mL, 0.13 mmol) was added to a solution of **386-8** (25, mg, 0.043 mmol), and the mixture was stirred at r.t. for 1 h. The mixture was concentrated, and **386** was purified by reverse phase HPLC (5 mg, 20%). LCMS: m/z 583.20 $[M+H]^+$.

EXAMPLE 188
Preparation of Compound 387



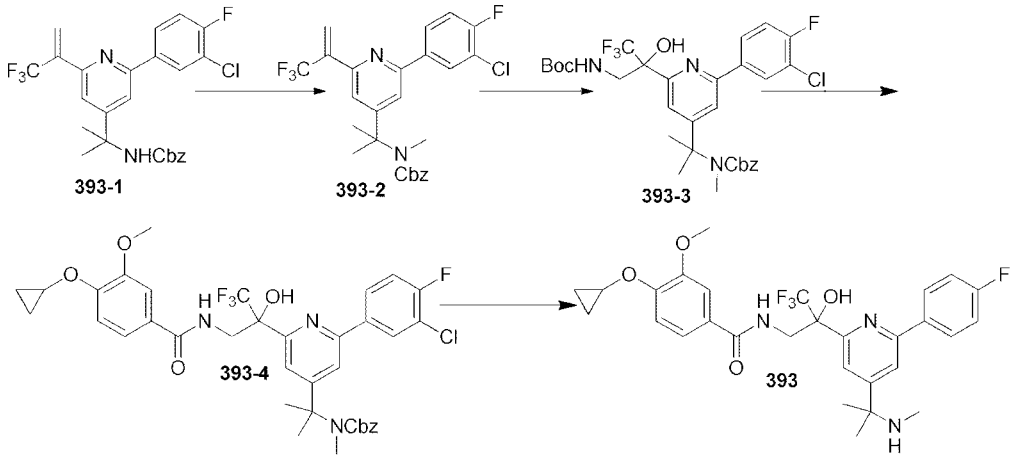
[0734] Compound **314** (10 mg, 0.021 mmol) was dissolved in CH_2Cl_2 (1 mL). Ethyl isocyanate (10 uL, 0.12 mmol) was added, and the mixture was stirred at r.t. for 5 h. The reaction was quenched with methanol (2 mL) and concentrated. Compound **314** was purified by HPLC (4.1 mg, 40%). LCMS: m/z 653.20 $[M+H]^+$.

EXAMPLE 189
Preparation of Compound 388



[0735] Sodium triacetoxyborohydride (48 mg, 0.23 mmol) was added to a solution of **318** (28 mg, 0.051 mmol) and acetaldehyde (9 uL, 0.16 mmol) in CH_2Cl_2 (1 mL). Additional acetaldehyde and reducing agent were added every 30 mins for 5 h. The reaction was quenched with ammonium chloride and extracted with CH_2Cl_2. Compound **388** was purified by reverse phase HPLC (14 mg, 50%) LCMS: m/z 576.20 $[M+H]^+$.

EXAMPLE 190
Preparation of Compound 393



[0736] NaH (9 mg, 0.22 mmol) was added to a solution of **393-1** (72 mg, 0.15 mmol) in DMF (1 mL) and stirred for 15 mins. Iodomethane (18 uL, 0.29 mmol) was added, and the mixture was stirred at r.t. for 3 h. The reaction was quenched with sat. NH_4Cl and extracted with EA. The combined organic extracts were washed with water and brine, dried over sodium sulfate and concentrated. The crude was purified by chromatography on silica gel (EA:hexane) to give **393-2** (51 mg, 66%). LCMS: m/z 507.10 $[M+H]^+$.

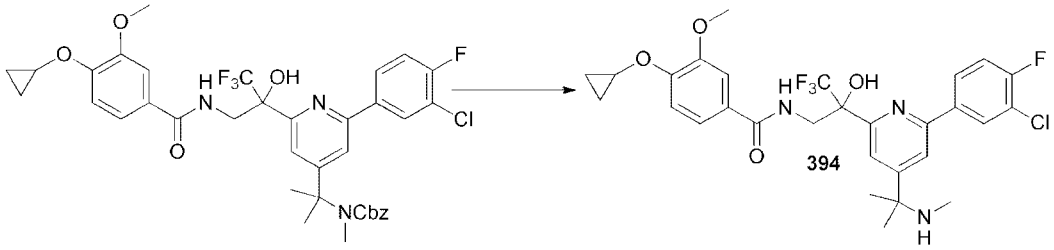
[0737] Potassium osmate (6 mg, 0.015 mmol) was added to a solution of **393-2** (51 mg, 0.10 mmol) and tert-butyl (tosyloxy)carbamate (41 mg, 0.15 mmol) in t-butanol (1 mL) and water (0.33 mL), and the solution was stirred overnight at r.t. The crude was

purified by chromatography on silica gel (EA:hexane) to give **393-3** (0.025 g, 50%). LCMS: m/z 640.20 $[M+H]^+$.

[0738] HCl (4N in dioxane, 1 mL) was added to **393-3** (0.025 g, 0.039 mmol), and the mixture was stirred for 1 h. The solvent was removed by evaporation and 4-cyclopropoxy-3-methoxybenzoic acid (24 mg, 0.12 mmol), HATU (60 mg, 0.16 mmol), and diisopropylethylamine (40 uL, 0.23 mmol) were added, and the mixture was stirred at r.t. for 1.5 h. The crude was diluted with EA and washed with 1N HCl, sodium bicarbonate and brine, dried over sodium sulfate and concentrated. The crude was purified by reverse phase HPLC to provide **393-4** (12 mg, 41%). LCMS: m/z 730.15 $[M+H]^+$.

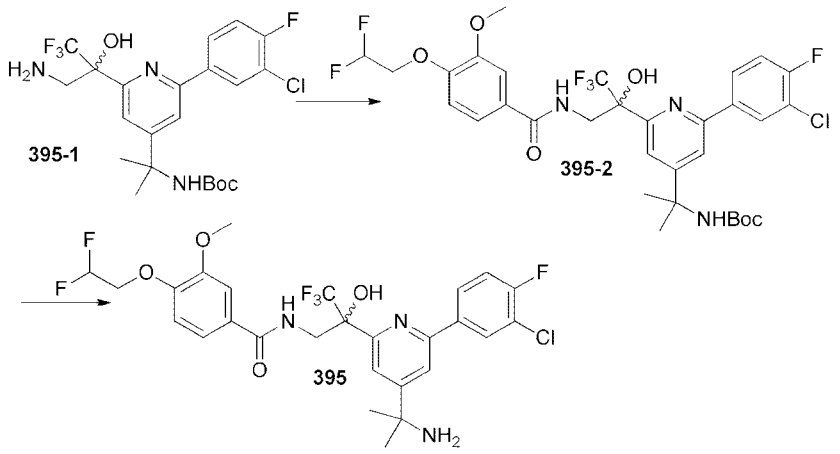
[0739] Pd/C (10%, 3 mg) was added to a solution of **393-4** (12 mg, 0.025 mmol) in EtOH (3 mL), and the mixture was stirred under hydrogen atmosphere for 2 h. The catalyst was removed by filtration, and the crude was purified by reverse phase HPLC to provide **393** (2.5 mg, 28%) LCMS: m/z 563.20 $[M+H]^+$.

EXAMPLE 191
Preparation of Compound 394



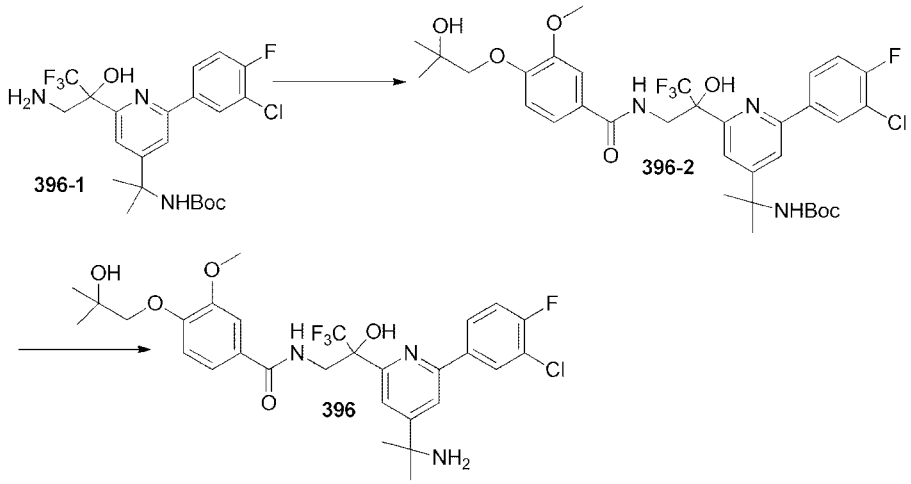
[0740] Sodium iodide (40 mg, 0.27 mmol) was added to a solution of **393-4** (40 mg, 0.55 mmol) and chlorotrimethylsilane (35 uL, 0.27 mmol) in acetonitrile (3 mL), and the mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with EA and washed with sat. $Na_2(SO_2)_3$, and brine, dried over Na_2SO_4 and concentrated. The product was purified by reverse phase HPLC to provide **394**. LCMS: m/z 597.15 $[M+H]^+$.

EXAMPLE 192
Preparation of Compound 395



[0741] Compound **395-2** was prepared in a similar manner as **364**. LCMS: m/z 706.20 $[M+H]^+$. Compound **395** was prepared in a similar manner as **396**. LCMS: m/z 607.10 $[M+H]^+$.

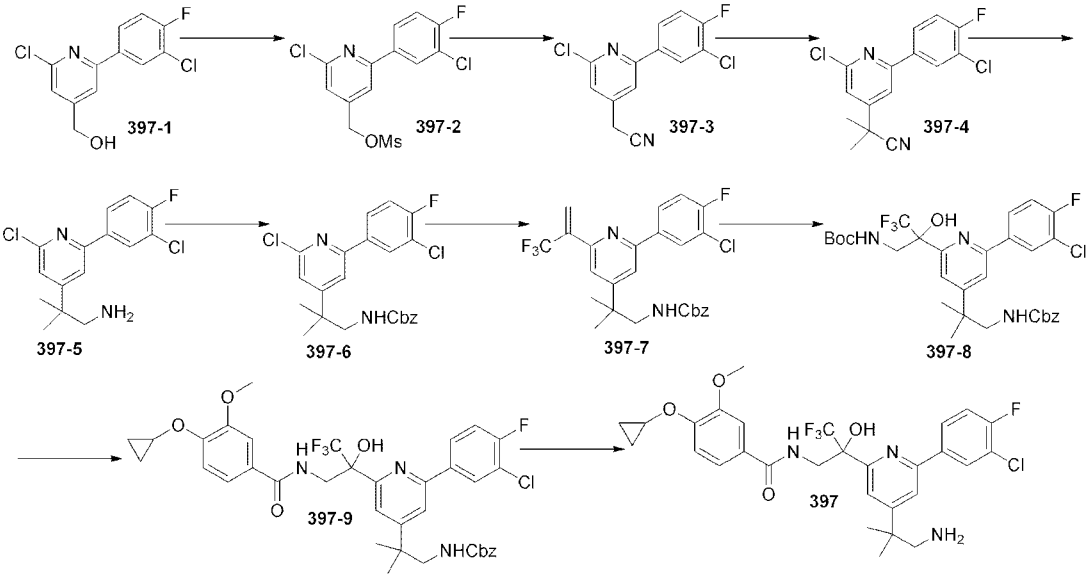
EXAMPLE 193
Preparation of Compound 396



[0742] Compound **396-2** was prepared in a similar manner as **364**. LC/MS:m/z 714.20 [M+H]. HCl (4N in dioxane, 2 mL) was added to **396-2** (80 mg, 0.11 mmol,) and the mixture was stirred for 2 h. The mixture was concentrated to remove volatile components, and **396** was purified by reverse phase HPLC (11 mg, 15%). LCMS: m/z 615.15 $[M+H]^+$.

EXAMPLE 194

Preparation of Compound 397



[0743] Methanesulfonyl chloride (0.30 mL, 4.0 mmol) was added dropwise to a solution of **397-1** (0.70 g, 2.7 mmol) and diisopropylethylamine (0.93 mL, 5.3 mmol) in CH_2Cl_2 (30 mL) at 0 °C for 30 mins. The mixture was washed with 1N HCl, and brine, dried over Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography (EA:hexane) to provide **397-2** (0.59 g, 85%). LCMS: m/z 349.95 $[M+H]^+$.

[0744] Sodium cyanide (0.14 g, 2.8 mmol) was added to a solution of **397-2** (0.59 g, 2.3 mmol) in ethanol (10 mL) and water (2 mL). The mixture was heated at 50 °C for 30 mins. The mixture was diluted with EA and washed with water and brine, dried over Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography (EA:hexane) to provide **397-3** (0.15 g, 23%). LCMS: m/z 280.95 $[M+H]^+$.

[0745] NaH (65 mg, 1.6 mmol) was added to a solution of **397-3** (0.15 g, 0.54 mmol) in DMF (1 mL) and stirred for 5 mins. Iodomethane (0.16 mL, 3.0 mmol) was added dropwise, and the mixture was stirred at r.t. for 1 h. The reaction was quenched with NH_4Cl and extracted with EA. The organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography (eluent: EA:hexane) to provide **397-4** (0.123 g, 72%). LCMS: m/z 308.95 $[M+H]^+$.

[0746] Borane-dimethylsulfide (0.11 mL, 0.11 mmol) was added dropwise to a solution of **397-4** (0.123 g, 3.9 mmol) in THF (2 mL), and the mixture was heated at 55 °C

for 1 h. The reaction was quenched with 6N HCl and heated at 55 °C for 15 mins. The volatile components were removed by evaporation, and **397-5** was used without further purification. LCMS: m/z 313.00 $[M+H]^+$.

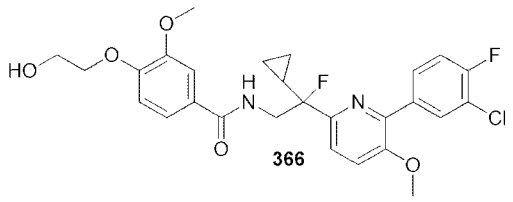
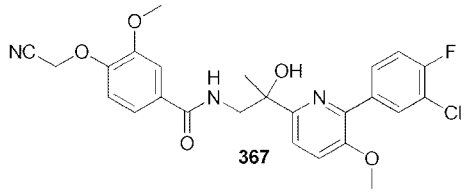
[0747] Benzyl chloroformate (85 uL, 0.59 mmol) was added dropwise to a solution of **397-5** (3.9 mmol) and diisopropylethylamine (0.20 mL, 1.2 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at r.t. for 1 h. The mixture was diluted with EA and washed with water and brine, dried over Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography (EA:hexane) to provide **397-6** (0.15 g, 87%). LCMS: m/z 447.05 $[M+H]^+$.

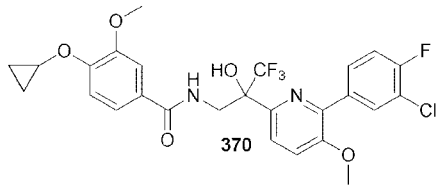
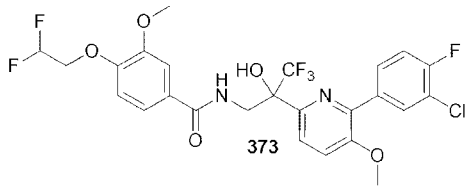
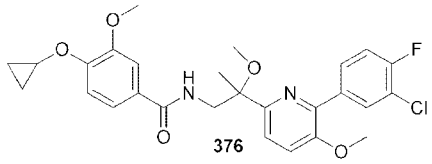
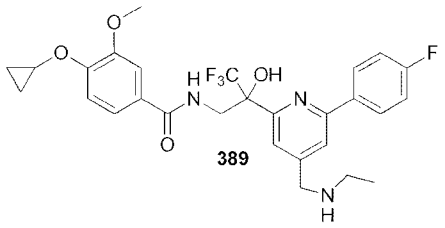
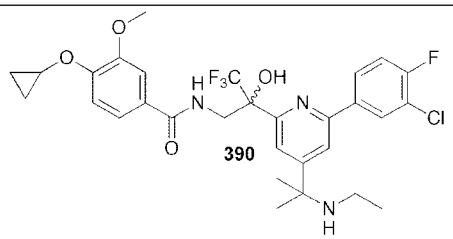
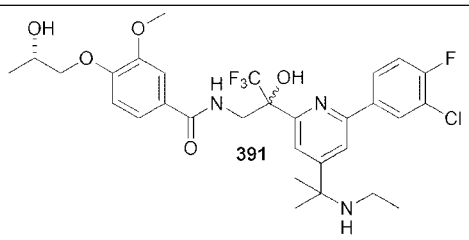
[0748] Compound **397-7** was prepared in a similar manner as **364**. LCMS: m/z 507.10 $[M+H]^+$. Compound **397-8** was prepared in a similar manner as **377**. LCMS: m/z 640.15 $[M+H]^+$. Compound **397-9** was prepared in a similar manner as **377**. LCMS: m/z 730.15 $[M+H]^+$. Compound **397** was prepared in a similar manner as **394**. LCMS: m/z 597.20 $[M+H]^+$.

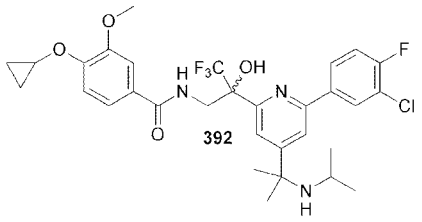
EXAMPLE 195

Preparation of Compounds 366, 367, 370, 373, 376, 389, 390, 391 and 392

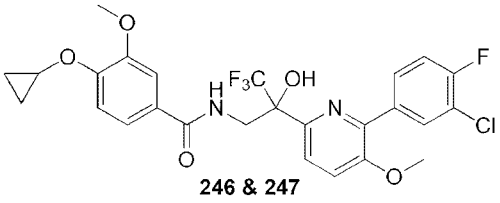
Table 7

Example Method	Structure	LCMS: m/z
Compound 365	 366	533.10 $[M+H]^+$
Compound 424	 367	500.1 $[M+H]^+$

Example Method	Structure	LCMS: m/z
Compound 369	 370	555.10 $[M+H]^+$
Compound 364	 373	579.05 $[M+H]^+$
Compound 364	 376	515.05 $[M+H]^+$
Compound 388	 389	548.20 $[M+H]^+$
Compound 388	 390	611.10 $[M+H]^+$
Compound 388	 391	628.20 $[M+H]^+$

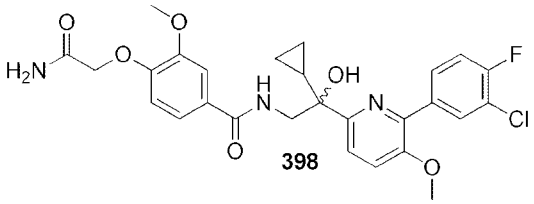
Example Method	Structure	LCMS: m/z
Compound 388	 392	625.15 $[M+H]^+$

EXAMPLE 196
Preparation of Compounds 246 and 247


246 & 247

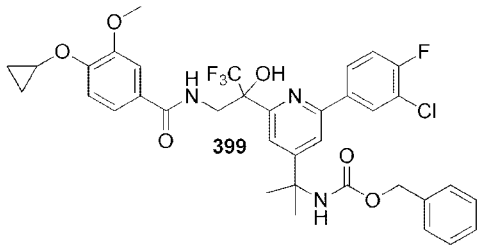
[0749] Compound **370** (270 mg, 0.49 mmol) was separated via SFC to give two enantiomers: **246** (100 mg, 74.0%) and **247** (110 mg, 81.5%). **246**: +ESI-MS:m/z 555.1 $[M+H]^+$. **247**: +ESI-MS:m/z 555.1 $[M+H]^+$.

EXAMPLE 197
Preparation of Compound 398


398

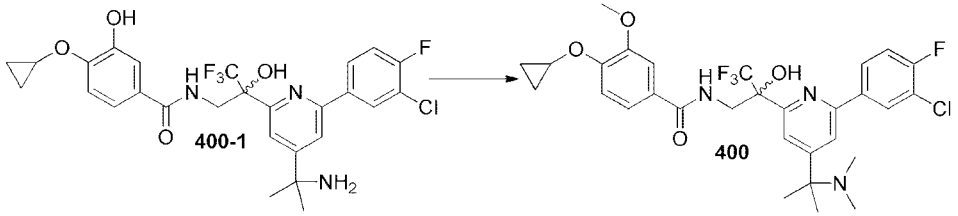
[0750] To a stirring mixture of 4-(2-amino-2-oxoethoxy)-3-methoxybenzoic acid (70 mg, 0.31 mmol) in DMF (1.5 mL) were added HATU (90 mg, 0.237 mmol) and DIPEA (84 μL, 0.474 mmol). The mixture was stirred at r.t. for 10 mins. 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl)-1-cyclopropylethan-1-ol in DMF (0.5 mL) as added. The mixture was stirred at for 10 mins, and then quenched with a 10% aq. solution of $NaHCO_3$ (10 mL). The mixture was diluted with DCM, and a normal aqueous work up with DCM was followed. The crude was purified via prep-HPLC to afford **398** as a white solid. LCMS: m/z 544.15 $[M+H]^+$.

EXAMPLE 198
Preparation of Compound 399



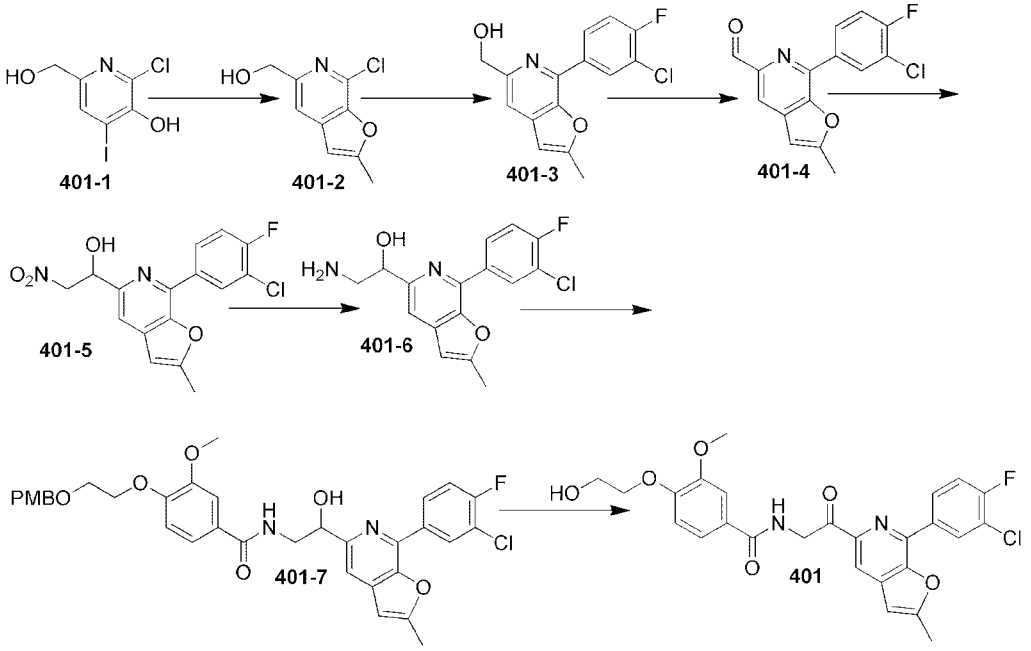
[0751] Compound **399** was prepared in a manner similar to **398**. LCMS: m/z 716.2 $[M+H]^+$.

EXAMPLE 199
Preparation of Compound 400



[0752] To a stirring mixture of **400-1** (50 mg, 0.088 mmol, obtained during the preparation of **314**) in DMF (2.0 mL) were added Cs_2CO_3 (143 mg, 0.44 mmol) and MeI (38 mg, 0.264 mmol). The mixture was stirred at r.t. until the starting material was consumed. The crude was diluted EtOAc and water. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound **400** was purified via HPLC to afford **400** as a white solid. LCMS: m/z 610.15 $[M+H]^+$.

EXAMPLE 200
Preparation of Compound 401



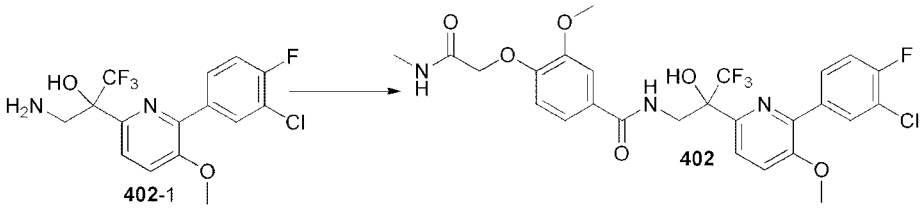
[0753] To a stirring mixture of **401-1** (460 mg, 1.6 mmol) in DMF (2.5 mL, deoxygenated) were added $PdCl_2(PPh_3)_2$ (32 mg, 0.045 mmol), CuI (26 mg, 0.136 mmol), piperidine (0.35 mL) and trimethyl(prop-2-yn-1-yl)silane (180 mg, 1.6 mmol). The mixture subjected to microwave irradiation at 60 °C for 3 h. The mixture was cooled to r.t. and diluted with EtOAc. The mixture was washed with brine, water and $NaHCO_3$. The mixture was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **401-2** as a yellow solid. LCMS: m/z 198.05 $[M+H]^+$.

[0754] To a stirring mixture of **401-2** (110 mg, 0.56 mmol) in DME (3 mL, deoxygenated) were added (3-chloro-4-fluorophenyl)boronic acid (191 mg, 1.1 mmol), $PdCl_2(dppf)_2$ and a solution of Cs_2CO_3 (0.6 mL, 3.7 M). The mixture subjected to under microwave irradition at 110 °C for 4 h. The mixture was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified via a silica gel column to afford **401-3** as a white solid. LCMS: m/z 292.0 $[M+H]^+$.

[0755] Compound **401-6** was prepared in 3 steps using methods similar to those for preparing **302**. LCMS: m/z 321.0 $[M+H]^+$. Compound 401-6 was coupled with 3-

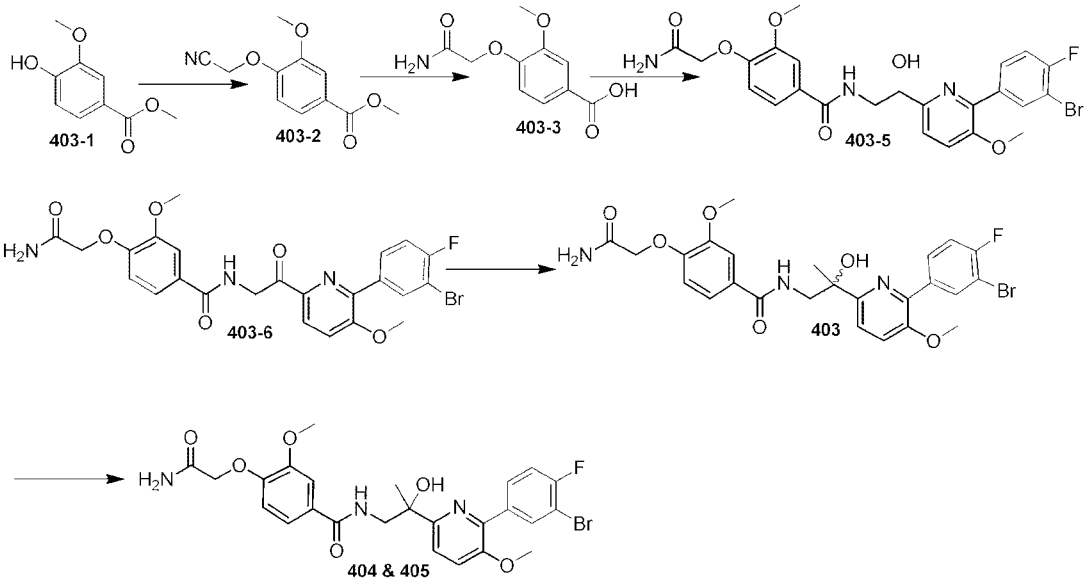
methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzoic acid followed by alcohol oxidation and deprotection to afford **401**. LCMS: m/z 513. 05 $[M+H]^+$.

EXAMPLE 201
Preparation of Compound 402



[0756] Diisopropylethylamine (24 uL, 0.14 mmol) was added to a solution of **402-1** (21 mg, 0.045 mmol), 3-methoxy-4-[(methylcarbamoyl)methoxy]benzoic acid (22 mg, 0.090 mmol) and HATU (38 mg, 0.099 mmol) in DMF (1 mL), and the mixture was stirred at r.t. for 2 h. The mixture was diluted with EA, washed with 1N HCl, water and brine, dried over Na_2SO_4 and concentrated. The crude was purified by reverse-phase HPLC to provide **402** (7.5 mg). LCMS: m/z 586.05 $[M+H]^+$.

EXAMPLE 202
Preparation of Compounds 403, 404 and 405



[0757] To a solution of **403-1** (6.0 g, 32.97 mmol) and K_2CO_3 (9.12 g, 66.1 mmol) in DMF (50 mL) was added 2-bromoacetonitrile (4.98 g, 39.52 mmol) dropwise. The mixture was stirred at 80 °C for 4 h. The mixture was diluted with water, and extracted with EA (3 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous

sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (5~10% EA:PE) to give **402-2** as a colorless oil (5.1 g, 70 %).

[0758] To a solution of **402-2** (8.0 g, 36.2 mmol) in MeOH:H_2O (2:1, 90 mL) was added NaOH (2.9 g, 72.4 mmol), and the mixture stirred at 50 ^oC for 1 h. The mixture was diluted with water and extracted with EA (2 x 50 mL). The aqueous layer was acidified to pH 4.0 using 2.0 M HCl solution. The aqueous phase was extracted with EA (2 x 150 mL). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated at low pressure to give **403-3** (5.6 g, 70%).

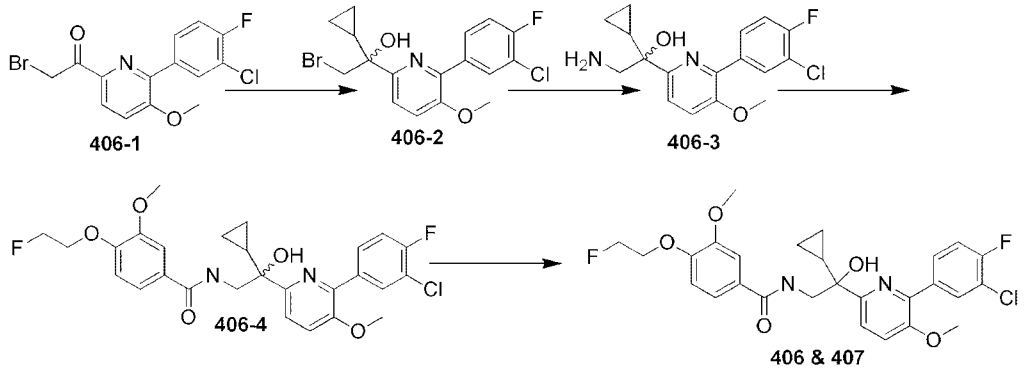
[0759] To a solution of **403-3** (530 mg, 2.35 mmol) in DMF (15 mL) were added DIPEA (590 mg, 7.04 mmol) and HATU (885 mg, 2.35 mmol), and the mixture was stirred at r.t. for 30 mins. The mixture was treated with 2-amino-1-(6-(3-bromo-4-fluorophenyl)-5-methoxypyridin-2-yl)ethanol (**403-4**, 800 mg, 2.35 mmol), and the mixture was stirred at r.t. for 2 h. The mixture was diluted with water, and extracted with EA (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA 1:1) to give **403-5** (1.0 g, 77.5%). +ESI-MS:m/z 547.9 $[M+H]^+$.

[0760] To a solution of **403-5** (600 mg, 1.10 mmol) in DCM (20 mL) was added DMP (948 mg, 2.2 mmol) in portions, and the mixture was stirred at r.t. for 1 h. The mixture was washed with sat. $Na_2S_2O_3$ solution and brine. The organic phase was dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by chromatography to give **403-6** as a white solid (400 mg, 66.7%). +ESI-MS:m/z 546.1 $[M+H]^+$.

[0761] To a solution of **403-6** (400 mg, 0.73 mmol) in THF (20 mL) was added CH_3MgBr (2.4 mL, 7.3 mmol) dropwise, and the mixture was stirred at r.t. for 30 mins. The reaction was quenched with water, and extracted with EA (3 x 30 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by prep-HPLC to give **403** (60 mg) as a white solid. +ESI-MS:m/z 562.1 $[M+H]^+$.

[0762] Compound **403** (~45 mg) was separated via SFC separation to give two isomers: **404** (10.0 mg) and **405** (12.5 mg). **404**: +ESI-MS:m/z 562.1 $[M+H]^+$. **405**: +ESI-MS:m/z 562.0 $[M+H]^+$.

EXAMPLE 203
Preparation of Compounds 406 and 407

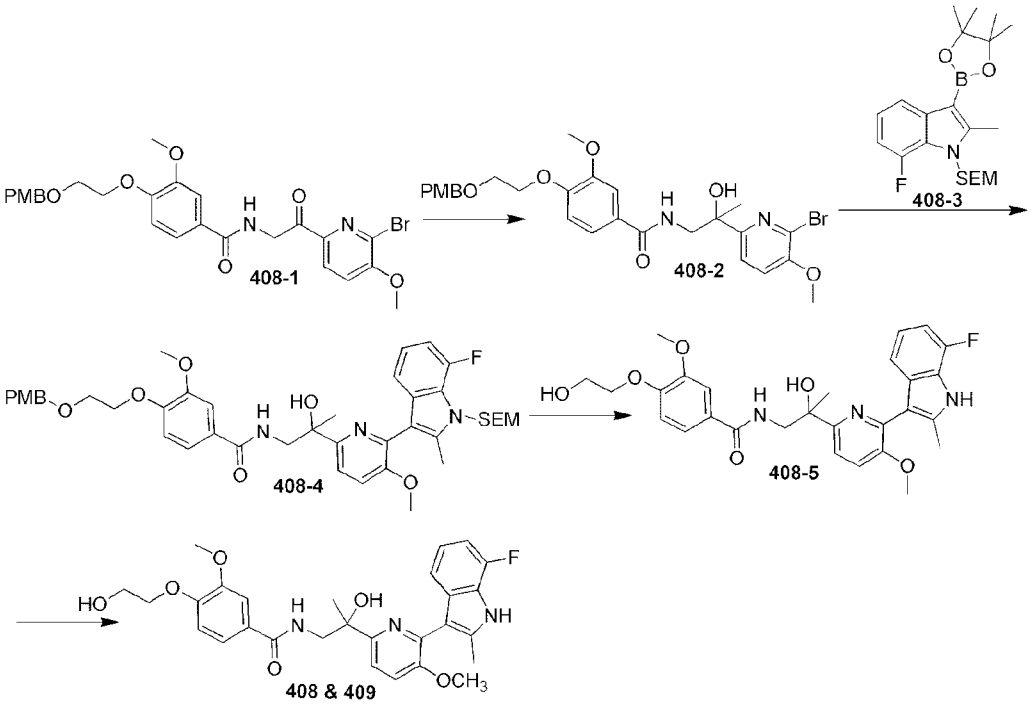


[0763] To a solution of **406-1** (540 mg, 1.53 mmol) in THF (4 mL) was added cyclopropylmagnesium bromide (4 mL, 0.5M in THF) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with water, and extracted with EA (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by chromatography (PE:EA 10:1) to give **406-2** (400 mg, 70%).

[0764] Compound **406-2** (400 mg, 1.0 mmol) was treated with concentrated ammonia water (10 mL) and ethanol (10 mL) in an autoclave. After sealing, the mixture was heated to 80 °C for 10 h with stirring. The mixture was cooled to r.t., and diluted with EA (30 mL). The mixture was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure to give **406-3**, which was used without further purification. +ESI-MS:m/z 337.1 $[M+H]^+$.

[0765] Compound **406-6** was prepared essentially as described in the preparation of **403** by using 4-(2-fluoroethoxy)-3-methoxybenzoic acid and **406-3**. The crude was purified by column chromatography (EA:PE 1:1) to give **406-4** as a white solid (201 mg, 73%). +ESI-MS:m/z 533.1 $[M+H]^+$. Compound **406-4** was separated via SFC separation to give two isomers: **406** (60 mg) and **407** (65 mg). **406**: +ESI-MS:m/z 533.1 [M+H]+. **407**: +ESI-MS:m/z 533.1 [M+H]+.

EXAMPLE 204
Preparation of Compounds 408 and 409



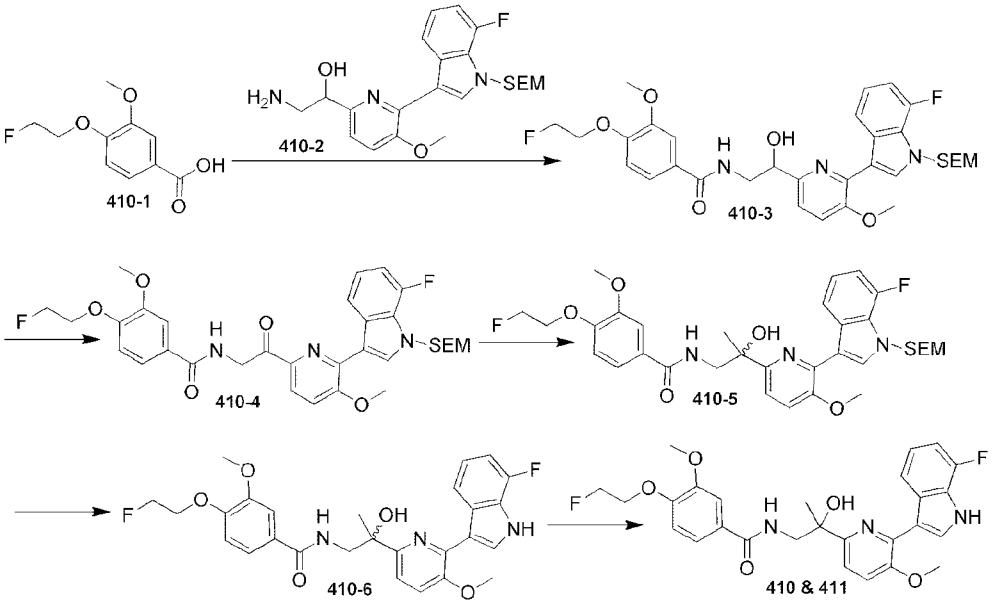
[0766] To a solution of **408-1** (560 mg, 0.2 mmol) in THF (4 mL) was added MeMgCl (1 mL, 3 M in Et_2O). The mixture was stirred at 0 °C for 1 h. The reaction was quenched with CBr_4 (5 g) in THF (10 mL). The mixture was diulted with EA (50 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silical gel to give **408-2** (402 mg, 70%). +ESI-MS:m/z 577.1 $[M+H]^+$.

[0767] Under N_2 atmosphere, a 50 mL flask with a magnetic stirring bar was charged with **208-3** (300 mg, 0.75 mmol), **408-2** (290 mg, 0.5 mmol), $Pd(dppf)Cl_2$ (8 mg, 1 mmol%), KF (180 mg, 3.0 mmol), and dioxane:H_2O (20 mL:5mL). The mixture was stirred for 10 h at 100 °C. The mixture was cooled to r.t. and diluted with water (50 mL) and EA (50 mL). The organic layer was separated, and the aqueous phase was extracted with EA (2 x 20 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA 10:1) to give **408-3** as a solid (280 mg, 70%). +ESI-MS:m/z 774.5 $[M+H]^+$.

[0768] To a solution of **408-3** (280 mg, 0.36 mmol) in dioxane (8 mL) wad added conc.HCl (2 mL). The mixture was stirred at 80 °C for 1 h. The mixture was cooled to r.t. and diluted with water (15 mL) and EA (20 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by prep-HPLC to give **408-4** (189 mg).

[0769] Compound **408-4** (189 mg) was separated via SFC separation to give two enantiomers: **408** (60 mg) and **409** (65 mg). **408**: +ESI-MS:m/z 524.1 $[M+H]^+$. **409**: +ESI-MS:m/z 524.1 $[M+H]^+$.

EXAMPLE 205
Preparation of Compounds 410 and 411

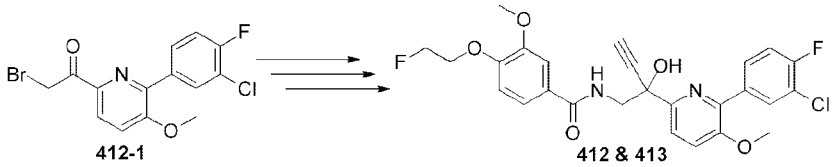


[0770] Compound **410-3** was prepared essentially as described in the preparation of **403** by using **410-1** and **410-2**. The crude was purified by column chromatography on silica gel (PE:acetone 5:1) to give **410-3** (1.8 g, 89 %). +ESI-MS:m/z 628.1 $[M+H]^+$.

[0771] Compound **410-4** was prepared essentially as described in the preparation of **403**. Crude **410-4** was obtained (0.8 g, 52.3%). +ESI-MS:m/z 626.1 $[M+H]^+$. Compound **410-5** was prepared essentially as described in the preparation of **403**. Crude **410-5** was purified by column chromatography on silica gel (PE:acetone 5:1) to give **410-5** (496 g, 51 %). +ESI-MS:m/z 642.1 $[M+H]^+$. Compound **410-5** was prepared essentially as described in the preparation of **403**. Crude **410-6** was purified by prep-HPLC to give **410-6** (302 mg, 70

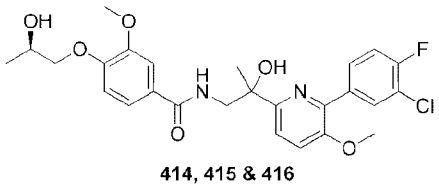
%). +ESI-MS:m/z 512.1 $[M+H]^+$. Compound **410-5** was separated via SFC separation to give **410** (30 mg) and **411** (28 mg). **410**: +ESI-MS:m/z 512.1 $[M+H]^+$. **411**: +ESI-MS:m/z 512.1 $[M+H]^+$.

EXAMPLE 206
Preparation of Compounds 412 and 413



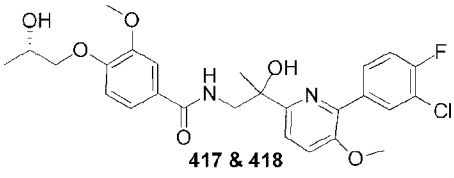
[0772] Compounds **412** and **413** were prepared essentially as described in the preparation of **403** by using **412-1** and ethynyl magnesium bromide. The product was purified by prep-HPLC and SFC separation. **412** (30 mg) and **413** (32 mg) were obtained as white solids. **412**: +ESI-MS:m/z 516.9 $[M+H]^+$. **413**: +ESI-MS:m/z 516.9 $[M+H]^+$.

EXAMPLE 207
Preparation of Compounds 414, 415 and 416



[0773] Racemic **414** was prepared essentially as described in the preparation of **403** by using **412-1** and *(R)*-4-(2-hydroxypropoxy)-3-methoxybenzoic acid. Compound **414** was obtained as a white solid (150 mg). Compound **414** was separated via SFC separation to give two enantiomers: **415** (35 mg) and **416** (38 mg). **415**: +ESI-MS:m/z 519.1 $[M+H]^+$. **416**: +ESI-MS:m/z 519.0 $[M+H]^+$.

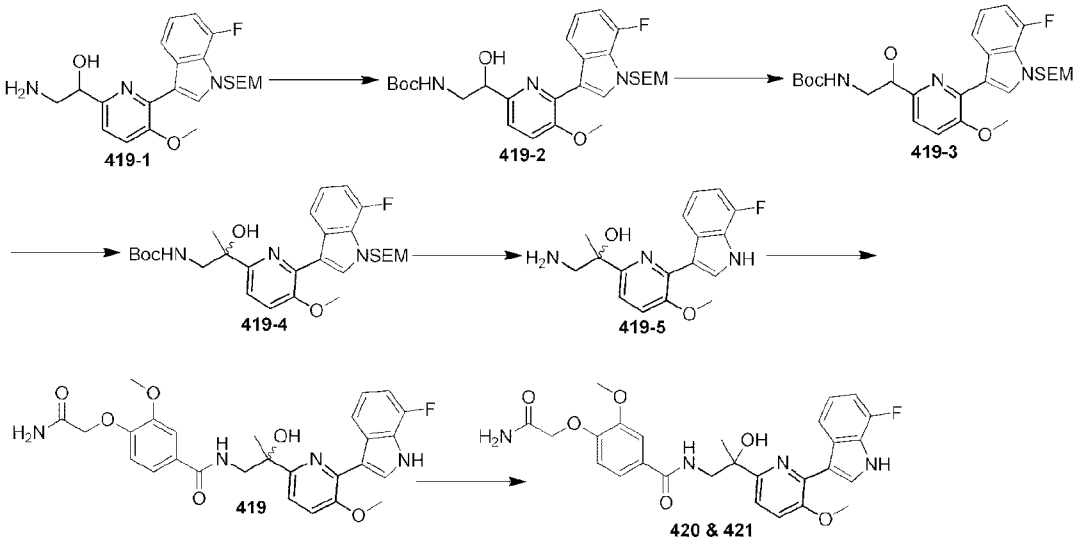
EXAMPLE 208
Preparation of Compounds 417 and 418



[0774] Compounds **417** and **418** were prepared essentially as described in the preparation of **403** by using **412-1** and *(S)*-4-(2-hydroxypropoxy)-3-methoxybenzoic acid.

Compounds **417** (36 mg) and **418** (39 mg). **417**: +ESI-MS:m/z 518.9 $[M+H]^+$. **418**: +ESI-MS:m/z 518.9 $[M+H]^+$.

EXAMPLE 209
Preparation of Compounds 419, 420 and 421



[0775] To a solution of **419-1** (1.0 g, 2.32 mmol) in dioxane:H_2O (4:1, 20 mL) was added $NaHCO_3$ (584.6 mg, 6.96 mmol) in one portion and Boc_2O (657.5 mg, 3.02 mmol) in portions. The mixture was stirred at r.t. for 2 h, and then diluted with water (50 mL) and EA (50 mL). The aqueous phase was extracted by EA (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuum. The residue was purified by column chromatography on silica gel (PE:EA 4:1) to give **419-2** (1.2 g, 97%). +ESI-MS:m/z 532.3 $[M+H]^+$.

[0776] To a solution of **419-2** (1.2 g, 2.26 mmol) in DCM (20 mL) was added DMP (1.95 g, 4.52 mmol) in portions. The mixture was stirred at r.t. for 1 h. The reaction was quenched with sat. Na_2SO_3 solution (50 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by chromatography to give **419-3** as a white solid (1.0 g, 83.3%). +ESI-MS:m/z 530.3 $[M+H]^+$.

[0777] To a solution of **419-3** (1.0 g, 1.89 mmol) in THF (15 mL) was added CH_3MgBr (6.30 mL, 18.90 mmol) dropwise at 0 °C, and the mixture was stirred at r.t. for 30 mins. The reaction was quenched with water, and extracted with EA (3 x 30 mL). The

combined organic phase was dried over anhydrous sodium sulfate and concentrated at low pressure. The crude was purified by column chromatography (PE:EA 3:1~2:1) to give **419-4** as a white solid (605 mg, 58.3%). +ESI-MS:m/z 546.2 $[M+H]^+$.

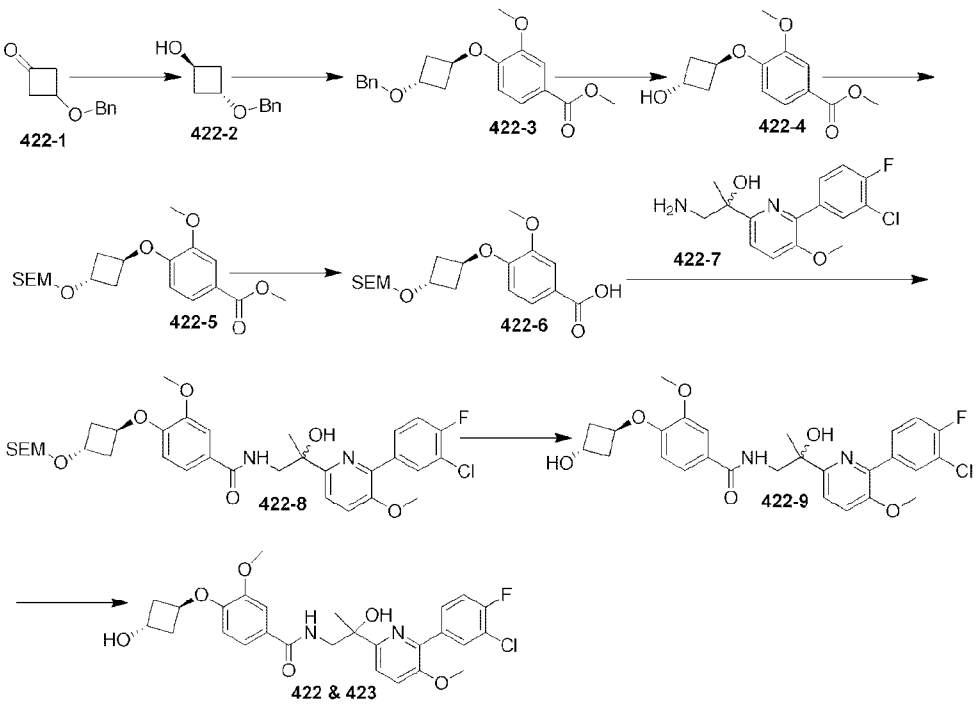
[0778] To a solution of **419-4** (600 mg, 1.1 mmol) in dioxane (16 mL) was added conc. HCl (8 mL). The mixture was stirred at 80 °C overnight. After cooled to r.t., the mixture was neutralized by sat. $NaHCO_3$ solution, and extracted with EA (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure to give **419-5** (301 mg, 87%).

[0779] Compound **419** was prepared essentially as described in the preparation of **403** by using **419-5** and 4-(2-amino-2-oxoethoxy)-3-methoxybenzoic acid. Compound **491** was obtained as a white solid (90 mg). +ESI-MS:m/z 523.1 $[M+H]^+$.

[0780] Compound **419** (90 mg, 0.172 mmol) was separated via SFC separation to give two enantiomers: **420** (15.0 mg) and **421** (22.0 mg). **420**: +ESI-MS:m/z 523.1 $[M+H]^+$. **421**: +ESI-MS:m/z 523.1 $[M+H]^+$.

EXAMPLE 210

Preparation of Compounds 422 and 423



[0781] To a solution of **422-1** (100 mg, 0.575 mmol) in THF (10 mL) was $NaBH_4$ (44 mg, 1.1 mmol) was added, and the mixture was stirred at r.t. for 30 mins. The reaction was quenched by water, and extracted with EA (3 x 20 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The crude was purified by chromatography (PE:EA 20:1 to 5:1) to afford **422-2** (90 mg, 89.1 %).

[0782] To a solution of **422-2** (534 mg, 3.0 mmol), methyl 4-hydroxy-3-methoxybenzoate (546 mg, 3.0 mmol) and PPh_3 (786 mg, 3.0 mmol) in THF (15 mL) at 0 °C was added DIAD (606 mg, 3.0 mmol) dropwise. The mixture was stirred at r.t. for 2 h. The reaction was quenched with sat. $NaHCO_3$ solution. The mixture was extracted with DCM (3 x 20 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by flash column chromatography on silica gel to give **422-3** (667 mg, 66%).

[0783] A solution of **422-3** (2.0 g, 5.85 mmol) and $Pd(OH)_2$ (0.2 g) in MeOH (20 mL) was stirred under H_2 atmosphere (50 psi) at r.t. overnight. The mixture was filtered, and the filtrate was evaporated to give crude **422-4** (1.5 g), which was used without further purification.

[0784] To a solution of **422-4** (150 mg, 0.597 mmol) in THF (10 mL) at 0 ^oC was added NaH (47.8 mg, 1.195 mmol), and the mixture was stirred at 0 ^oC for 0.5 h. The mixture was treated with SEMCl (149 mg, 0.896 mmol), and the mixture was allowed to warm to r.t. over 30 mins. The reaction was quenched with water, and extracted with EA (2 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA 20:1) to give **422-5** (110 mg, 48.2 %).

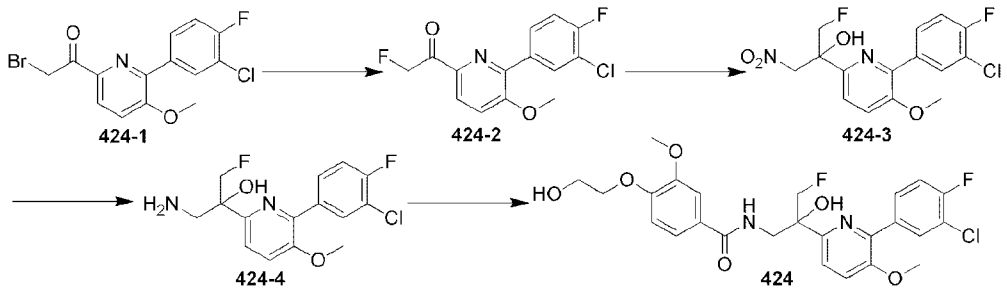
[0785] To a solution of **422-5** (600 mg, 1.57 mmol) in co-solvent THF:H_2O (1:1, 10 mL) was added NaOH (126 mg, 3.14 mmol in 2 mL water). The mixture was stirred at r.t. for 1 h. The organic solvent was evaporated under reduced pressure, and the aqueous layer was acidified to pH 4~5 with 1M HCl solution. The mixture was extracted with EA (2 x 20 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated at low pressure to give **422-6** (480 mg, 83.0 %).

[0786] Compound **422-8** was prepared essentially as described in the preparation of **403** by using **422-6** and **422-7**. Compound **422-8** was obtained as a white solid (180 mg, 66.9 %). +ESI-MS:m/z 661.0 $[M+H]^+$.

[0787] A suspension of **422-8** (180 mg, 0.273 mmol) in HCl:dioxane (4M, 15 mL) was stirred at r.t. for 30 mins. The mixture was concentrated under reduced pressure to give crude **422-9**. The residue was diluted with sat. $NaHCO_3$ (10 mL), and extracted with EA (2 x 10 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA 5:1 to 1:1) to give **422-9** (90 mg, 62.3 %).

[0788] Compound **422-9** (90 mg) was separated by SFC separation to give two enantiomers: **422** (25 mg) and **423** (27 mg). **422**: +ESI-MS:m/z 531.0 $[M+H]^+$. **423**: +ESI-MS:m/z 531.0 $[M+H]^+$.

EXAMPLE 211
Preparation of Compound 424



[0789] To a solution of **424-1** (1.05 g, 3.0 mmol) and 18-crowm-6 (800 mg, 3.1 mmol) in CH_3CN (50 mL) was added CsF (900 mg, 6.0 mmol). The mixture was heated to reflux for 1 h and the concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 10:1) to provide **424-2** as a white solid (360 mg, 40 %).

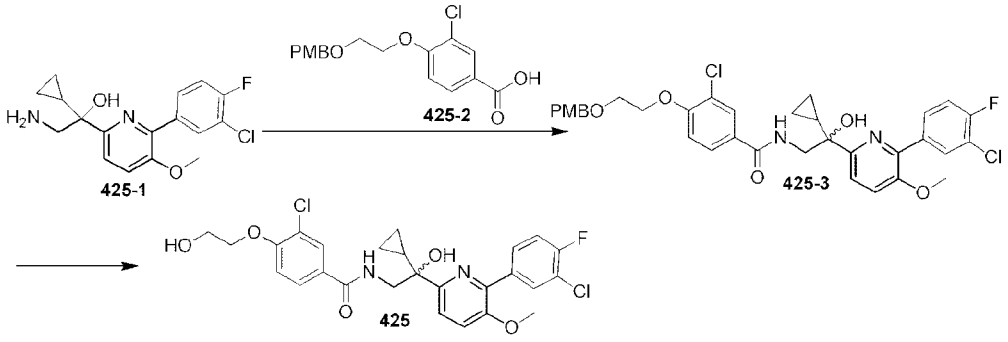
[0790] A 50 mL round bottom flask with a magnetic stirring bar was charged with **424-2** (360 mg, 1.2 mmol), $MeNO_2$ (5 mL) and Et_3N (303 mg, 3.0 mmol). The mixture was stirred at r.t. for 10 h and then concentrated under reduced pressure. The residue was purified by column chromatography (PE:DCM 2:1) to give **424-3** (270 mg, 63%).

[0791] To a stirred mixture of **424-3** (271 mg, 0.75 mmol) and $NiCl_2$ (127 mg, 1 mmol) in MeOH (10 mL) was added $NaBH_4$ (380 mg, 1.0 mmol) in portions until the starting materials was consumed. The mixture was concentrated under reduced pressure, and the

residue was purified by column chromatography (EA:EtOH 10:1) to give **424-4** as a colorless oil (130 mg, 50%). +ESI-MS:m/z 328.8 $[M+H]^+$.

[0792] Compound **424** was prepared essentially as described in the preparation of **403** by using the **424-4** and 4-(2-hydroxyethoxy)-3-methoxybenzoic acid. The product was purified by prep-HPLC. Compound **424** was obtained as a white solid (180 mg, 66.9 %). +ESI-MS:m/z 523.2 $[M+H]^+$.

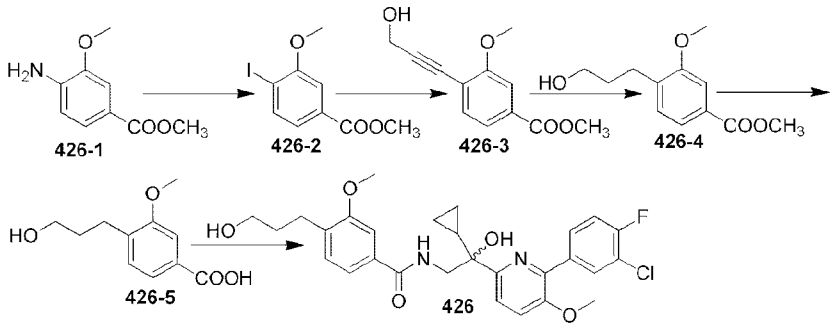
EXAMPLE 212
Preparation of Compound 425



[0793] Compound **425-3** was prepared essentially as described in the preparation of **403** by using **425-1** and **425-2**. The crude was purified by column chromatography (PE:EA 1:1) to give **425-3** (190 mg). +ESI-MS:m/z 654.9 $[M+H]^+$.

[0794] To a solution of **425-3** (190 mg, 0.29 mmol) in dioxane (15 mL) was added conc. HCl (5.0 mL). The mixture was stirred at r.t. for 1 h, neutralized with sat. $NaHCO_3$ solution and extracted with EA (3 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, and concentrated at low pressure. The residue was purified by prep-HPLC to give **425** (21 mg, 13.5%) as a white solid. +ESI-MS:m/z 534.9 $[M+H]^+$.

EXAMPLE 213
Preparation of Compound 426



[0795] To a stirred solution of **426-1** (16.2 g, 90mmol) in HCl (6 *N*, 300 mL) at 0 °C was added a solution of $NaNO_2$ (6.90 g, 99 mmol) in water (15 mL) dropwise. The mixture was stirred at 0 °C for 1 h and then treated with a solution of KI (75 g, 450 mmol) in water (150 mL). The mixture was stirred for 30 mins and then extracted with EA (4 x 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography (PE:EA 10:1) to give **426-2** (21.2 g, 80.5%) as a light yellow solid.

[0796] To a suspension of **426-2** (8.77 g, 30 mmol), CuI (1.14 g, 6 mmol), $PdCl_2(PPh_3)_2$ (1.05 g, 1.5 mmol) and NEt_3(21 mL, 150 mmol) in THF(150 mL) was added propiolic alcohol (3.36 g, 60 mmol) under N_2 atmosphere. The mixture was stirred at r.t. overnight and then filtered through a celite pad. The filtrate was concentrated to dryness and the residue was diluted with EA (200 mL). The solution was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA 1:1) to give **426-3** (5.1 g, 77.3%) as a light yellow solid.

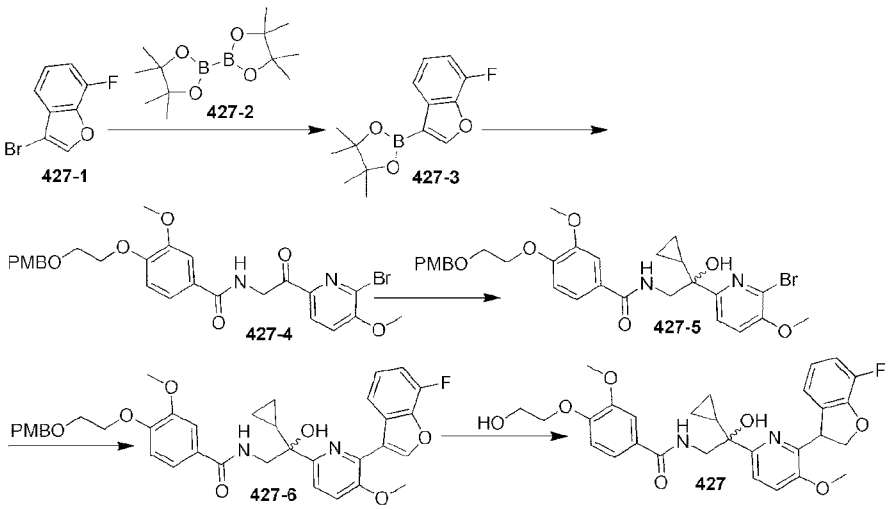
[0797] To a solution of **426-3** (2.2 g, 10 mmol) in MeOH (100 mL) was added Pd/C (0.5 g) under N_2. The mixture was degassed and refilled with hydrogen (3x). The mixture was stirred under H_2 atmosphere (40 psi) overnight. The mixture was filtered through a celite pad and the filtrate was concentrated in vacuum to give crude **426-4**. The residue was purified by column chromatography on silica gel (PE:EA 1:1) to give **426-4** (1.62 g, 72.3%) as a light yellow oil.

[0798] To a solution of **426-4** (0.67 g, 3 mmol) in EtOH (7.5 mL) and water (2.5 mL) was added NaOH (0.48 g, 12 mmol). The mixture was stirred at 50 °C for 1 h, cooled to 0 °C, and acidified to pH 5 with HCl (2 M) solution. The mixture was extracted with EA (4 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuum to give **426-5** (0.50 g, 80.0%) as a yellow solid, which was used without further purification.

[0799] Compound **426** was prepared essentially as described in the preparation of **403** by using **426-5** and 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl)-1-

cyclopropylethanol. The crude was purified by prep-HPLC to give **426** (35 mg, 13.3%) as a white solid. +ESI-MS:m/z 529.0 $[M+H]^+$.

EXAMPLE 214
Preparation of Compound 427



[0800] To a suspension of **427-1** (1.0 g, 4.67 mmol) in dioxane (30 mL) were added **427-2** (2.37 g, 9.346 mmol), AcOK (1.37 g, 14.0 mmol) and $Pd(dppf)Cl_2$ (0.346 g, 0.467 mmol). The mixture was stirred at 80 °C under N_2 atmosphere for 16 h. The mixture was cooled to r.t., poured into water (100 mL), and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography (PE:EA 50:1) to give **427-3** (1.4 g, contain 0.3-0.4 g of **427-2**).

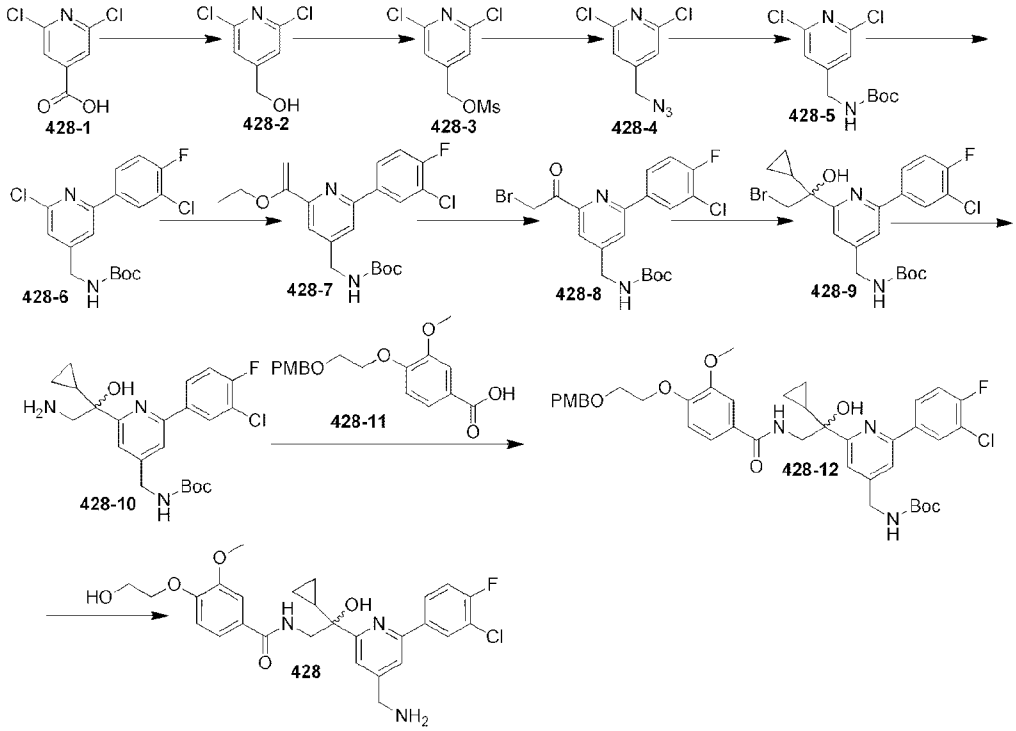
[0801] To a solution of **427-4** (310 mg, 0.554 mmol) in THF (10 mL) at 0 °C was added cyclopropyl-magnesium bromide (11 mL, 0.5 M in THF) dropwise. The mixture was stirred for 1 h and then warmed to r.t. The reaction was quenched with sat. NH_4Cl (10 mL) solution, and extracted with EA (2 x 20 mL). The combined organic phase was washed with sat. $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography on silica gel (30% EA in PE) to give **427-5** (170 mg, 51.0 %). +ESI-MS:m/z 601.1 $[M+H]^+$.

[0802] To a suspension of **427-5** (120 mg, 0.2 mmol) in a mixture of dioxane and H_2O (9:1, 10 mL) were added Cs_2CO_3 (195.6 mg, 0.6 mmol), **427-3** (108.6 mg, 0.3 mmol) and $Pd(dppf)Cl_2$ (16.3 mg, 0.02 mmol) under N_2 atmosphere. The mixture was stirred at 70

°C for 2 h. The mixture was cooled to r.t., poured into water (50 mL) and extracted with EA (2 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (10~30% EA in PE) to give **427-6** (121 mg, 92.2 %). +ESI-MS:m/z 657.1 $[M+H]^+$.

[0803] A suspension of **427-6** (121 mg, 0.184 mmol) and Pd/C (20 mg) in MeOH (20 mL) was stirred under H_2 atmosphere (balloon) at r.t. overnight. The solution was filtered, and the filtrate was concentrated in vacuum. The residue was purified by prep-HPLC to give **427** (17 mg, 10.1%) as a white solid. +ESI-MS:m/z 539.1 $[M+H]^+$.

EXAMPLE 215
Preparation of Compound 428



[0804] Compound **428-2** was prepared as provided in Mello et al., *J. Am. Chem. Soc.* (2005) 127(29):10124-10125, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **428-2**. Compound **428-3** was prepared as provided in PCT Publication No. WO 2002/034745, published May 2, 2002, which is hereby

incorporated by reference for the limited purpose of its description of the preparation of **428-3**.

[0805] To a solution of **428-3** (8 g, 38 mmol) in DMF (100 mL) were added K_2CO_3 (9.5 g, 69 mmol) and NaN_3 (3 g, 46 mmol) at r.t. The solution was stirred for 2 h, poured into H_2O (100 mL) and extracted with EA (3 x 100 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography (PE:EA 10:1) to give **428-4** (5.1 g, 66.1%).

[0806] To a solution of **428-4** (5 g, 23.4 mmol) in EtOH (50 mL) were added Boc_2O (6.11 g, 28 mmol) and Pd/C (1 g) at r.t. under N_2. The solution was degassed and refilled with H_2 (3x). The mixture was stirred at r.t. under H_2 atmosphere (balloon) for 18 h. The solution was filtered, and the filtrate was concentrated to dryness. The residue was purified by chromatography on silica gel (PE:EA 10:1) to give **428-5** (2.2 g, 34.4%).

[0807] To a solution of **428-5** (2.2 g, 7.9 mmol) and (3-chloro-4-fluorophenyl)boronic acid (1.39 g, 7.9 mmol) in a mixture of dioxane and H_2O (20 mL/5 mL) were added $Pd(dppf)Cl_2$ (289 g,0.395 mmol) and K_2CO_3 (1.63 g, 11.85 mmol). The mixture was degassed and refilled with N_2 (3x). The mixture was stirred under N_2 at 40 °C for 3 h. The mixture was cooled to r.t., and diluted with EA (100 mL) and water (100 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE:EA 10:1) to give **428-6** (2.923 g, 100%) as a white solid. +ESI-MS:m/z 370.8 $[M+H]^+$.

[0808] To a solution of **428-6** (1.2 g, 3.24 mmol), tributyl(1-ethoxyvinyl)stannane (2.34 g, 6.48 mmol) and KF (751 mg, 12.96 mmol) in DMF (15 mL) was added $Pd(dppf)Cl_2$ (237 mg, 0.324 mmol) under N_2. The mixture was stirred at 80 °C for 2 h. After cooling to r.t., the mixture was diluted with EA (100 mL) and water (50 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure to give crude **428-7** (1.35 g crude), which was used in the next step directly. +ESI-MS:m/z 407.1 $[M+H]^+$.

[0809] Compound **428-7** (1.315 g, 3.24 mmol) was dissolved in THF (20 mL) and H_2O (2 mL). The solution was treated with NBS (1.13 g, 6.4 mmol) at r.t., and stirred for

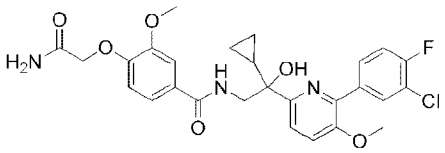
20 mins. The mixture was concentrated at low pressure, and the residue was purified by column chromatography on silica gel (PE:EA 10:1) to give **428-8** (1.4 g, 94.5%). +ESI-MS:m/z 459.1 $[M+H]^+$.

[0810] Compound **428-9** was prepared essentially as described in the preparation of **406** by using **428-8**. Crude **428-9** (410 mg, 63%) was used directly in the next step. Compound **428-10** was prepared essentially as described in the preparation of **406** by using crude **428-9**. Crude **428-10** (205 mg, 57.6%) was used directly in the next step. +ESI-MS:m/z 436.3 $[M+H]^+$. Compound **428-11** was prepared essentially as described in the preparation of **406** by using crude **428-10** and 3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzoic acid. Crude **428-11** was purified by column chromatography on silica gel (50% EA in PE) to give purified **428-11** (106 mg, 30.1%).

[0811] To a solution of **428-11** (100 mg, 0.13 mmol) in dioxane (2 mL) was added conc. HCl (2 mL) at r.t., and the mixture was stirred for 30 mins. The mixture was neutralized using a sat. Na_2CO_3 solution, and extracted with EA (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by prep-HPLC to give **428** (15 mg, 21.2%) as a white solid. +ESI-MS:m/z 530.0 $[M+H]^+$.

EXAMPLE 216

Preparation of Compounds 429, 430 and 431

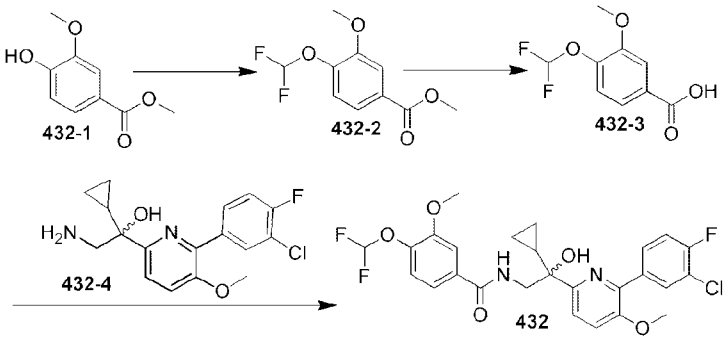


429, 430 & 431

[0812] Compound **429** was prepared essentially as described in the preparation of **403** by using **403-3** and **406-3**. Compound **429** was obtained as a white solid (50 mg). +ESI-MS:m/z 544.1 $[M+H]^+$.

[0813] Compound **429** was separated via SFC separation to give two enantiomers: **430** (3.22 mg, 12.9%) and **431** (3.45 mg, 13.8%). **430**: +ESI-MS:m/z 544.1 $[M+H]^+$. **431**: +ESI-MS:m/z 544.1 $[M+H]^+$.

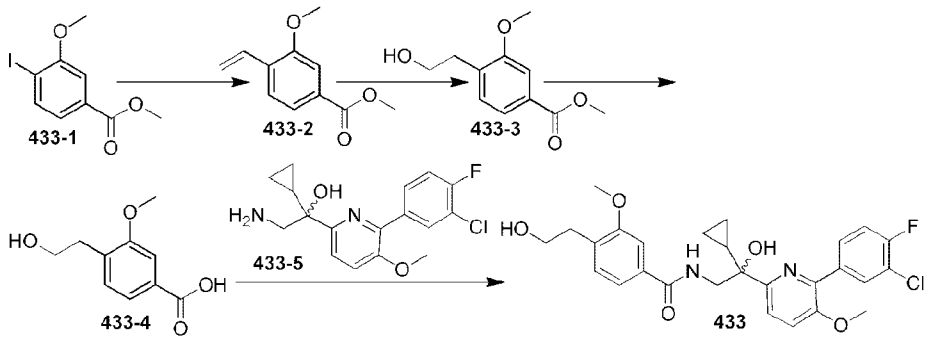
EXAMPLE 217
Preparation of Compound 432



[0814] To a solution of **432-1** (2.0 g, 10.99 mmol) in DMF (20 mL) were added $ClCF_2COONa$ (3.0 g, 19.74 mmol) and K_2CO_3 (4.4 g, 31.88 mmol). The mixture was stirred at 95 °C for 5 h. After cooling to r.t., the mixture was poured into water (100 mL) and extracted with EA (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (5~20% EA in PE) to give **432-2** (1.3 g, 51.0%).

[0815] Compound **432-3** was prepared essentially as described in the preparation of **426** using **432-2**. Compound **432-3** was obtained as a white solid (1.19 g, 97.5%). Compound **432** was prepared essentially as described in the preparation of **406** by using **432-3** and **432-4**. Compound **432** was obtained after purification by prep-HPLC as a white solid (70 mg, 21.7%). +ESI-MS:m/z 537.1 $[M+H]^+$.

EXAMPLE 218
Preparation of Compound 433



[0816] To a solution of **433-1** (2 g, 6.8 mmol), potassium trifluoro(vinyl)borate (0.917 mg, 6.8 mmol) and Et_3N (1.73 g, 17.12 mmol) in MeOH (30 mL) was added $Pd(dppf)Cl_2$ (497 mg, 0.68 mmol) under N_2. The mixture was stirred under N_2 at 70 °C for

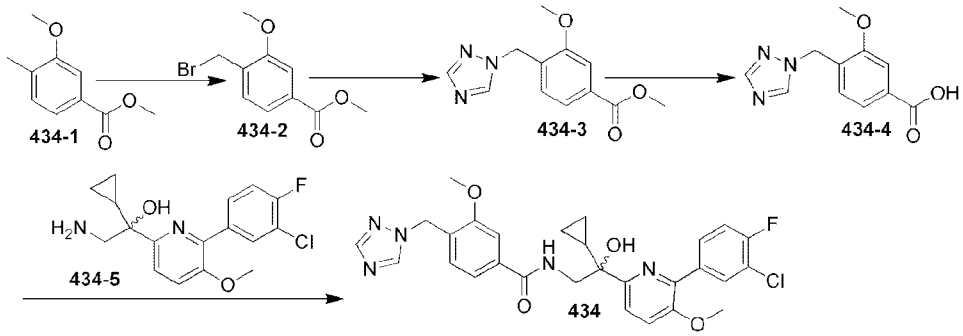
15 h. The solution was cooled to r.t., and diluted with EA (100 mL) and water (50 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography on silica gel (3% EA in PE) to give **433-2** as a colorless oil (1.1 g, 84.6%).

[0817] To a solution of **433-2** (730 mg, 3.84 mmol) in THF (15 mL) was added BH_3 • THF (4 mL, 1 M) at 0 °C, and the reaction was stirred at 0 °C for 1 h. The solution was treated with NaOH (10 mL, 1 M in water) and H_2O_2 (3 mL) at 0 °C. The mixture was stirred at r.t. for 1 h, and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography (PE:EA 5:1) to give **433-3** (320 mg, 40.4%).

[0818] Compound **433-4** was prepared essentially as described in the preparation of **426** using **433-3**. Compound **433-4** obtained as a white solid (210 mg, 70.7%). Compound **433** was prepared essentially as described in the preparation of **406** by using **433-4** and **433-5**. Compound **433** was obtained after purification by prep-HPLC as a white solid (32 mg, 8.2%). +ESI-MS:m/z 515.0 $[M+H]^+$.

EXAMPLE 219

Preparation of Compound 434



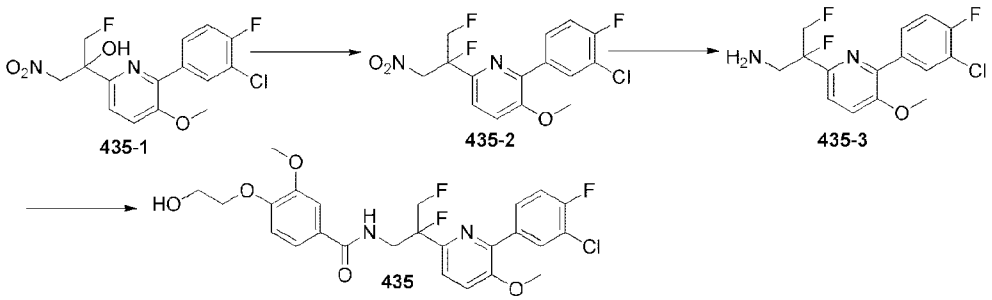
[0819] Compound **434-2** was prepared as described in PCT Publication No. WO 2009/055077, published on April 30, 2009, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **434-2**.

[0820] To a suspension of 1, 2, 4-triazole (0.52 g, 7.51 mmol), and K_2CO_3 (2.57 g, 20.49 mmol) in DMF (15 mL) was added **434-2** (1.77 g, 6.83 mmol) at 0 °C, and stirred at r.t. overnight. The mixture was poured into water (100 mL), and extracted by EA (4 x 100

mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated at low pressure. The residue was purified by column chromatography

[0821] Compound **434-4** was prepared essentially as described in the preparation of **426** by using **434-3**. Compound **434-4** was obtained as a white solid (0.4 g, 57.2%). Compound **434** was prepared essentially as described in the preparation of **406** by using **434-4** and **434-5**. Compound **434** was obtained after purification by prep-HPLC as a white solid (135 mg, 27.2%). +ESI-MS:m/z 552.1 $[M+H]^+$.

EXAMPLE 220
Preparation of Compound 435



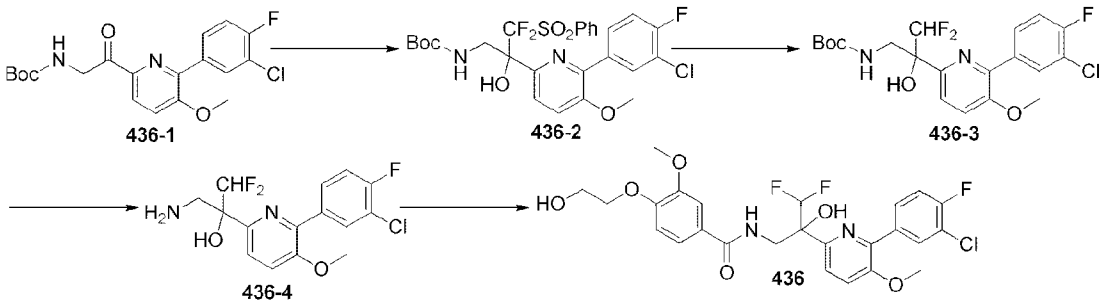
[0822] To a solution of **435-1** (270 mg, 0.75 mmol) in DCM (10 mL) was added BAST (220 mg, 1.0 mmol) at r.t. The mixture was stirred at r.t. for 1 h. The reaction was quenched with sat. $NaHCO_3$ solution (20 mL), extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Crude **435-2** (271 mg, 99 %) was used without further purification.

[0823] To a solution of **435-2** (271 mg, 0.75 mmol) and $NiCl_2$ (127 mg, 1 mmol) in MeOH (10 mL) was added $NaBH_4$ (380 mg, 1.0 mmol) in portions until the starting materials was consumed. The reaction was quenched by water (10 mL), and extracted with EA (3 x 30 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10% EtOH in EA) to give **435-3** as a colorless oil (130 mg, 50%). +ESI-MS:m/z 331.1 $[M+H]^+$.

[0824] Compound **435** was prepared essentially as described in the preparation of **406** by using **435-4** and **435-5**. Compound **435** was obtained after purification by prep-HPLC as a white solid (85 mg, 47%). +ESI-MS:m/z 525.2 $[M+H]^+$.

EXAMPLE 221

Preparation of Compound 436



[0825] To a stirred solution of **436-1** (800 mg, 2.02 mmol) and $PhSO_2CHF_2$ (465 mg, 2.42 mmol) in THF (10 mL) was added LDA (2 mL, 4 mmol) dropwise at -78 °C under N_2 atmosphere. The mixture was stirred at -78 °C for 2 h, and warmed to 0 °C for 30 mins. The reaction was quenched with sat. NH_4Cl solution, and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 3:1) to give **436-2** (610 mg, 51.6%). +ESI-MS:m/z 587.1 $[M+H]^+$.

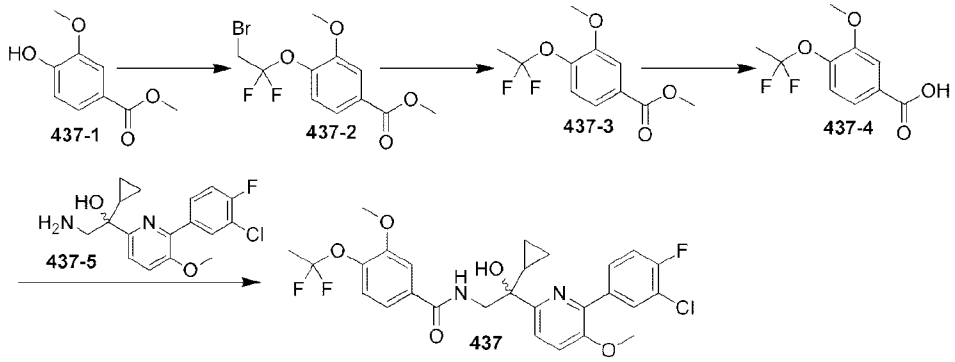
[0826] To a solution of **436-2** (610 mg, 1.04 mmol) in DMF (5 mL) were added HOAc (1 mL) and H_2O (1 mL) at r.t. The mixture was treated with magnesium (250 mg, 10.4 mmol) in portions. After stirring at r.t. for 6 h, the mixture was poured into ice-water (50 mL) and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give **436-3** (320 mg, 68.9 %). +ESI-MS:m/z 446.9 $[M+H]^+$.

[0827] To a solution of **436-3** (320 mg, 0.72 mmol) in EA (3 mL) was added HCl/EA (3 mL, 4M). The solution was stirred at r.t. for 30 mins, and then concentrated to dryness. Crude **436-4** (220 mg, 90.9%) was used without purification.

[0828] Compound **436** was prepared essentially as described in the preparation of **406** by using **436-4** and 4-(2-hydroxyethoxy)-3-methoxybenzoic acid. Compound **436** was

obtained after purification by prep-HPLC as white solid (40 mg, 11.7%). +ESI-MS:m/z 541.0 $[M+H]^+$.

EXAMPLE 222
Preparation of Compound 437

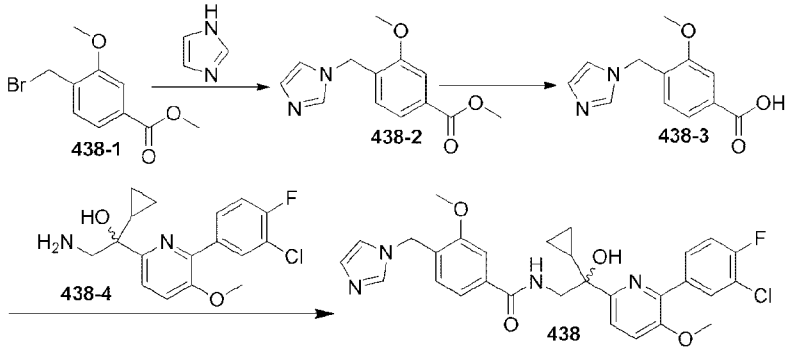


[0829] To a solution of **437-1** (1.0 g, 5.5 mmol) and K_2CO_3 (1.0 g, 7.3 mmol) in a mixture of CH_3CN (10 mL) and H_2O (2 mL) was added 2-bromo-1,1-difluoroethene (10.0 mL, ~2 M in acetonitrile) at 0 °C. The mixture was stirred at 50 °C for 10 h. After cooling to r.t, the mixture was poured into water (50 mL) and extracted with EA (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 10:1) to give **437-2** as an oil (0.4 g crude).

[0830] To a solution of **437-2** (0.4 g, 1.2 mmol) in MeOH (20 mL) was added Pd/C (0.3 g) under N_2. The suspension was degassed and refilled with H_2 (3x). The mixture was stirred under H_2 (50 psi) at r.t. for 5 h. The suspension was filtered through a Celite pad, and the filtrate was concentrated to dryness. The residue was purified by column chromatography (PE:EA 9:1) to give **437-3** as a white solid (250 mg, 84.7%).

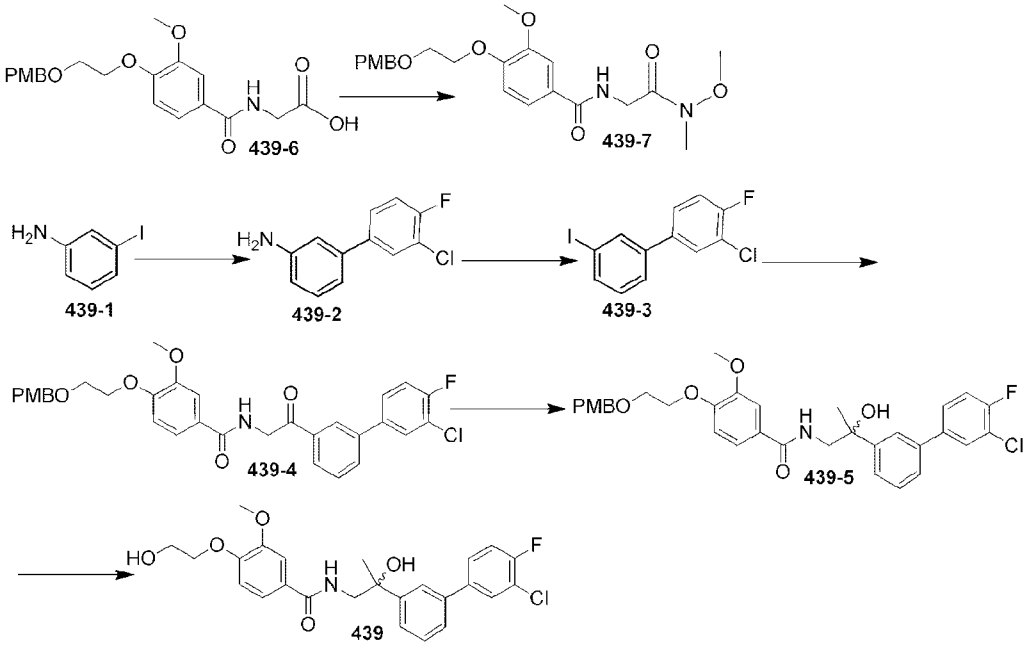
[0831] Compound **437-4** was prepared essentially as described in the preparation of **426** by using **437-3**. Compound **437-4** was obtained as a white solid (201 mg, 85.1%). Compound **437** was prepared essentially as described in the preparation of **406** by using **437-4** and **437-5**. Compound **437** was obtained after purification by prep-HPLC as white solid (50 mg, 36.4%). +ESI-MS:m/z 551.2 $[M+H]^+$.

EXAMPLE 223
Preparation of Compound 438



[0832] Compound **438-1** was prepared in a similar manner as **434**. Compound **438-4** was prepared in a similar manner as **406**. Compound **438** was prepared essentially as described in the preparation of **434** by using **438-3** and **438-4**. Compound **438** was obtained after purification by prep-HPLC as white solid (230 mg, 23%). +ESI-MS:m/z 551.0 $[M+H]^+$.

EXAMPLE 224
Preparation of Compound 439



[0833] To a solution of **439-6** (2.334 g, 6 mmol) in DMF (20 mL) were added N,O-dimethyl-hydroxylamine hydrochloride (873 mg, 9 mmol), DIPEA (2.322 g, 18 mmol) and HATU (3.42 g, 9 mmol), and the mixture was stirred at r.t. for 1 h. The mixture was

poured into water (50 mL), and extracted with EA (3 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (20~50% EA in PE) to give **439-7** (2.4 g, 92.7 %). +ESI-MS:m/z 433.1 $[M+H]^+$.

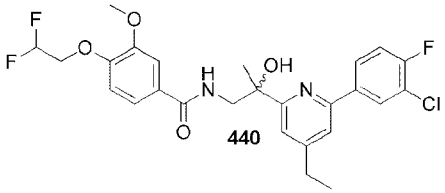
[0834] Compound **439-2** was prepared essentially as described in the preparation of **428** by using **439-1** and 3-chloro-4-fluorophenylboronic acid. Compound **439-2** was obtained as a white solid (0.61 g, 69.0 %). Compound **439-3** was prepared essentially as described in the preparation of **426** by using **439-2**. Compound **439-3** was obtained as a white solid (0.97 g, 58.8%).

[0835] To a solution of **439-3** (1.6 g, 4.8 mmol) and **439-7** (2.1 g, 4.8 mmol) in anhydrous THF (20 mL) was added isopropyl-magnesium chloride (18.5 mL, 24.1 mmol) dropwise at 0 °C, and the mixture was stirred at r.t. for 1 h. The mixture was quenched with water, and extracted with EA (2 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (10~50% EA in PE) to give **439-4** (1.2 g, 64 %). +ESI-MS:m/z 578.0 $[M+H]^+$.

[0836] Compound **439-5** was prepared essentially as described in the preparation of **403** by using **439-4**. Compound **439-5** was obtained as a white solid (160 mg, 27.0 %). +ESI-MS:m/z 594.0 [M+H]+. Compound **439** was prepared essentially as described in the preparation of **425** by using **439-5**. Compound **439** was obtained as a white solid (101 mg, 79.2 %). +ESI-MS:m/z 473.8 $[M+H]^+$.

EXAMPLE 225

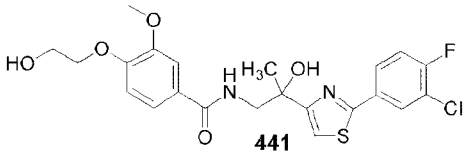
Preparation of Compound 440



440

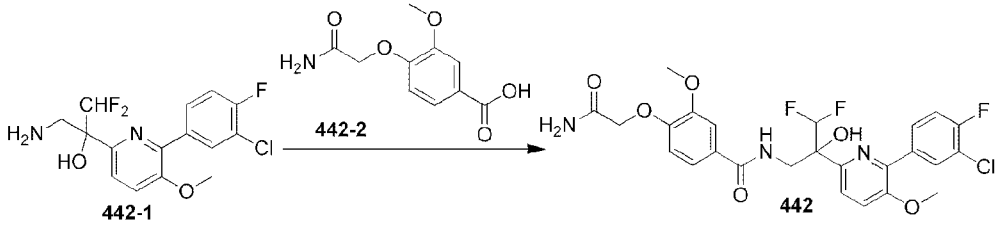
[0837] Compound **440** was prepared essentially as described in the preparation of **406** by using 2-bromo-1-(6-(3-chloro-4-fluorophenyl)-4-ethylpyridin-2-yl)ethanone. Compound **440** was obtained as a white solid (197 mg, 73%). +ESI-MS:m/z 523.1 $[M+H]^+$.

EXAMPLE 226
Preparation of Compound 441



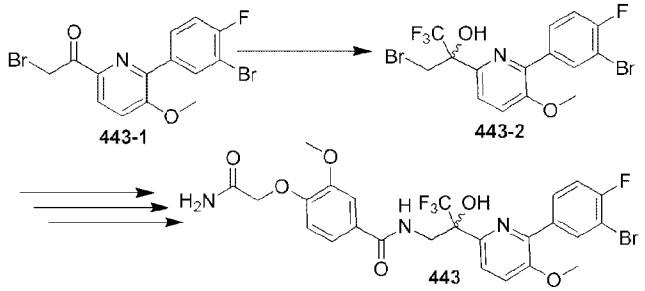
[0838] Compound **441** was prepared essentially as described in the preparation of **428** by using 2,4-dibromothiazole. Compound **441** was obtained as a white solid (60 mg, 35.7 %). +ESI-MS:m/z 480.8 $[M+H]^+$.

EXAMPLE 227
Preparation of Compound 442



[0839] Compound **442-1** was prepared as essentially described in the preparation of **436**. Compound **442-2** was prepared as essentially described in the preparation of **403**. Compound **442** was prepared essentially as described in the preparation of **406** by using **442-1** and **442-2**. Crude **442** was purified by prep-HPLC to give **442** as a white solid (65 mg, 13.3%). +ESI-MS:m/z 554.1 $[M+H]^+$.

EXAMPLE 228
Preparation of Compound 443

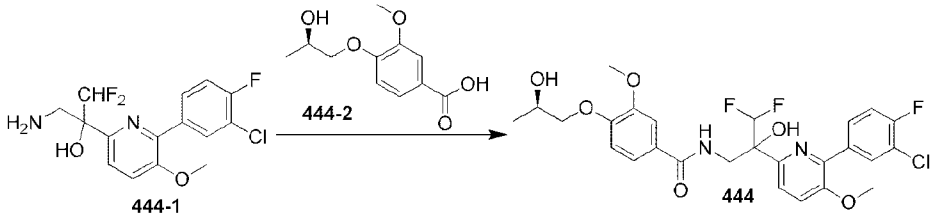


[0840] To a solution of **443-1** (511 mg, 1.27 mmol) in anhydrous DMF (5 mL) were added TMS-CF_3 (217 mg, 1.53 mmol) and LiOAc (8.4 mg, 0.127 mmol) at r.t., and the mixture was stirred for 24 h. The mixture was treated with HCl (1.5 mL, 1 M) solution, and

stirred at r.t. for 1 h. The mixture was diluted with water (20 mL), and extracted with EA (2 x 40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE:EA 5:1) to give **443-2** (131 mg, 21.8%).

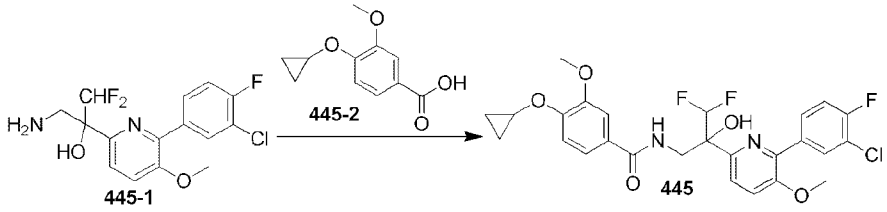
[0841] Compound **443** was prepared essentially as described in the preparation of **428** by using **443-2** and **442-2**. Compound **443** was obtained as a white solid (92 mg, 53.2%). +ESI-MS:m/z 616.0 $[M+H]^+$.

EXAMPLE 229
Preparation of Compound 444



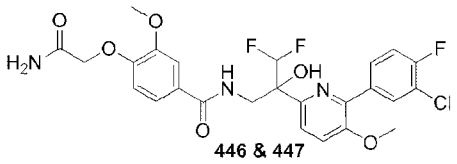
[0842] Compound **444** was prepared essentially as described in the preparation of **406** by using **444-1** and **444-2**. Compound **444** was purified by prep-HPLC to give **444** as a white solid (55 mg, 25.4%). +ESI-MS:m/z 555.0 $[M+H]^+$.

EXAMPLE 230
Preparation of Compound 445



[0843] Compound **445** was prepared essentially as described in the preparation of **406** by using **445-1** and **445-2**. Compound **445** was purified by prep-HPLC to give **445** as a white solid (56 mg, 36.3%). +ESI-MS:m/z 537.0 $[M+H]^+$.

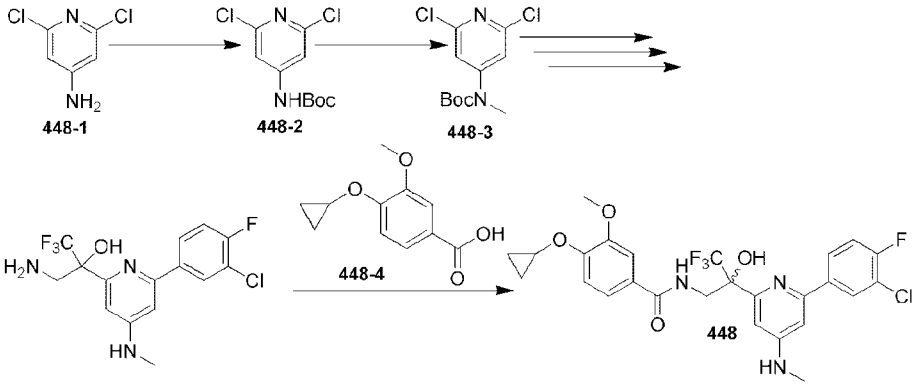
EXAMPLE 231
Preparation of Compounds 446 and 447



[0844] Compound **442** (60 mg) was separated via SFC separation to give two isomers: **446** (25 mg) and **447** (25 mg). **446**: +ESI-MS:m/z 554.0 $[M+H]^+$. **447**: +ESI-MS:m/z 554.1 $[M+H]^+$.

EXAMPLE 232

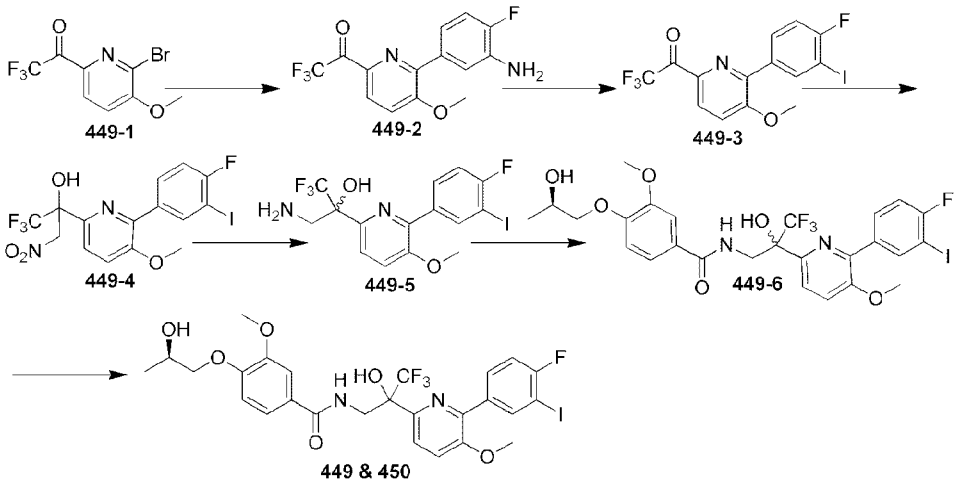
Preparation of Compound 448



[0845] Compound **448-2** was prepared essentially as described in Jang et al., *Tet. Lett.* (2006) 47(50):8917-8920, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **448-2**. To a suspension of **448-2** (6.0 g, 22.9 mmol) and K_2CO_3 (6.3 g, 45.6 mmol) in CH_3CN (40 mL) was added MeI (6.5 g, 45.6 mmol) at r.t. The solution was heated to 80 °C and stirred for 8 h. The precipitate was removed by filtration, and the organic layer was concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 20:1) to give **448-3** (5.5 g, 87.3%) as a white solid.

[0846] Compound **448** was prepared essentially as described in the preparation of **428** and **443** by using **448-3** and **448-4**. Crude **448** was purified by prep-HPLC to give **448** as a white solid (40 mg, 51.9%). +ESI-MS:m/z 554.0 $[M+H]^+$.

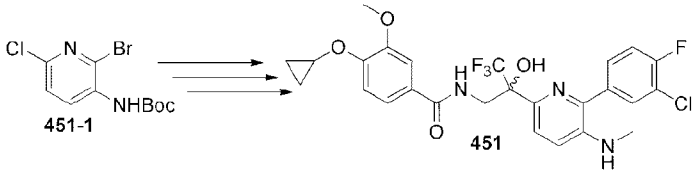
EXAMPLE 233
Preparation of Compounds 449 and 450



[0847] Step 1 and step 3 were conducted as essentially as described in the preparation of **232**. Step 2 was conducted as essentially as described in the preparation of **426**. To a solution of **449-4** (1.0 g, 2.06 mmol) in AcOH (10 mL) was added Fe (576 mg, 10.3 mmol) powder in portions. The mixture was stirred at 80 °C for 2 h. After cooling to r.t, the mixture was neutralized with sat. Na_2CO_3 solution, and extracted with EA (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column (PE:EA 3:1) to give **449-5** (435 mg, 46.4%). +ESI-MS:m/z 457.0 $[M+H]^+$.

[0848] Compound **449-6** was prepared essentially as described in the preparation of **406** by using **449-5** and (R)-4-(2-hydroxypropoxy)-3-methoxybenzoic acid. Crude **449-6** was purified by prep-HPLC to give **449-6** (92 mg, 40.4%). +ESI-MS:m/z 665.0 $[M+H]^+$. Compound **449-6** (92 mg) was separated via SFC separation to give two isomers: **449** (32 mg) and **450** (33 mg). **449**: +ESI-MS:m/z 665.0 $[M+H]^+$. **450**: +ESI-MS:m/z 665.1 $[M+H]^+$.

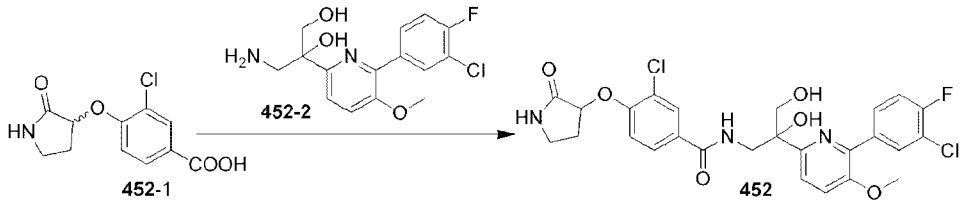
EXAMPLE 234
Preparation of Compound 451



[0849] Compound **451** was prepared essentially as described in the preparation of **443** and **448** by using **451-1**. Crude **451** was purified by prep-HPLC to give **451** as a white solid (42 mg, 16.0%). +ESI-MS:m/z 553.9 $[M+H]^+$.

EXAMPLE 235

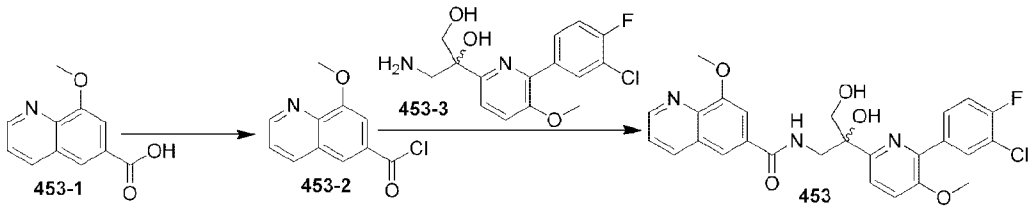
Preparation of Compound 452



[0850] Compound **452-1** was prepared essentially as described in the preparation of **259**. Compound **452-2** was prepared essentially as described in the preparation of **471**. Compound **452** was prepared essentially as described in the preparation of **406** by using **452-1** and **452-2**. Crude **452** was purified by prep-HPLC to give **452** as a white solid (90 mg, 19 %). +ESI-MS:m/z 564.0 $[M+H]^+$.

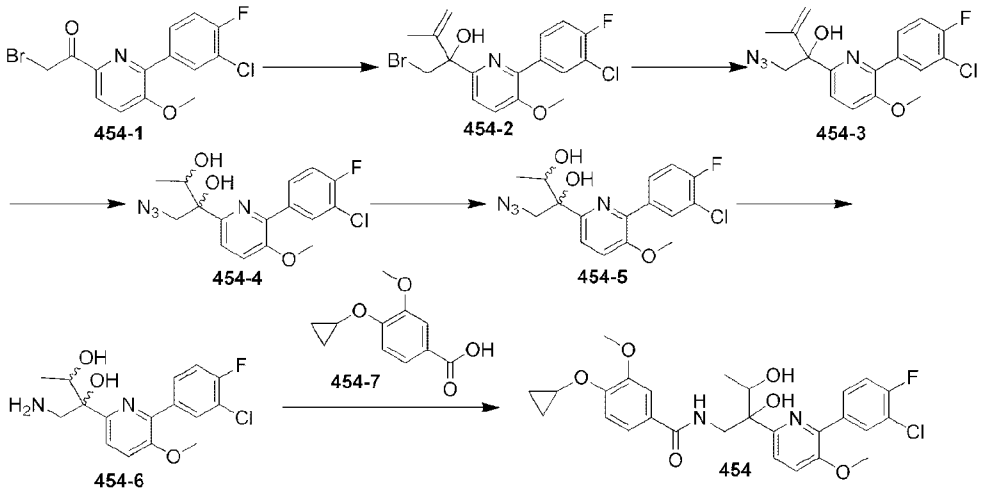
EXAMPLE 236

Preparation of Compound 453



[0851] To a solution of **453-1** (100 mg, 0.493 mmol) in $SOCl_2$ (3 mL) was added DMF (one drop) at 0 °C, and stirred at r.t. for 1 h. The mixture was co-evaporated with toluene (2x), and re-dissolved in anhydrous DCM (5 mL). The solution was treated with TEA (99.6 mg, 0.986 mol) and **453-3** (164.2 mg, 0.493 mol). The mixture was stirred at r.t. for 1 h. The mixture was diluted with DCM (20 mL) and washed with brine (20 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **453** (42 mg, yield: 16.7%). +ESI-MS:m/z 512.1 $[M+H]^+$.

EXAMPLE 237
Preparation of Compound 454



[0852] Compound **454-2** was prepared essentially as described in the preparation of **406** by using **454-1** and prop-1-en-2-ylmagnesium bromide. Crude **454-2** was purified by column chromatography (PE:EA 8:1) to give **454-2** as a solid (0.8 g). +ESI-MS:m/z 401.9 $[M+H]^+$.

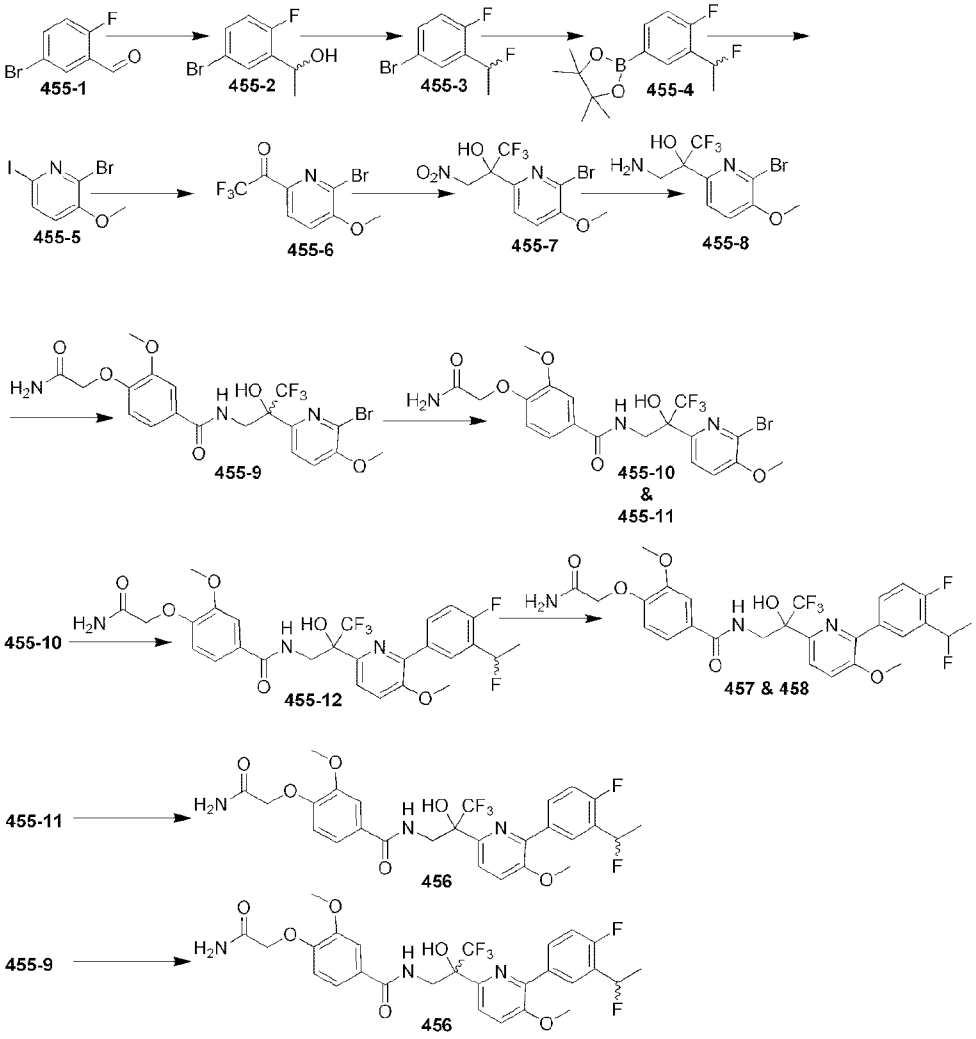
[0853] To a solution of **454-2** (800 mg, 2.0 mmol) in DMSO (10 mL) was added NaN_3 (650 mg, 10.0 mmol) at r.t., and the mixture was stirred for 5 h. The reaction was quenched with water (30 mL), and extracted by EA (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 6:1) to give **454-3** (402 mg, 55.1%) as a white solid. +ESI-MS:m/z 362.9 $[M+H]^+$.

[0854] Ozone was bubbled into a solution of **454-3** (402 mg, 1.1 mmol) in anhydrous methanol (20 mL) at -78 °C for 10 mins. After excess ozone was purged by nitrogen, $NaBH_4$ (125 mg, 3.3 mmol) was added. The mixture was stirred at r.t. for 30 mins. The reaction was quenched with water and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 5:1) to give **454-4** as an oil (303 mg, 74.6%).

[0855] Compound **454** was prepared essentially as described in the preparation of **428** from **454-4** and **454-7**. Crude **454** was purified by prep-HPLC to give **454** as a white solid (40 mg, 31.4%). +ESI-MS:m/z 531.0 $[M+H]^+$.

EXAMPLE 238

Preparation of Compounds 455, 456, 457 and 458



[0856] Compound **455-2** was prepared essentially as described in PCT Publication No. WO 2012/057247, published May 3, 2012, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **455-2**. To a solution of **455-2** (2.0 g, 9.17 mmol) in DCM (50 mL) was added DAST (6.0 g, 36 mmol) at 0 °C, and the mixture was stirred at r.t. for 1 h. The reaction was quenched with water (50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under

reduced pressure. The residue was purified by colomn chromatography (PE:EA 100:1) to give **455-3** (1.2 g, 60%).

[0857] To a solution of **455-3** (1.2 g, 5.4 mmol) in anhydrous THF (40 mL) was added *n*-BuLi (3 mL, 2.5M in hexane) dropwise at -78 °C, and the solution was stirred for 1 h. 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5 g, 8.1 mmol) was added dropwise, and the mixture was stirred at -78 °C for 1 h. The reaction was quenched with water (50 mL), and extracted with EA (2 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by colomn chromatography (PE:EA 100:1) to give **455-4** (0.4 g, 28%).

[0858] Compounds **455-5** to **455-7** was prepared essentially as described in the preparation of **449** by using **455-4**. Crude **455-7** was purified by gel colomn to give **455-7** (0.9 g, 67%). A suspension of **455-7** (1.0 g, 2.9 mmol) and $SnCl_2 \cdot 2H_2O$ (2.6 g, 12 mmol) in EA (15 mL) was stirred at 70 °C overnight. After cooling to r.t., $NH_3 \cdot H_2O$ (5 mL) was added, and the mixture was stirred for 30 mins. A white precipitate was formed and removed by filtration. The filtrate was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Compound **455-8** (0.8 g) was used without further purification.

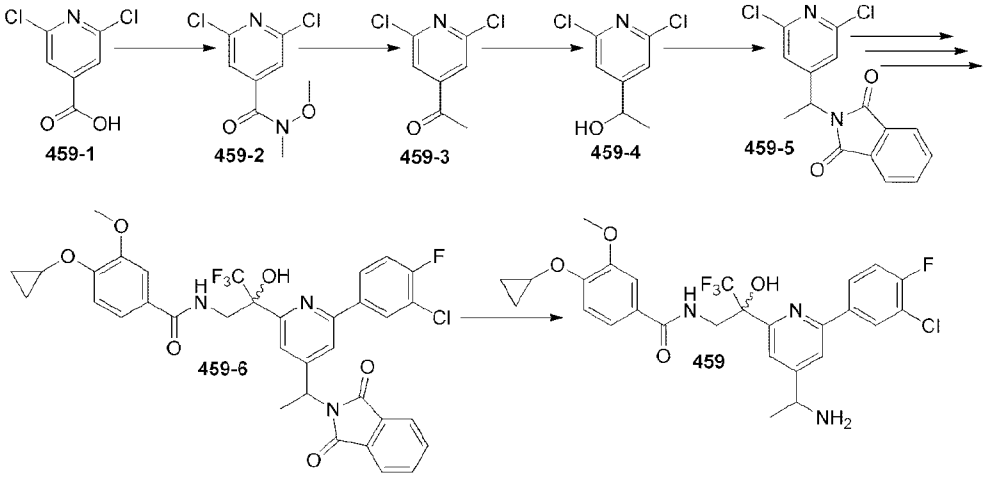
[0859] Compound **455-9** was prepared essentially as described in the preparation of **406** by using **455-8** and 4-(2-amino-2-oxoethoxy)-3-methoxybenzoic acid. Crude **455-9** was purified by prep-HPLC to give **455-9** as a white solid (570 mg, 41%). +ESI-MS:m/z 521.8 $[M+H]^+$. Compound **455-9** (570 mg, 1.09 mmol) separated via SFC separation to give two enantiomers: **455-10** (230 mg) and **455-11** (220 mg, 42%).

[0860] To a solution of **455-10** (100 mg, 0.19 mmol) and **455-4** (150 mg, 0.56 mmol) in co-solvent dioxane (4 mL) and H_2O (0.5mL) were added $Pd(dppf)Cl_2$ (10 mg, 0.012 mmol) and K_2CO_3 (55 mg, 0.4 mmol). The mixture was degassed and then refilled with N_2 (3x). The mixture was heated to 150 °C by microwave for 50 mins. The mixture was cooled to r.t., and diluted with EA (30 mL) and water (30 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **455-12** as a white solid (80 mg, 70%).

[0861] Compound **455-12** (80 mg, 0.15 mmol) was separated via SFC separation to give two isomers: **457** (30 mg) and **458** (29 mg). **457**: +ESI-MS:m/z 584.1 $[M+H]^+$. **458**: +ESI-MS:m/z 584.1 $[M+H]^+$.

[0862] Compound **456** was prepared by using **455-11** and **455-4**. Crude **456** was purified by prep-HPLC to give **456** as a white solid (75 mg, 65%). +ESI-MS:m/z 584.1 $[M+H]^+$. Compound **455** was prepared by using **455-9** and **455-4**. Crude **455** was purified by prep-HPLC to give **455** as a white solid (40 mg, 23.3%). +ESI-MS:m/z 584.1 $[M+H]^+$.

EXAMPLE 239
Preparation of Compound 459



[0863] Compound **459-2** was prepared essentially as described in Hay et al., *J. Med. Chem.* (2010) 53(2):787-797, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **459-2**. Compound **459-3** was prepared essentially as described in PCT Publication No. WO 2012/020786, published Feb. 16, 2012, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **459-3**.

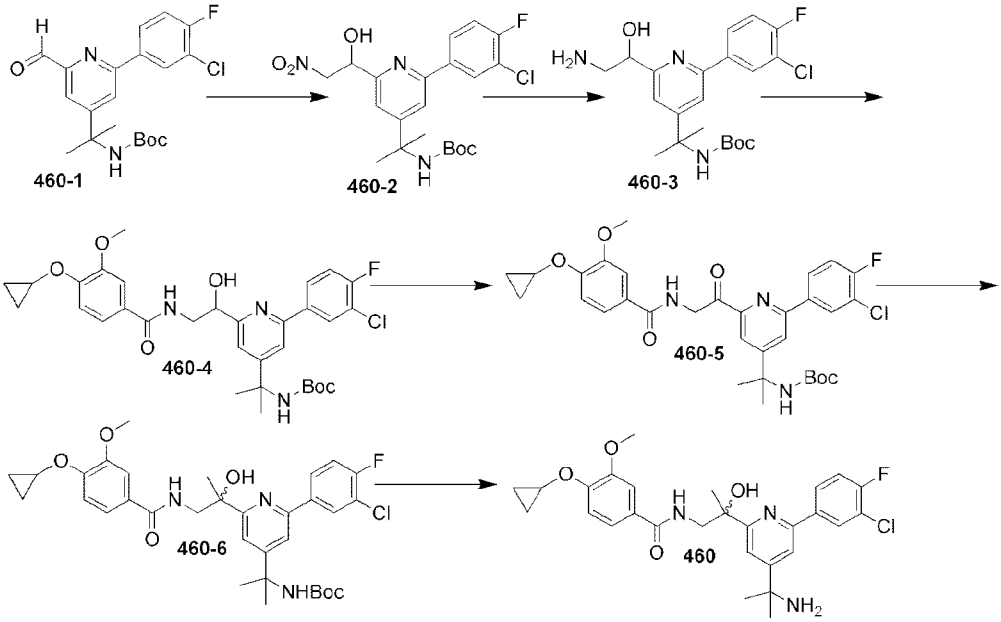
[0864] To a solution of $NaBH_4$ (60 mg, 1.58 mmol) in a mixture of THF (5 mL) and MeOH (1 mL) was added **459-3** (150 mg, 0.794 mol) in portions. The mixture was stirred at r.t. for 1 h. The reaction was quenched with water (10 mL), and extracted with EA (3 x 10 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by colomn chromatography (10~20% EA in PE) to give **459-4** (97 mg, 63.8 %).

[0865] To a solution of **459-4** (573 mg, 3.0 mmol), isoindoline-1,3-dione (441 mg, 3.0 mmol) and PPh_3 (943 mg, 3.0 mmol) in anhydrous THF (15 mL) was added DIAD (727 mg, 3.0 mmol) dropwise at 0 °C under N_2. The mixture was stirred for 2 h at r.t. The reaction was quenched by sat. $NaHCO_3$ solution (30 mL). The mixture was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 10:1) to give **459-5** (604 mg, 62.9%).

[0866] Compounds **459-5** to **459-12** was prepared essentially as described in the preparation of **428**. Crude **459-12** was purified by flash column chromatography (10~20% EA in PE) to give **459-12** (127 mg, 65.8%). A suspension of **459-12** (127 mg, 0.326 mmol) in $N_2H_4 \cdot H_2O$ (10 mL) was stirred at r.t. for 2 h. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to give **459** (35 mg, 33.9%). +ESI-MS:m/z 568.0 $[M+H]^+$.

EXAMPLE 240

Preparation of Compound 460

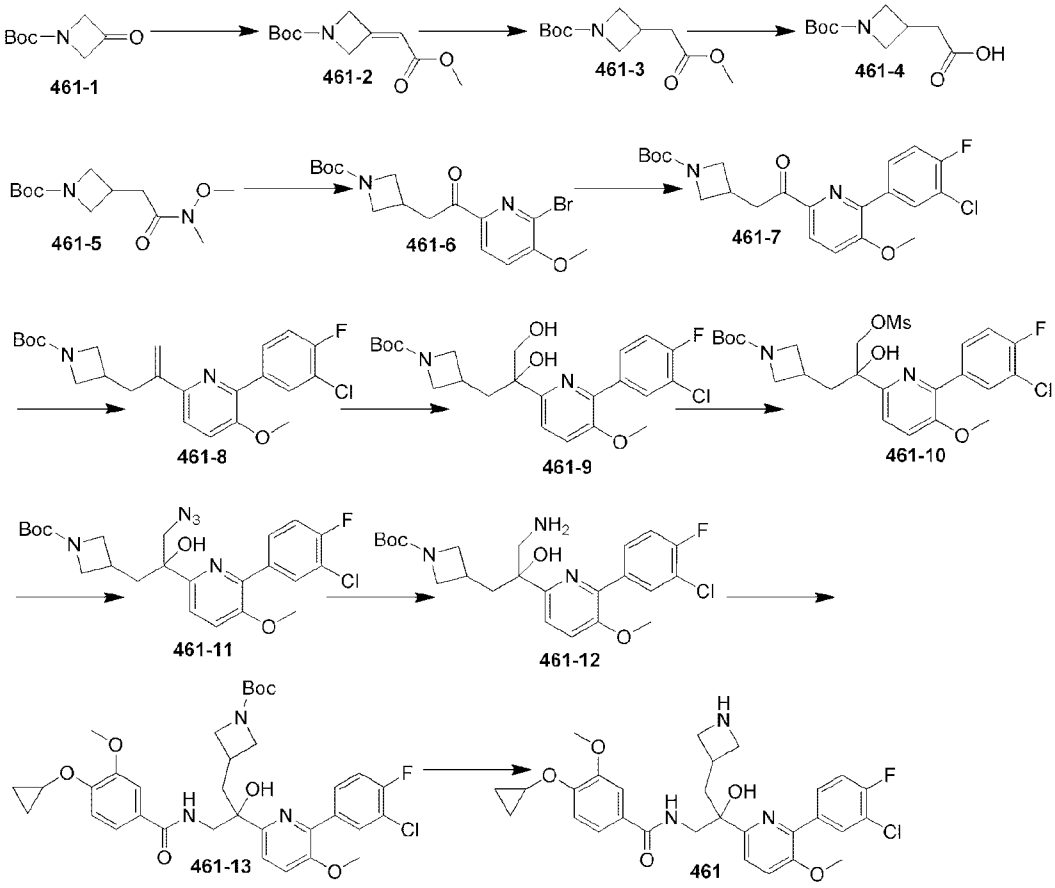


[0867] Compounds **460-1** to **460-6** were prepared essentially as described in the preparation of **272** and **403**. Crude **460-6** was purified by prep-HPLC to give **460-6** as a white solid (67 mg, 50%). To a solution of **460-6** (100 mg, 0.16 mmol) in DCM (5mL) was

added TFA (1 mL). The mixture was stirred at r.t. for 1 h. and then concentrated under reduced pressure. The residue was purified by prep-HPLC to give **460** (30 mg, 60%). +ESI-MS:m/z 528.1 $[M+H]^+$.

EXAMPLE 241

Preparation of Compound 461



[0868] Compound **461-2** was prepared essentially as described in PCT Publication No. WO 2013/055645, published April 18, 2013, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **461-2**. Compound **461-3** was prepared essentially as described in Podlech et al., *Helv. Chimica Acta* (1995) 78(5):1238-1246, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **461-3**. Compound **461-4** was prepared essentially as described in PCT Publication No. WO 2009/154780, published Dec. 23, 2009, which is

hereby incorporated by reference for the limited purpose of its description of the preparation of **461-4**.

[0869] To a solution of **461-4** (9.0 g, 39.3 mmol) in anhydrous DMF (50 mL) were added DIPEA (15.2 g, 117.9 mmol) and HATU (14.9 g, 39.3 mmol), and the mixture was stirred at r.t. for 30 mins. N,O-dimethylhydroxylamine (3.85 g, 39.3 mmol) was added, and the mixture was stirred at r.t. for 2 h. The mixture was diluted with water (100 mL), and extracted with EA (3 x 100 mL). The combined organic phase was washed brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 10:1) to give **461-5** (8.5 g, 70.7%).

[0870] To a solution of **461-5** (8.0 g, 31.0 mmol) and 2-bromo-6-iodo-3-methoxypyridine (9.7 g, 31.0 mmol) in anhydrous THF (120 mL) was added i-PrMgCl (23.5 mL, 46.51 mmol) dropwise at 0 °C, and the mixture was stirred at r.t. for 2 h. The reaction was quenched with water (50 mL) and extracted with EA (3 x 150 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 8:1) to give **461-6** (6.0 g, 49.6 %). +ESI-MS:m/z 385.01 $[M+H]^+$.

[0871] Compound **461-7** was prepared as essentially as described in the preparation of **428** by using **461-6**. Compound **461-7** (4.2 g) was obtained after purification by column chromatography.

[0872] To a suspension of $CH_3P^+Ph_3Br^-$ (2.46 g, 6.92 mmol) in toluene (20 mL) was added NaHMDS (6.92 mL, 1 M in THF) dropwise at 0 °C under N_2. The mixture was stirred for 30 mins. The mixture was cooled to -78 °C and **461-7** (2.0 g, 4.6 mmol) was added, and then stirred at -78 °C to reflux overnight. The reaction was quenched by water (30 mL) and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 5:1) to give **461-8** (1.2 g, 61.0%).

[0873] To a solution of **461-8** (1.3 g, 3.0 mmol) in DCM (20 mL) were added NMO (1.05 g, 9.0 mmol) and OsO_4 (38.4 mg, 0.15 mmol), and the mixture was stirred at r.t. overnight. The reaction was quenched with sat. Na_2SO_3 solution (50 mL) and extracted with EA (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous

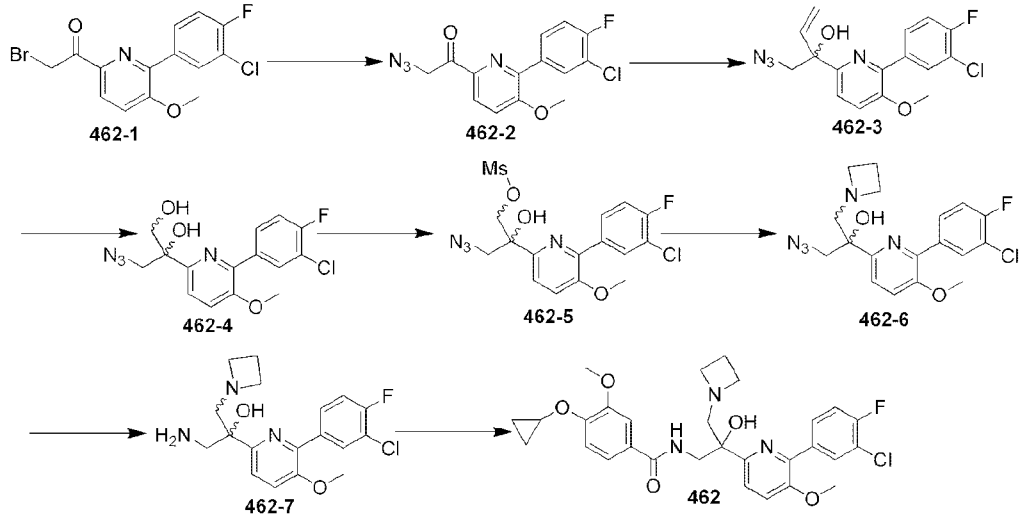
Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 3:1) to give **461-9** (0.85 g, 60.7%).

[0874] To an ice-cold solution of **461-9** (265 mg, 0.725 mmol) and TEA (220 mg, 2.2 mmol) in anhydrous DCM (20 mL) was added MsCl (1.0 g, 8.7 mmol) dropwise, and the mixture was stirred at r.t. for 1 h. The mixture was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 5:1) to give **461-10** (250 mg, 63.4%).

[0875] Compound **461** was prepared essentially as described in the preparation of **428** from **461-10**. Crude **461** was purified by prep-HPLC to give **461** as a white solid (36 mg, 20.2%). +ESI-MS:m/z 556.1 $[M+H]^+$.

EXAMPLE 242

Preparation of Compound 462



[0876] To a solution of **462-1** (3.56 g, 10.0 mmol) in DMSO (30 mL) was added NaN_3 (1.95 g, 30.0 mmol) at 25 °C in portions, and the mixture was stirred for 30 mins. The mixture was poured into water (50 mL), and extracted with EA (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 5:1) to give **462-2** (2.4 g, 75.1%) as a white solid. +ESI-MS:m/z 320.9 $[M+H]^+$.

[0877] To a solution of **462-2** (2.4 g, 7.5 mmol) in anhydrous THF (30 mL) was added vinyl-magnesium bromide (7.5 mL, 1.0M in THF) dropwise at -30 °C under N_2, and

the mixture was stirred for 30 mins. The reaction was quenched with sat. NH_4Cl solution (50 mL). The mixture was allowed to warm to r.t. and extracted with EA (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 5:1) to give **462-3** as a white solid (2.0 g, 76.9%). +ESI-MS:m/z 349.0 $[M+H]^+$.

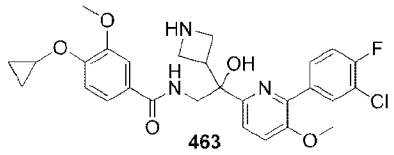
[0878] Ozone was bubbled into a solution of **462-3** (2.0 g, 5.7 mmol) in anhydrous MeOH (20 mL) at -78 °C for 10 mins. After excess Ozone was purged by N_2, $NaBH_4$ (800 mg, 21.1 mmol) was added at r.t. in portions. The mixture was stirred at r.t. for 30 mins. The reaction was quenched with water (30 mL) and extracted with EA (2 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 1:1) to give **462-4** as an oil (1.6 g, 80.1%). +ESI-MS:m/z 352.9 $[M+H]^+$.

[0879] To a solution of **462-4** (1.6 g, 4.5 mmol) and TEA (900 mg, 8.9 mmol) in anhydrous DCM (20 mL) was added MsCl (500 mg, 4.4 mmol) dropwise at 0 °C. The solution was stirred at r.t. for 30 mins. The reaction was quenched with H_2O (30 mL) and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 4:1) to give **462-5** as a solid (1.6 g, 84.2%). +ESI-MS:m/z 431 $[M+H]^+$.

[0880] To a solution of **462-5** (1.6 g, 3.7 mmol) in CH_3CN (20 mL) was added azetidine hydrochloride (1.6 g, 17.2 mmol) at r.t. The solution was heated to 70 °C and stirred for 8 h. After cooling to r.t., the reaction was quenched with H_2O (30 mL) and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 1:1) to give **462-6** as an oil (500 mg, 35.7%). +ESI-MS:m/z 391.9 $[M+H]^+$.

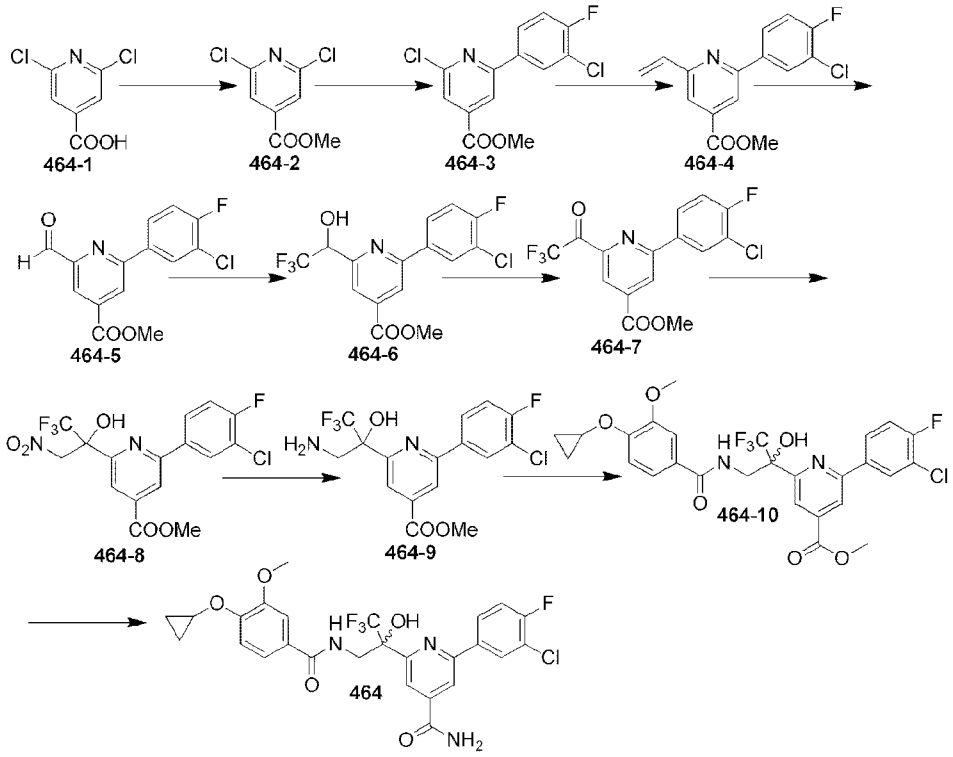
[0881] Compound **462** was prepared essentially as described in the preparation of **428** by using **462-6**. Crude **462** was purified by prep-HPLC to give **462** as a white solid (10 mg, 6.5%). +ESI-MS:m/z 556.1 $[M+H]^+$.

EXAMPLE 243
Preparation of Compound 463



[0882] Compound **463** was prepared essentially as described in the preparation of **461** by using 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid. Compound **463** was obtained as white solid (40 mg, 40%). +ESI-MS:m/z 542.1 $[M+H]^+$.

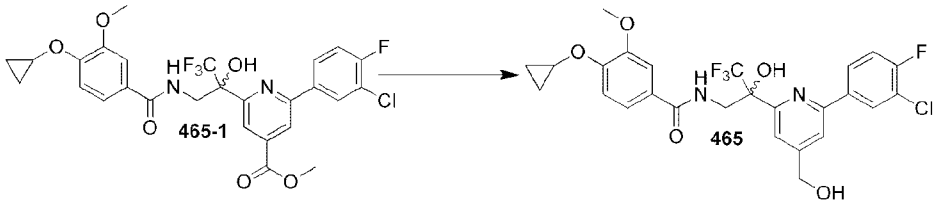
EXAMPLE 244
Preparation of Compound 464



[0883] Compound **464-2** was prepared essentially as described in Zornik et al., *Chem. Eur. J.* (2011) 17(5):1473-1484 and S1473/1-S1473/121, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **464-2**. Compound **464-10** was prepared essentially as described in the preparation of **272** by using **464-2**. Compound **464-10** was obtained as white solid (300 mg, 68.5%). +ESI-MS:m/z 582.9 $[M+H]^+$.

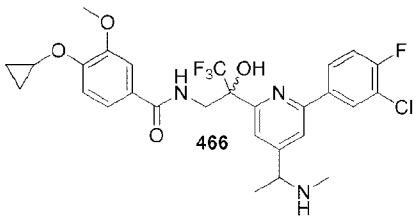
[0884] To a solution of **464-10** (50 mg, 0.086 mmol) in 1,4-dioxane (5 mL) was added ammonia water (2 mL) in a sealed tube. The mixture was then stirred at 100 °C overnight. After cooling to r.t., the mixture was concentrated to dryness, and the residue was purified by prep-HPLC to give **464** (15 mg, 30.8%) as a white solid. +ESI-MS:m/z 568.0 $[M+H]^+$.

EXAMPLE 245
Preparation of Compound 465



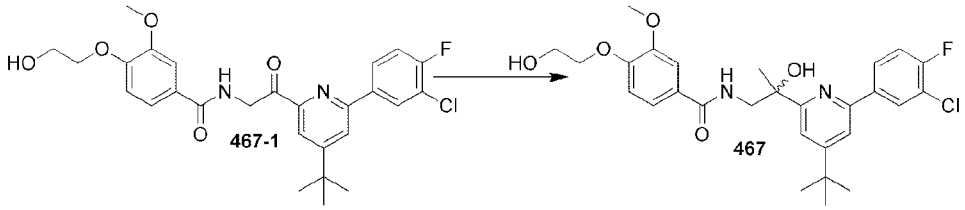
[0885] To a stirred solution of **465-1** (87.3 mg, 0.15 mmol) in THF (5 mL) at 0°C was added LAH (5.7 mg, 0.15 mmol) under N_2. After stirring at 0 °C for 1 h, the reaction was quenched by water (10 mL), and extracted by EA (3 x 10 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by prep-HPLC to give **465** (50 mg, 60.2%) as a white solid. +ESI-MS:m/z 555.0 $[M+H]^+$.

EXAMPLE 246
Preparation of Compound 466



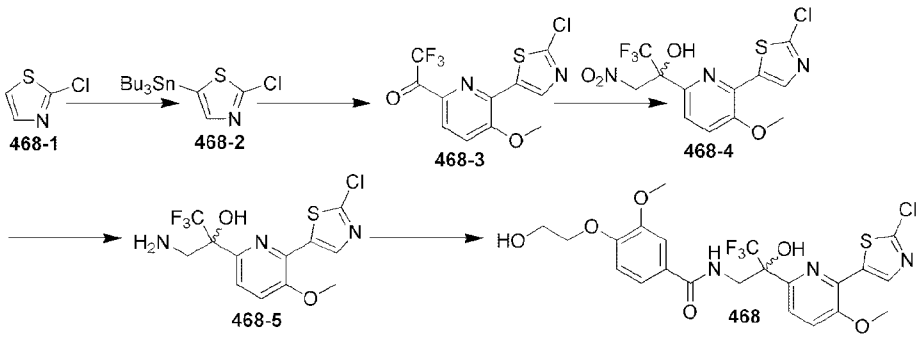
[0886] Compound **466** was prepared essentially as described in the preparation of **459** by using 1-(2,6-dichloropyridin-4-yl)ethanone. Compound **466** was obtained as white solid (20 mg, 18.5 %). +ESI-MS:m/z 582.1 $[M+H]^+$.

EXAMPLE 247
Preparation of Compound 467



[0887] To a solution of **467-1** (60 mg, 0.12 mmol) in THF (4 mL) was added MeMgCl (1 mL, 3 M in ether) dropwise at 0 °C, and the mixture was stirred at for 1 h. The reaction was quenched with sat. NH_4Cl solution, and extracted with EA (3 x 10 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **467** (30 mg, 47%) as a white solid. +ESI-MS:m/z 531.3 $[M+H]^+$.

EXAMPLE 248
Preparation of Compound 468



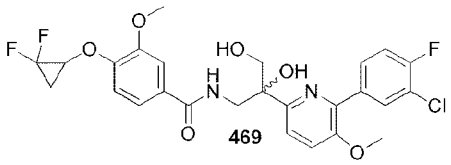
[0888] To a solution of **468-1** (2.4 g, 20 mmol) in anhydrous THF (50mL) was added *n*-BuLi (8 mL, 2.5M in hexane) at -78 °C under N_2, and the mixture was stirred for 0.5 h. The mixture was treated with tributylchlorostannane (6.5 g, 20 mmol) in portions, and stirred at -78 °C for 1 h. The reaction was quenched by water (50 mL), and extracted with EA (3x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 10:1) to give **468-2** (6 g, 74 %).

[0889] A mixture of **468-2** (2.02 g, 5.0 mmol), $Pd(dppf)Cl_2$ (90 mg, 2% eq.) and 1-(6-bromo-5-methoxypyridin-2-yl)-2,2,2-trifluoroethanone (1.5 g, 5mL) was dissolved in dry DMF (10 mL) under N_2. The mixture was heated to 130 °C by microwave and stirred for

0.5 h. After cooling to r.t., the mixture was poured into water (50 mL) and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 5:1) to give **468-3** (1.4 g, 82 %).

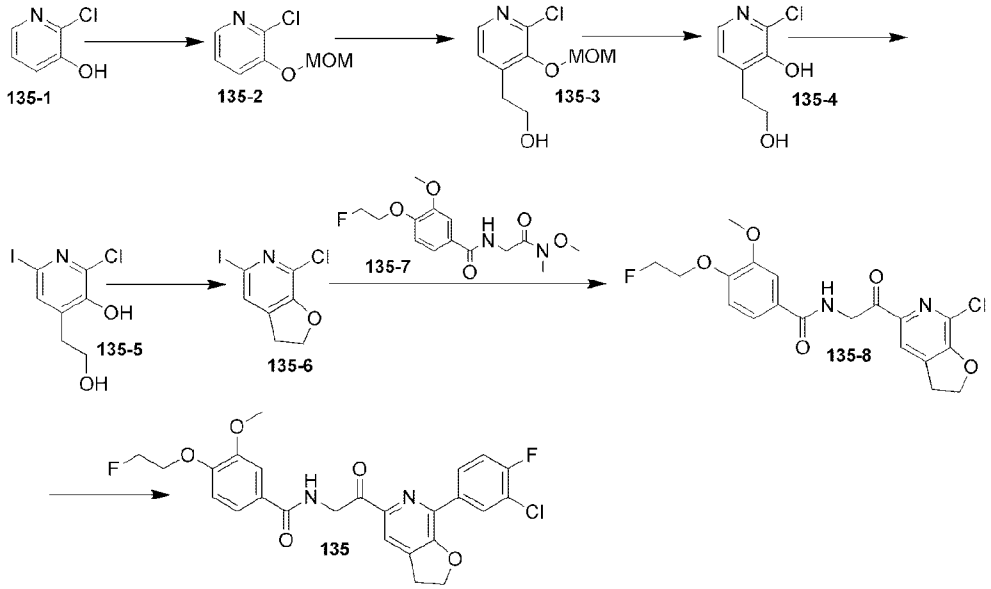
[0890] Compound **468** was prepared essentially as described in the preparation of **424** by using **468-3**. Crude **468** was purified by pre-HPLC to give **468** as a white solid (50 mg, 20 %). +ESI-MS:m/z 547.9 $[M+H]^+$.

EXAMPLE 249
Preparation of Compound 469



[0891] Compound **469** was prepared according to the method described in the preparation of **176**. LCMS: m/z 553.10 $[M+H]^+$.

EXAMPLE 250
Preparation of Compound 135



[0892] Compound **135-2** was prepared essentially as described in Granzhan et al., *Angew. Chem. Int'l Ed.* (2010) 49(32): 5515-5518, S5515/1-S5515/30, which is hereby

incorporated by reference for the limited purpose of its description of the preparation of **135-2**.

[0893] To a solution of **135-2** (10.0 g, 57.8 mmol) in anhydrous THF (60 mL) was added *n*-BuLi (35 mL, 2.5 M in hexane) dropwise at -78 °C under N_2. The mixture was stirred at -78 °C for 30 mins. under N_2 and oxirane (15.5 mL, 289 mmol) was added. The mixture was warmed to r.t. and stirred for 2 h. The reaction was quenched with H_2O, and extracted with EA (3 x 100 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 3:1) to give **135-3** (3.5 g, 28%). +ESI-MS:m/z 217.9 $[M+H]^+$.

[0894] To a solution of **135-3** (3.5 g, 16.1 mmol) in MeOH (60 mL) was added conc. HCl solution (15 mL, 12 N) at r.t., and stirred at 60 °C for 5 h. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with EA (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 1:1) to give **135-4** (1.02 g, 36%).

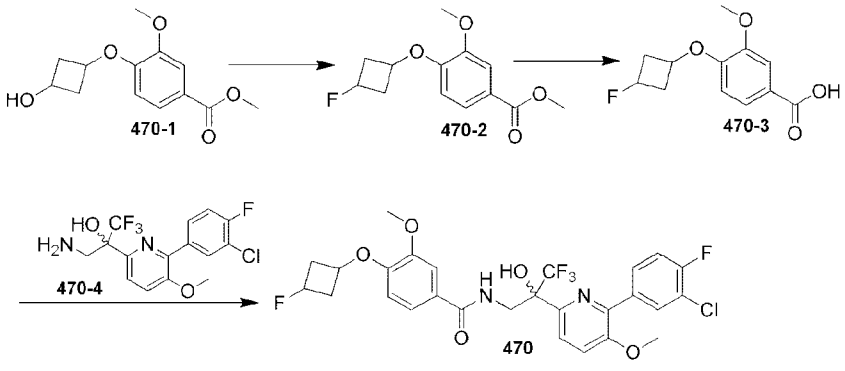
[0895] To a solution of **135-4** (1.02 g, 5.7 mmol) and K_2CO_3 (1.5 g, 11.5 mmol) in a mixture of THF (10 mL) and H_2O (10 mL) was added I_2 (1.5 g, 6.0 mmol) in portions, and the mixture was stirred at r.t. for 30 mins. The reaction was quenched with sat. NaS_2O_3 solution, and extracted with EA (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 2:1) to give **135-5** (1.1 g, 62.5%).

[0896] To a solution of **135-5** (1.1 g, 3.7 mmol) and PPh_3 (1.5 g, 5.7 mmol) in anhydrous THF (10 mL) was added DIAD (1.2 g, 5.7 mmol) at r.t. under N_2. The mixture was heated to 70 °C for 1 h and then cooled to r.t. The reaction was quenched with H_2O, and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 2:1) to give **135-6** (0.8 g, 78%). +ESI-MS:m/z 281.8 $[M+H]^+$.

[0897] To a solution of **135-6** (0.8 g, 7.1 mmol) and **135-7** (2.2 g, 7.1 mmol) in THF (10 mL) was added i-PrMgBr (21mL, 1.0 M in THF) dropwise under N_2, and the mixture was stirred at r.t. for 1 h. The reaction was quenched with sat. NH_4Cl solution and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 1:1) to give **135-8** (1.2 g, 77%). +ESI-MS:m/z 408.9 $[M+H]^+$.

[0898] To a solution of **135-8** (408 mg, 1.0 mmol), (3-chloro-4-fluorophenyl)boronic acid (175 mg, 1.0 mmol) and Cs_2CO_3 (276 mg, 2.0 mmol) in dioxane (5 mL) and water (1 mL) was added $Pd(dppf)Cl_2$ (82 mg, 0.1 mmol) under N_2. The mixture was heated to 120 °C under microwave irradiation and stirred for 30 mins. The mixture was cooled to r.t., poured into cold H_2O and extracted with EA (3 x 10 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **135** (80 mg) as a white solid. +ESI-MS:m/z 502.9 $[M+H]^+$.

EXAMPLE 251
Preparation of Compound 470



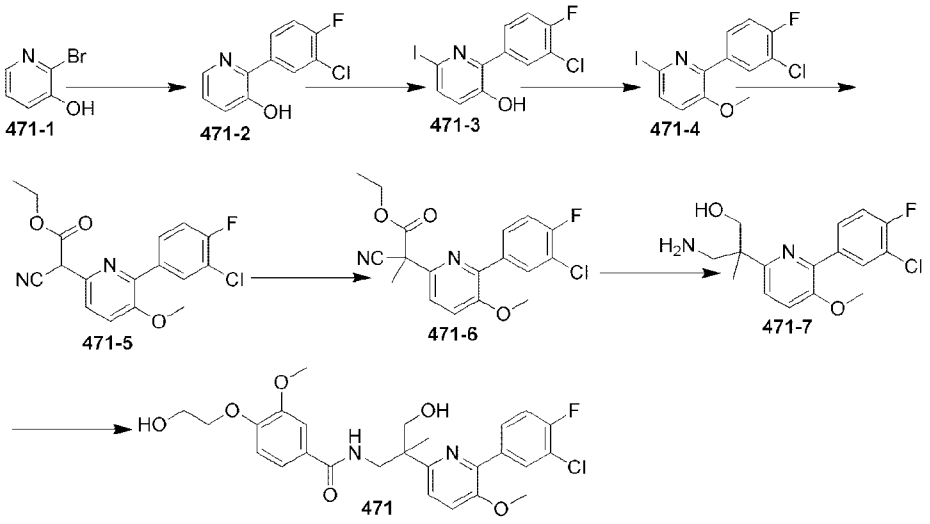
[0899] To a solution of **470-1** (1.7 g, 6.7 mmol) in DCM (10 mL) was added DAST (3 mL) at 0 °C, and the mixture was stirred at 0°C for 30 mins. The resulting was quenched with sat. $NaHCO_3$ solution at 0 °C and extracted by EA (3 x 20 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 15:1) to give **470-2** as a white solid (800 mg, 47.1%).

[0900] To a solution of **470-2** (254 mg, 1.0 mmol) in MeOH (5 mL) was added NaOH (5 mL, 2*N*), and the mixture was stirred at reflux for 1 h. The mixture was cooled to r.t. and acidified to pH 4~5 using HCl (2 M). The mixture was extracted with EA (3 x 20 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give **470-3** as a white solid (100 mg, 41.6%).

[0901] To a solution of **470-3** (100 mg, 0.42 mmol), HATU (190 mg, 0.5 mmol) and DIPEA (129 mg, 1.0 mmol) in anhydrous DCM (5 mL) was added **470-4** (140 mg, 0.39 mmol) at 25 °C. The solution was stirred for 1 h and then quenched with aq. $NaHCO_3$ solution. The aqueous phase was extracted with DCM (2 x 10 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **470** as a white solid (60 mg, 24.5%). +ESI-MS:m/z 586.9 $[M+H]^+$.

EXAMPLE 252

Preparation of Compound 471



[0902] To a solution of bromide **471-1** (5.0 g, 28.9 mmol) and (3-chloro-4-fluorophenyl)boronic acid (5.5 g, 31.8 mmol) in dioxane (50 mL) were added $Pd(dppf)Cl_2$ (816 mg, 1.0 mmol) and a freshly prepared Cs_2CO_3 solution (11 g in 50 mL of water) under N_2. The mixture was stirred at 70 °C for 3 h. The solution was cooled to r.t., poured into ice water and extracted with EA (3 x 100 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue

was purified by column chromatography (PE:EA 10:1~5:1) to give **471-2** (5.5 g) as a white solid.

[0903] To a solution of **471-2** (3.9 g, 17.4 mmol) and K_2CO_3 (3.0 g, 21.7 mmol) in DMF (50 mL) was added I_2 (1.4 g, 5.5 mmol) in portions at r.t., and the mixture was stirred for 2 h. The reaction was quenched with sat. $Na_2S_2O_3$ solution, and extracted with EA (3 x 50 mL). The combined organic phase was washed with brine, dried over anhyrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 50:1~25:1) to give **471-3** as a white solid (2.1g, 50%). +ESI-MS:m/z 349.8 $[M+H]^+$.

[0904] To a solution of **471-3** (2.0 g, 5.7 mmol) and K_2CO_3 (790 mg, 5.7 mmol) in DMF (25 mL) was added MeI (1.5 g, 11 mmol) dropwise at 0 °C. The mixture was stirred at r.t. for 2 h. The reaction was quenched with water, and extracted with EA (3 x 50 mL). The combined organic phase was washed with brine, dried over anhyrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 50:1) to give **471-4** as a white solid (1.1g, 55%).

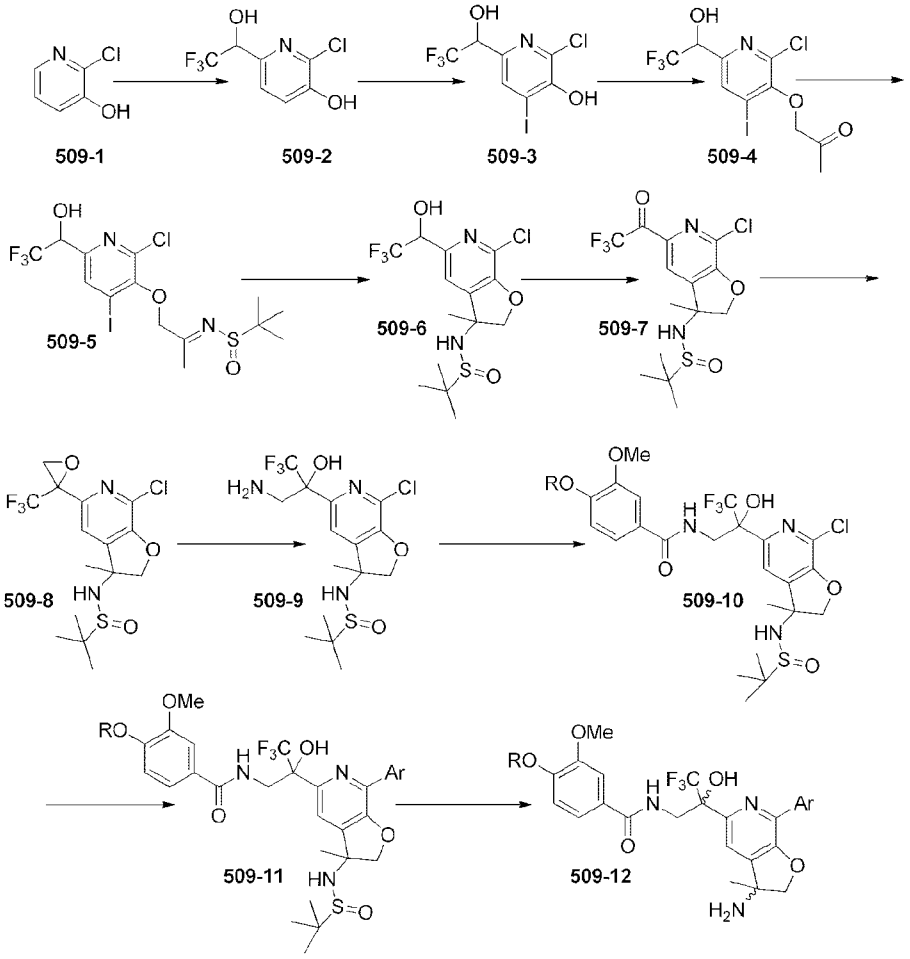
[0905] To a solution of **471-4** (1.1 g, 3.0 mmol), picolinic acid hydrochloride (240 mg, 1.5 mmol), Cs_2CO_3 (2.8 g, 8.7 mmol) and CuI (165 mg, 0.75 mmol) in DMF (20 mL) was added ethyl 2-cyanoacetate (650 mg, 6.0 mmol) under N_2. The mixture was heated to 130 °C under microwave irradiation and stirred for 30 mins. The mixture was cooled to r.t., poured into water and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhyrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 10:1~5:1) to give **471-5** as a yellow solid (720 mg, 65%). +ESI-MS:m/z 348.8 $[M+H]^+$.

[0906] To a solution of **471-5** (720 mg, 2.04 mmol) in anhydrous DMF (15 mL) was added NaH (130 mg, 3.12 mmol) in portions at 0 °C. After stirring for 30 mins., MeI (840 mg, 6 mmol) was added. The mixture was stirred at 0 °C for 2 h. The reaction was quenched with water, and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhyrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA 25:1) to give **471-6** as a white solid (468 mg, 65%). +ESI-MS:m/z 362.8 $[M+H]^+$.

[0907] To a solution of **471-6** (460 mg, 1.27 mmol) in anhydrous THF (15 mL) was added LAH (250 mg, 5 mmol) at 0 °C under N_2, and the mixture stirred at 0 °C for 2 h. The reaction was quenched with water, and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhyrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-TLC to give **471-7** (150 mg, 36%). +ESI-MS:m/z 324.8 $[M+H]^+$.

[0908] To a solution of 4-(2-hydroxyethoxy)-3-methoxybenzoic acid (60 mg, 0.3 mmol), HATU (70 mg, 0.5 mmol) and DIEA (300 mg, 0.7 mmol) in DCM (15 mL) was added amine **471-7** (100 mg, 0.3 mmol). After stirring at r.t. for 30 mins., the reaction was quenched with sat. $NaHCO_3$ solution, and extracted with DCM (3 x 10 mL). The combined organic phase was washed with brine, dried over anhyrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **471** as a white solid (55 mg, 32%). +ESI-MS:m/z 519.0 $[M+H]^+$.

EXAMPLE 253
Preparation of Compounds 509-513



[0909] Potassium carbonate (29.8 g, 216 mmol) and trifluoroacetaldehyde ethyl hemiacetal (19 mL, 162 mmol) were sequentially added to a suspension of **509-1** (14.0 g, 108 mmol) in water (210 mL). The reaction was stirred at 100 °C overnight. Additional trifluoroacetaldehyde ethyl hemiacetal (19 mL, 162 mmol) was added. The reaction was stirred at 100 °C for 7 h, and further trifluoroacetaldehyde ethyl hemiacetal (19 mL, 162 mmol) was added. After 16 h at 100 °C, the reaction was cooled to 0 °C, neutralized with 1M aq. HCl solution and extracted with EtOAc. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 70:30) afforded **509-2** (24.0 g, 80% purity A/A UV).

[0910] Iodine (40.1 g, 158 mmol) was added to a solution of **509-2** (24.0 g) and potassium carbonate (28.9 g, 210 mmol) in water (350 mL). The mixture was stirred at r.t. overnight. A 1M aq. sodium thiosulfate solution was added. The mixture was treated with 3N aq. HCl until a white solid formed. EtOAc was added and the layers were separated. The aqueous phase was extracted with EtOAc (3x). The combined organic portions were dried with Na_2SO_4 and filtered. The solvents were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 70:30) afforded **509-3** as a white solid (21.0 g, 50% over two steps). UPLC/MS(ES^+) m/z: 354.03 $[M+H]^+$.

[0911] Chloroacetone (2.6 mL, 32.8 mmol) was added to a solution of **509-3** (10.5 g, 29.8 mmol) and potassium carbonate (6.18 g, 44.8 mmol) in acetone (170 mL). The reaction was stirred at 50 °C overnight. The volatiles were removed under reduced pressure, and the residue was partitioned between water and EtOAc. The layers were separated, and the organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was tritrated with DCM, and the precipitate dried to afford **509-4** as a white solid (6.80 g, 55%). UPLC/MS(ES^+) m/z: 409.92 $[M+H]^+$. The supernatant was concentrated under reduced pressure, and the residue chromatographed (cyclohexane:EtOAc, 100:0 to 0:100) to afford unreacted **509-3** (1.20 g, 11%).

[0912] The reaction was performed in 8 batches. A mixture of **509-4** (841 mg, 2.05 mmol), 2-methylpropane-2-sulfinamide (273 mg, 2.26 mmol) and titanium(IV) ethoxide (1.03 g, 4.51 mmol) in THF (16 mL) was heated to 70 °C (sealed vial, degassed and purged with N_2). The mixture was stirred at 70 °C for 3 h. The 8 batches were unified. EtOAc and water were added. The mixture was stirred for 5 mins, and then filtered through a pad of celite. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 50:50 to 0:100) afforded **509-5** (5.36 g, 63%). UPLC/MS(ES^+): m/z 513.10 $[M+H]^+$.

[0913] *n*-Buthyllithium (1.6M solution in THF, 6.60 mL, 10.5 mmol) was added to a solution of EtMgBr (1M in THF, 5.23 mL, 5.23 mmol) in THF (15 mL), which had been pre-cooled to 0°C. After 10 mins, the mixture was cooled to -78 °C. A solution of **509-5** (2.68 g, 5.23 mmol) in THF (15 mL) was added dropwise. The reaction was stirred at -78°C

for 15 mins. The reaction was quenched with MeOH and diluted with EtOAc. The organic portion was washed with brine, and the aqueous portion extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **509-6** as a yellow wax (2.60 g, 64%).

[0914] Dess-Martin periodinane (3.14 g, 7.46 mmol) was added to a stirred solution of **509-6** (2.60 g, 6.73 mmol) in DCM (36 mL). The reaction was stirred at r.t. under N_2 atmosphere for 3 h. The reaction was quenched with a 1:1 mixture of 2M aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. After 30 mins of vigorous stirring, the layers were separated. The organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **509-7** as a white solid (2.11 g, 81%). UPLC/MS(ES^+): m/z 385.16 $[M+H]^+$, 403.18 $[M+H_3O]^+$.

[0915] The reaction was performed in 2 batches. Trimethylsulfoxonium iodide (601 mg, 2.73 mmol) was added in 1 portion to a mixture of tBuOK (305 mg, 2.73 mmol) in CH_3CN (50 mL), which had been previously degassed. The mixture was further degassed and stirred at r.t. for 30 mins. The solution containing the ylide was filtered from the solid and added to a solution of **509-7** (1.05 g, 2.73 mmol) in CH_3CN (50 mL), which had been previously degassed. The reaction was stirred at r.t. for 1 h. The 2 batches were combined, and the volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **509-8** as a colorless wax (1.45 g, 66%). UPLC/MS(ES^+): m/z 399.14 $[M+H]^+$.

[0916] A solution of **509-8** (1.45 g, 3.64 mmol) in 7M NH_3-MeOH (800 mL) was stirred at r.t. for 2 h. The volatiles were removed under reduced pressure to afford **509-9** (1.43 g), which was used in the next step.

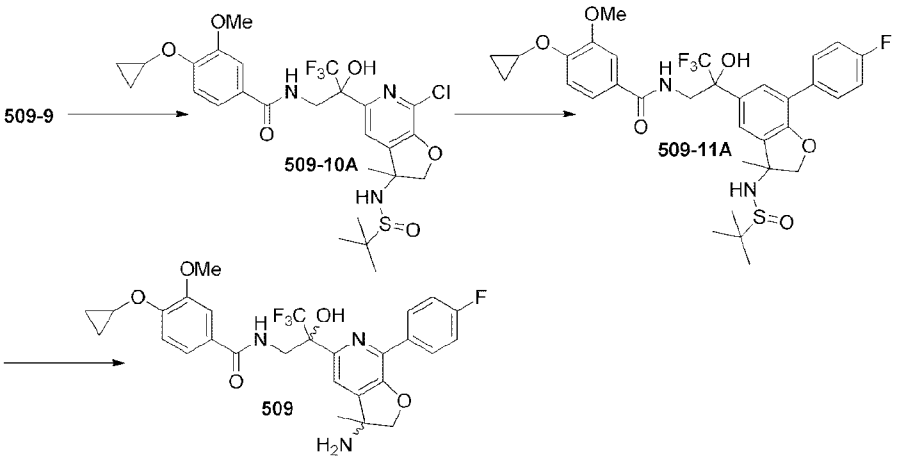
[0917] Method A: A mixture of **509-9** (750 mg), EDC (448 mg, 2.35 mmol), HOBT (317 mg, 2.35 mmol), TEA (500 uL, 3.60 mmol) and acid (1.80 mmol) in DCM (18 mL) was stirred at r.t. for 2 h. Water was added, and the mixture was stirred for 10 mins. The layers were separated, and the organic portion was dried with Na_2SO_4. The solvent was

evaporated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc) afforded **509-10**.

[0918] Method B: A solution of acid (0.120 mmol), HATU (44 mg) and DIPEA (110 uL) in DMF or DCM (1 mL) was stirred at r.t. for 15 mins. A solution of **509-9** (50 mg) in DMF (or DCM, 1 mL) was added to the reaction. The mixture was stirred at r.t. for 20 mins. The majority of the volatiles were removed under reduced pressure. The residue was taken up with EtOAc, and the organic portion was washed with 1M aq. NaOH and 1M aq. HCl, dried with Na_2SO_4, filtered and concentrated under reduced pressure to give **509-10**.

[0919] A mixture of **509-10** (0.582 mmol), boronic acid (0.872 mmol), K_3PO_4 (247 mg, 1.16 mmol), KH_2PO_4 (158 mg, 1.16 mmol) and $Pd(dbpf)Cl_2$ (13.8 mg, 0.029 mmol) in a DME:EtOH:H_2O mixture (5:3:1, 9 mL) was degassed and warmed to 50 °C for 6 h. DCM and water were added. The layers were separated, and the organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc) afforded **509-11**.

[0920] A 4M HCl-dioxane solution (1 mL) was added to a solution of **509-11** (0.508 mmol) in MeOH (5 mL). After 15 mins, the volatiles were removed under reduced pressure. The residue was dissolved in DCM. The organic portion was washed with 5% aq. $NaHCO_3$ solution and water, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford **509-12**.



[0921] Coupling of **509-9** with 4-cyclopropoxy-3-methoxybenzoic acid according to Method A afforded **509-10A** as a white solid (85%). UPLC/MS(ES^+): m/z 606.24

$[M+H]^+$. Suzuki coupling of **509-10A** with 4-fluorophenylboronic acid followed by sulfinamide hydrolysis afforded **509** as a white solid (53% over two steps). UPLC/MS(ES^+): m/z 562.20 $[M+H]^+$.

[0922] **509** (53 mg) was dissolved in DCM. The solution was washed with sat. aq. $NaHCO_3$ solution, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The amine was resolved by prep-HPLC [Chiralpak AD-H (25 x 3 cm, 5 um), mobile phase: n-hexane/(ethanol+0.1% ipa) 80:20 % v/v, flow rate: 32mL/min, UV detection DAD 220 nm]. Two fractions were recovered based on retention times: a mixture of **510, 512** and **513**: t_R= 21.0 min; and **511**: white solid (7.3 mg, t_R= 28.5 min). UPLC/MS(ES^+): m/z 562.20 $[M+H]^+$.

[0923] The mixture of **510, 512** and **513** was resolved by prep-HPLC [Chiralpak IC (25 x 3 cm, 5 um), mobile phase: n-hexane/(ethanol + 0.1% ipa) 70/30 % v/v, flow rate: 32 mL/min, UV detection DAD 220 nm]. Two fractions were recovered based on retention times: a mixture of **512** and **513**: t_R= 8.2 min; and **510**: white solid (7.1 mg, t_R= 10.6 min). UPLC/MS(ES^+): m/z 562.20 $[M+H]^+$.

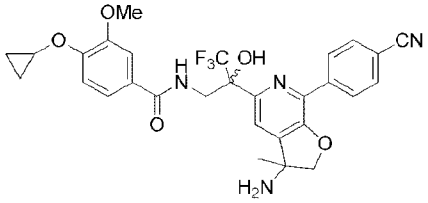
[0924] The mixture of **512** and **513** was resolved by prep-HPLC [Chiralpak OJ-H (25 x 3 cm, 5 um), mobile phase: n-hexane/(ethanol/MeOH 1/1 + 0.1% ipa) 65/35 % v/v, flow rate: 38 mL/min, UV detection DAD 220 nm]. Two fractions were recovered based on retention times: **512**: white solid (6.0 mg, t_R= 7.2 min). UPLC/MS(ES^+): m/z 562.20 $[M+H]^+$; and **513**: white solid (6.0 mg, t_R= 11.3 min). UPLC/MS(ES^+): m/z 562.20 $[M+H]^+$.

[0925] Alternatively, **509** (220 mg) was resolved by prep-HPLC [Chiralpak IC (25 x 2 cm, 5 um), mobile phase: n-hexane/(ethanol/methanol 1/1 +0.1% ipa) 86/14% v/v, flow rate: 16 mL/min, UV detection DAD 220 nm]. Three fractions were recovered based on retention times: a mixture of **512** and **513**: (104 mg, t_R= 13.4 min); **511**: (40 mg, 14%, t_R= 15.0 min). UPLC/MS(ES^+): m/z 562.20 $[M+H]^+$; and **510**: (35 mg, 12%, t_R= 17.5 min). UPLC/MS(ES^+): m/z 562.20 $[M+H]^+$.

[0926] The mixture of **512** and **513**: was resolved by prep-HPLC [Chiralcel OJ-H (25 x 3 cm, 5 um), mobile phase: n-hexane/(ethanol/methanol 1/1 +0.1% ipa) 65/35% v/v, flow rate: 40 mL/min, UV detection DAD 220 nm]. Two fractions were recovered based on

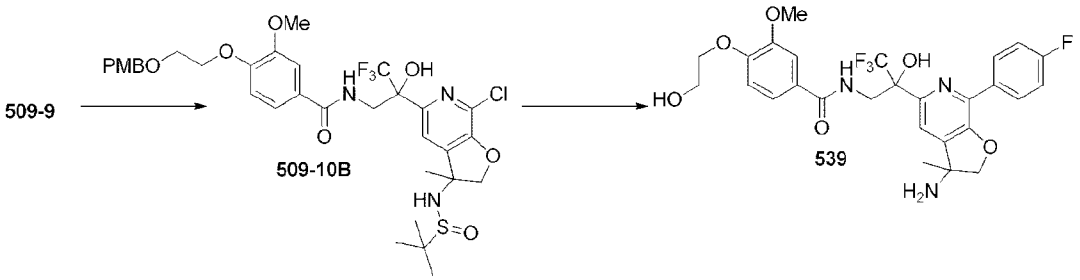
retention times: **512** (41 mg, 14%, t_R= 7.5 min). UPLC/MS(ES^+): m/z 562.20 $[M+H]^+$; and **513** (46.6 mg, 16%, t_R= 12.0 min). UPLC/MS(ES^+): m/z 562.20 $[M+H]^+$.

EXAMPLE 254
Preparation of Compound 542



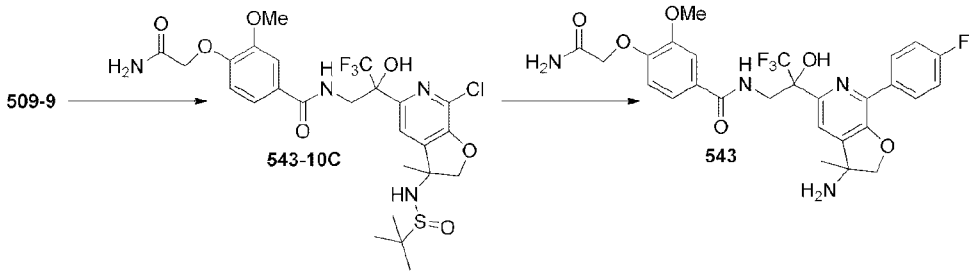
[0927] Suzuki coupling of **509-10A** with 4-cyanophenylboronic acid followed by hydrolysis of the resulting sulfinamide afforded **542** (78% over 2 steps). UPLC/MS(ES^+): m/z 569.40 $[M+H]^+$.

EXAMPLE 255
Preparation of Compound 539



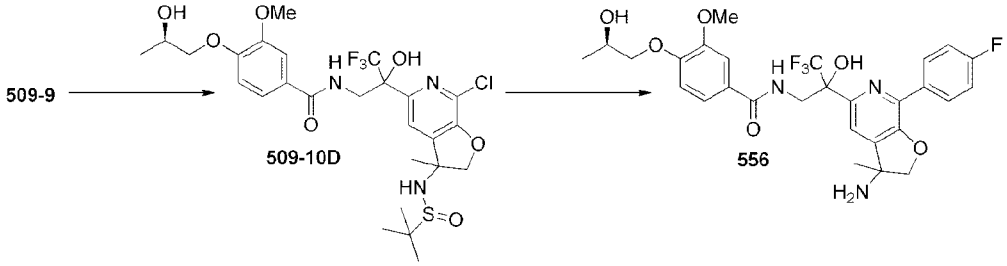
[0928] Coupling of **509-9** (50 mg) with 4-(2-(4-methoxybenzyloxy)ethoxy)-3-methoxybenzoic acid according to Method B afforded **509-10B**. Suzuki coupling of **509-10B** with 4-fluorophenylboronic acid followed by sulfinamide hydrolysis and PMB-group removal afforded **539** as an off-white solid (10 mg). UPLC/MS(ES^+): m/z 566.30 $[M+H]^+$.

EXAMPLE 256
Preparation of Compound 543



[0929] Coupling of **509-9** (80 mg) with 4-(carbamoylmethoxy)-3-methoxybenzoic acid according to Method B afforded **509-10 C**. Suzuki coupling of **509-10C** with 4-fluorophenylboronic acid followed by sulfinamide hydrolysis afforded **543** as an off-white solid (8.7 mg). UPLC/MS(ES^+): m/z 579.40 $[M+H]^+$.

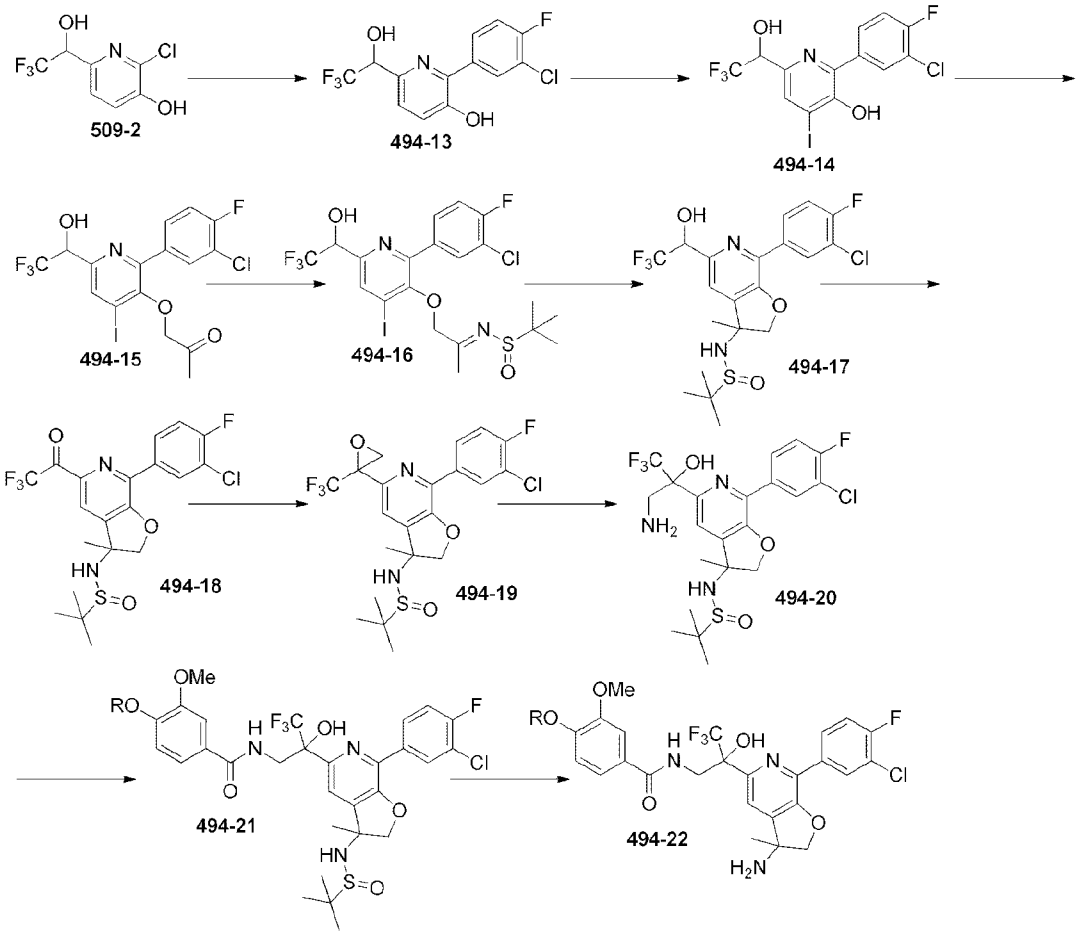
EXAMPLE 257
Preparation of Compound 556



[0930] Coupling of **509-9** with 4-[(2R)-2-hydroxypropoxy]-3-methoxybenzoic acid according to Method A afforded **509-10D**. UPLC/MS(ES^+): m/z 624.20 $[M+H]^+$. Suzuki coupling of **509-10D** with 4-fluorophenylboronic acid followed by sulfinamide hydrolysis afforded **556** as an off-white solid (50% over 2 steps). UPLC/MS(ES^+): m/z 580.33 $[M+H]^+$.

EXAMPLE 258

Preparation of Compounds 494, 498, 482 and 483



[0931] A mixture of **509-2** (5.00 g, 22.0 mmol), (3-chloro-4-fluorophenyl)boronic acid (7.66 g, 44.0 mmol), $Pd(dppf)Cl_2$ (1.60 g, 2.20 mmol) and Na_2CO_3 (2M aq solution, 22.0 mL, 44.0 mmol) in DCE (250 mL) was degassed and heated to reflux for 16 h. Additional $Pd(dppf)Cl_2$ (0.05 eq), (3-chloro-4-fluorophenyl)boronic acid (1 eq.) and aq Na_2CO_3 (1 eq) were added. The reaction was refluxed for 4 h and then water was added. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:DCM, 70:30 to 0:100) afforded **494-13** as a yellow solid (2.74 g). UPLC/MS(ES^+): m/z 322.10 $[M+H]^+$.

[0932] Iodine (1.77 g, 6.98 mmol) was added to a solution of **494-13** (2.24 g, 6.98 mmol) and potassium carbonate (2.89 g, 20.9 mmol) in water (100 mL). The mixture was

stirred at r.t. for 30 mins. A 1M aq. sodium thiosulfate solution was added. The mixture was treated with 3N aq. HCl until a white solid formed. EtOAc was added, and the layers were separated. The aqueous phase was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4 and filtered. The solvents were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 80:20) afforded **494-14** as a light yellow solid (2.80 g, 90%). UPLC/MS(ES^+): m/z 448.05 $[M+H]^+$.

[0933] Chloroacetone (548 μL, 6.89 mmol) was added to a solution of **494-14** (2.80 g, 6.26 mmol) and potassium carbonate (1.30 g, 9.40 mmol) in acetone (40 mL). The reaction was stirred at 50 °C for 24 h. The volatiles were removed under reduced pressure, and the residue was partitioned between water and EtOAc. The layers were separated, and the organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:DCM, 60:40 to 30:70) afforded **494-15** as a white solid (2.38 g, 75%). UPLC/MS(ES^+): m/z 504.27 $[M+H]^+$.

[0934] A mixture of **494-15** (1.87 g, 3.72 mmol), 2-methylpropane-2-sulfinamide (495 mg, 4.09 mmol) and titanium(IV) ethoxide (1.86 g, 8.18 mmol) in THF (30 mL) was heated to 70 °C (sealed vial, degassed and purged with N_2). The mixture was stirred at 70 °C overnight. EtOAc and water were added. The mixture was filtered through a pad of celite. The layers were separated, and the organic portion was dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 80:20 to 20:80) afforded **494-16** as a light yellow solid (1.00 g, 45%). UPLC/MS(ES^+): m/z 607.07 $[M+H]^+$.

[0935] *n*-Buthyllithium (1.6 M solution in THF, 2.07 mL, 3.32 mmol) was added to a solution of EtMgBr (1 M solution in THF, 1.66 mL, 1.66 mmol) in THF (5 mL), which had been pre-cooled to 0°C. After 10 mins, the mixture was cooled to -78°C. A solution of **494-16** (1.00 g, 1.66 mmol) in THF (5 mL) was added dropwise, and the reaction was stirred at -78 °C for 15 mins. The reaction was quenched with MeOH and diluted with EtOAc. The organic portion was washed with brine, and the aqueous portion extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 50:50 to 0:100) afforded **494-17** (775 mg, 70% purity A/A UV).

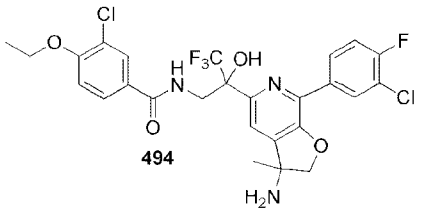
[0936] Dess-Martin periodinane (822 mg, 1.94 mmol) was added to a stirred solution of **494-17** (775 mg) in DCM (7mL). The reaction was stirred at r.t. for 2 h and quenched with a 1:1 mixture of 2M aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. After 20 mins of vigorous stirring, the layers were separated. The aqueous portion was extracted with DCM. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 50:50 to 0:100) afforded **494-18** (480 mg, 60% over 2 steps).

[0937] Trimethylsulfoxonium iodide (57.5 mg, 0.261 mmol) was added in one portion to a mixture of tBuOK (29.2 mg, 0.261 mmol) in CH_3CN (5 mL), which had been previously degassed. The mixture was further degassed and stirred at r.t. for 30 mins. The solution containing the ylide was filtered from the solid and added to a solution **494-18** (125 mg, 0.261 mmol) in CH_3CN (4 mL), which had been previously degassed. The reaction was stirred at r.t. for 15 mins. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 80:20 to 0:100) afforded **494-19** as a colorless wax (51 mg, 40%). UPLC/MS(ES^+): m/z 493.20 $[M+H]^+$.

[0938] A solution of **494-19** (51 mg) in 7M NH_3-MeOH (30 mL) was stirred at r.t. for 18 h. The volatiles were removed under reduced pressure to afford **494-20** (62 mg), which was directly in the next step.

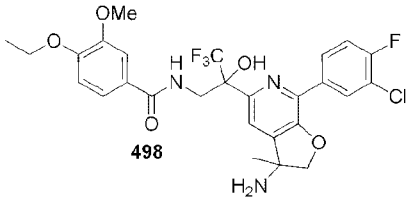
[0939] A mixture of acid (0.136 mmol), HATU (51.7 mg, 0.136 mmol) and DIPEA (43 uL, 0.246 mmol) in DCM (2 mL) was stirred at r.t. for 30 mins. A solution of **494-20** (62 mg) in DCM (2 mL) was added, and the mixture was stirred at r.t. for 1 h. The reaction was partitioned between DCM and water, and the layers were separated. The organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue afforded **494-21**.

[0940] A 4M HCl-dioxane solution (1 mL) was added to a solution of **494-21** (0.060 mmol) in MeOH (5 mL). After 30 mins, the volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography to afford **494-22**.

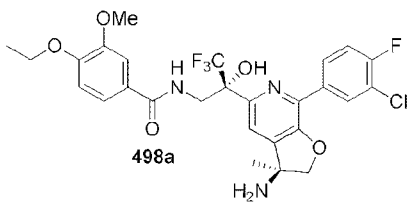


494

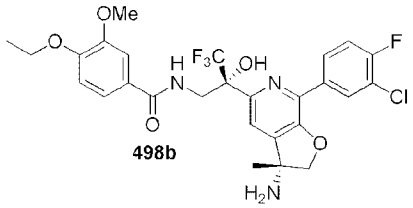
[0941] Coupling of **494-20** with 3-chloro-4-ethoxybenzoic acid followed by hydrolysis of the resulting sulfinamide afforded **494** (42% over 3 steps). UPLC/MS(ES$^+$): m/z 588.20 $[M+H]^+$.



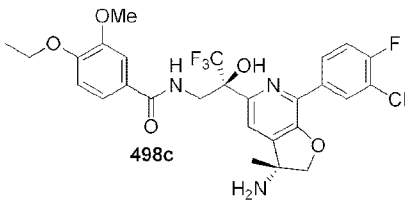
498



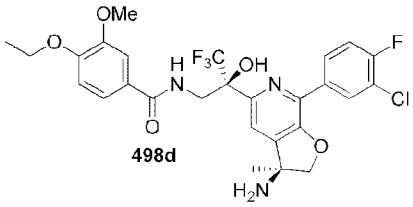
498a



498b

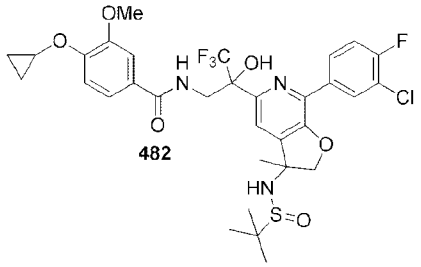


498c



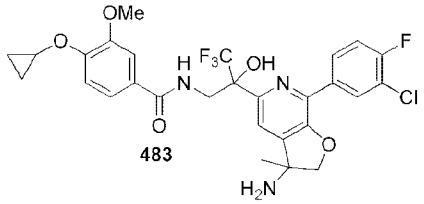
498d

[0942] Coupling of **494-20** with 4-ethoxy-3-methoxybenzoic acid followed by hydrolysis of the resulting sulfinamide afforded **498** (28% over three steps). UPLC/MS(ES$^+$): m/z 584.30 $[M+H]^+$.



482

[0943] Coupling of **494-19** with 4-cyclopropoxy-3-methoxybenzoic acid afforded **482** (68% over 2 steps). UPLC/MS(ES$^+$): m/z 700.32 $[M+H]^+$.



483

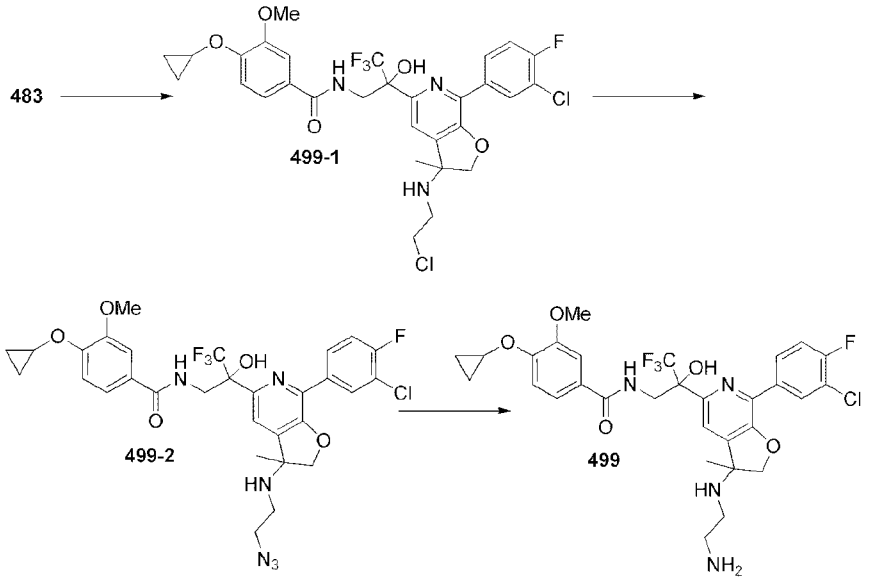
[0944] Hydrolysis of **482** according to general procedure afforded **483** as a white solid (formic acid salt, 76%). Alternatively, **483** was prepared by Suzuki coupling of **509-10A** with 3-chloro-4-fluorophenylboronic acid and subsequent hydrolysis of the resulting sulfinamide (53% over 2 steps). UPLC/MS(ES^+): m/z 596.29 $[M+H]^+$.

[0945] **483** (100 mg) was resolved by prep-HPLC [Chiralpak AD-H (25 x 2 cm, 5 um), mobile phase: n-hexane/(ethanol+0.1% ipa) 80/20% v/v, flow rate: 14 mL/min, UV detection DAD 220 nm]. Two fractions were recovered based on retention times: a mixture of **498a** and **498b**: 32 mg (t_R= 14.3 min); and a mixture of **498c** and **498d**: 31 mg (t_R= 19.0 min).

[0946] The mixture of **498a** and **498b** (32 mg) was resolved by prep-HPLC [Chiralcel OJ-H (25 x 2 cm, 5 um), mobile phase: n-hexane/(ethanol/methanol +0.1% ipa) 55/45% v/v, flow rate: 17 mL/min, UV detection DAD 220 nm]. Two fractions were recovered based on retention times: **498a**: 9.3 mg (t_R= 5.7 min). UPLC/MS(ES^+): m/z 596.25 $[M+H]^+$; and **498b**: 10.2 mg (t_R= 8.8 min). UPLC/MS(ES^+): m/z 596.25 $[M+H]^+$.

[0947] The mixture of **498c** and **498d** (31 mg) was resolved by prep-HPLC [Chiralpak IC (25 x 2 cm, 5 um), mobile phase: n-hexane/(2-propanol +0.1% ipa) 55/45% v/v, flow rate: 18 mL/min, UV detection DAD 220 nm]. Two fractions were recovered based on retention times: **498c**: 10 mg (t_R= 6.7 min). UPLC/MS(ES^-): m/z 596.25 $[M+H]^+$; and **498d**: 8 mg (t_R= 10.5 min). UPLC/MS(ES^+): m/z 596.25 $[M+H]^+$.

EXAMPLE 259
Preparation of Compound 499

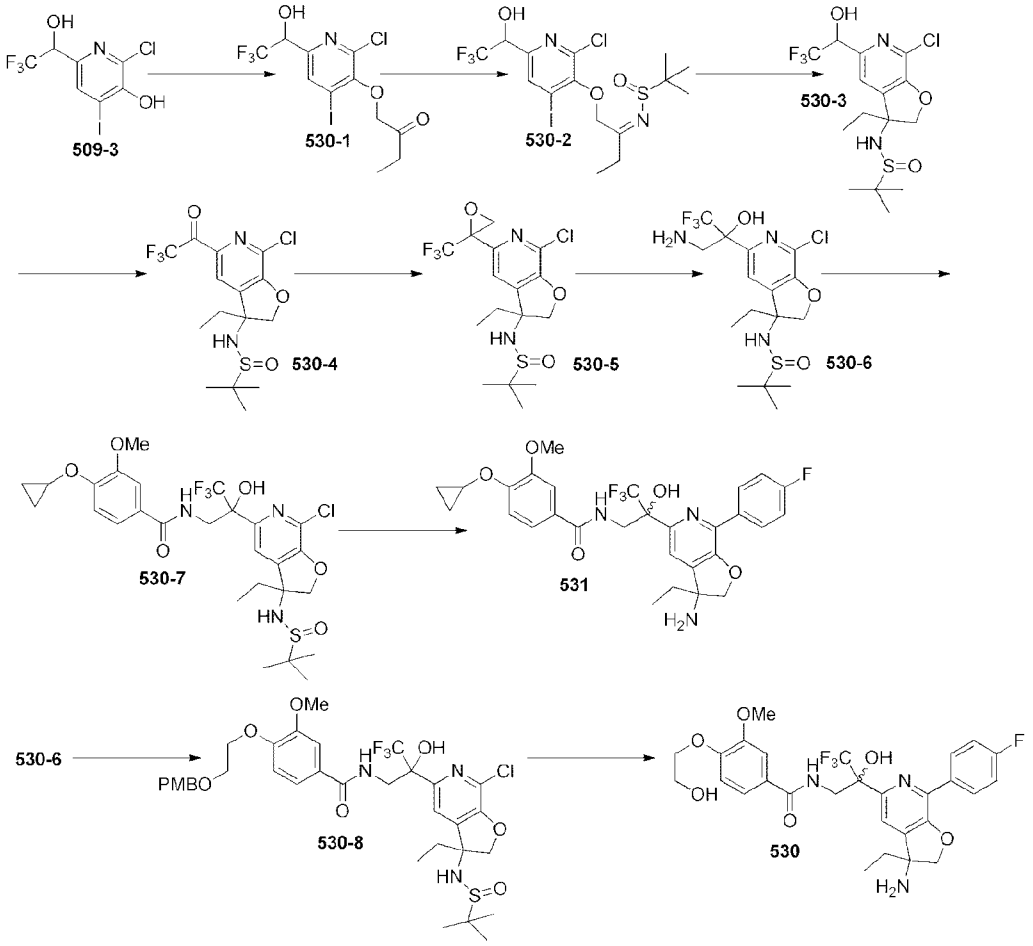


[0948] A solution of **483** (30 mg) and chloroacetaldehyde (50% aq. solution, 30 uL) in MeOH (1.5 mL) was stirred at r.t. for 1 h. $NaBH_3CN$ (2 mg) was added, and the mixture was stirred at r.t. for 18 h. The volatiles were removed under reduced pressure to afford a mixture of **499-1** and unreacted starting material (2:1), which was dissolved in DMF (1.5 mL). NaN_3 (10 mg) was added. The reaction was stirred at 70 °C for 20 h. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 80:20 to 0:100) afforded **499-2** as a pale yellow oil (20 mg). UPLC/MS(ES^+): m/z 665.30 $[M+H]^+$.

[0949] A mixture of **499-2** (20 mg) and PPh_3 (10 mg) in 2:1 THF-H_2O (1.5 mL) was stirred while heating to 60 °C for 2 h. The volatiles were removed under reduced pressure. The residue was loaded on to an SCX column and eluted with 2M NH_3-MeOH to afford **499** (7 mg). UPLC/MS(ES^+): m/z 639.30 $[M+H]^+$.

EXAMPLE 260

Preparation of Compounds 530 and 531



[0950] Compounds **530** and **531** were prepared by using a strategy that follows the procedure described for **509**.

[0951] 1-Bromo-2-butanone (300 mg, 1.98 mmol) was added to a solution of **509-3** (1.00 g, 2.84 mmol) and potassium carbonate (520 mg, 4.26 mmol) in acetone (16.5 mL). The reaction was stirred at 50°C for 1 h. The volatiles were removed under reduced pressure, and the residue was partitioned between water and EtOAc. The layers were separated. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with DCM-cyclohexane to afford **530-1** as a white solid (1.02 g, 85%). UPLC/MS(ES^+): m/z 423.93 $[M+H]^+$.

[0952] The reaction was performed in 2 batches. A mixture of **530-1** (510 mg, 1.20 mmol), 2-methylpropane-2-sulfinamide (160 mg, 1.32 mmol) and titanium(IV) ethoxide (602 mg, 2.64 mmol) in THF (9.5 mL) was heated to 70 °C (sealed vial, degassed and purged with N_2). The mixture was stirred at 70 °C for 4 h. The 2 batches were unified, and EtOAc and water were added. The mixture was filtered through a pad of celite. The layers were separated and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 95:5 to 60:40) afforded **530-2** (850 mg, 67%). UPLC/MS(ES^+): m/z 527.00 $[M+H]^+$.

[0953] EtMgBr (1M solution in THF, 1.61 mL, 1.61 mmol) was added to a solution of *n*-BuLi (1.6M solution in THF, 2.01 mL, 3.23 mmol) in dry THF (5 mL), which had been pre-cooled to 0°C. After 30 mins, the mixture was cooled to -78 °C. A solution of **530-2** (850 mg, 1.61 mmol) in dry THF (4 mL) was added dropwise, and the reaction was stirred at -78 °C for 20 mins. The reaction was quenched with MeOH and diluted with EtOAc. The organic portion was washed with water and the aqueous portion extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 30:70) afforded **530-3** as a white foam (441 mg).

[0954] Dess-Martin periodinane (932 mg, 2.20 mmol) was added to a stirred solution of **530-3** (441 mg) in DCM (5 mL). The reaction was stirred at r.t. for 1 h and quenched with a 1:1 mixture of 1M aq. $Na_2S_2O_3$ and 5% aq. $NaHCO_3$. After 20 min of vigorous stirring, the layers were separated. The aqueous portion was extracted with DCM. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 0:100) afforded **530-4** as a white foam (320 mg, 50% over two steps). UPLC/MS(ES^+): m/z 417.10 $[M+H_3O]^+$.

[0955] Trimethylsulfoxonium iodide (175 mg, 0.790 mmol) was added in one portion to a mixture of tBuOK (88 mg, 0.790 mmol) in CH_3CN (15 mL), which had been previously degassed. The mixture was further degassed and stirred at r.t. for 30 mins. The solution containing the ylide was filtered from the solid and added to a solution **530-4** (317

mg, 0.790 mmol) in CH_3CN (15 mL), which had been previously degassed. The reaction was stirred at r.t. for 1 h. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **530-5** as a colorless wax (207 mg, 64%). UPLC/MS(ES^+): m/z 413.12 $[M+H]^+$.

[0956] A solution of **530-5** (207 mg) in 7M NH_3-MeOH (142 mL) was stirred at r.t. for 2 h. The volatiles were removed under reduced pressure to afford crude **530-6** (203 mg) which was directly progressed to the next step.

[0957] A mixture of acid (0.233 mmol), HATU (86 mg, 0.252 mmol) and DIPEA (58 uL, 0.336 mmol) in DCM (2 mL) was stirred at r.t. for 30 mins. A solution of **530-6** (100 mg) in DCM (2 mL) was added. The mixture was stirred at r.t. for 1 h. The reaction was partitioned between DCM and water, and the layers were separated. The organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography to give **530-7** or **530-8**.

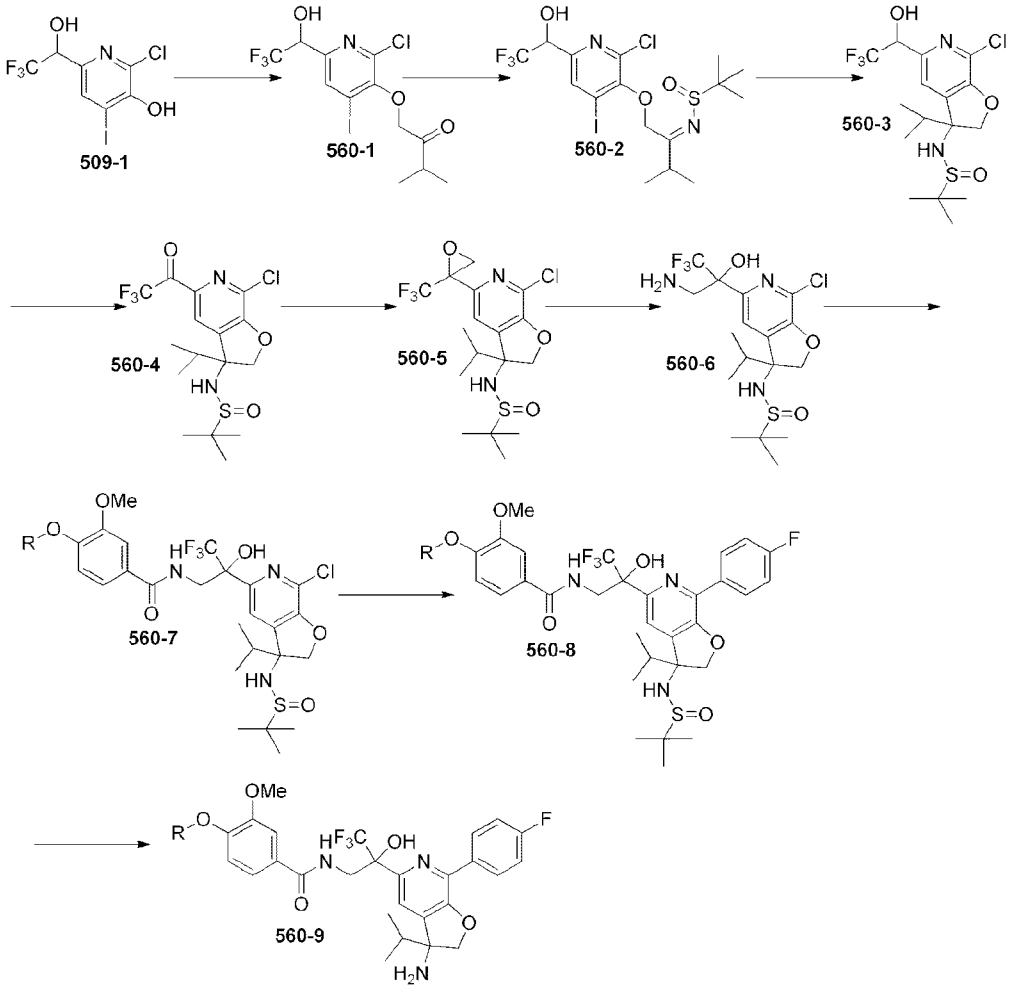
[0958] A mixture of **530-7** or **530-8** (0.134 mmol), 4-fluorophenylboronic acid (38 mg), K_3PO_4 (29 mg), KH_2PO_4 (18 mg) and $Pd(dbpf)Cl_2$ (17 mg) in a DME:EtOH:H_2O mixture (10:5:3, 3.6 mL) was degassed and warmed to 50 °C- 70 °C. DCM and water were added. The layers were separated. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography. A solution of sulfinamide (80 mg) in 4M HCl-dioxane was stirred at r.t. for 10 mins. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography.

[0959] Coupling of **530-6** with 4-cyclopropoxy-3-methoxybenzoic acid afforded **530-7**, which was subjected to Suzuki coupling and sulfinamide hydrolysis as described herein to afford **531** as a white solid (formic acid salt, 25% overall). UPLC/MS(ES^+): m/z 576.30 $[M+H]^+$.

[0960] Coupling of **530-6** with 4-(2-(4-methoxybenzyloxy)ethoxy)-3-methoxybenzoic acid afforded **530-8**, which was subjected to Suzuki coupling and protecting groups removal as described herein to afford **530** as a white powder (26% overall). UPLC/MS(ES^+): m/z 580.34 $[M+H]^+$.

EXAMPLE 261

Preparation of Compounds 560, 565 and 568



[0961] Compounds **560**, **565** and **531** were prepared by using a strategy that follows the procedure described for **509**.

[0962] 1-Bromo-3-methylbutan-2-one (659 mg, 3.99 mmol) was added to a solution of **509-3** (2.01 g, 5.71 mmol) and potassium carbonate (1.18 g, 8.56 mmol) in acetone (34 mL). The reaction was stirred at 50°C for 1 h. The volatiles were removed under reduced pressure and the residue was partitioned between water and EtOAc. The layers were separated. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was tritured with cyclohexane and the precipitate dried to afford **560-1** as a white solid (1.38 g, 55%). UPLC/MS(ES^+): m/z 438.10 $[M+H]^+$.

[0963] A mixture of **560-1** (1.38 g, 3.15 mmol), 2-methylpropane-2-sulfinamide (419 mg, 3.46 mmol) and titanium(IV) ethoxide (1.58 g, 6.93 mmol) in THF (25 mL) was heated to 70 °C (sealed vial, degassed and purged with N_2) and stirred at 70 °C for 4 h. EtOAc and water were added. The mixture was filtered through a pad of celite. The layers were separated. The organic portion was dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:Et_2O, 90:10 to 60:40) afforded **560-2** (841 mg, 50%). UPLC/MS(ES^+): m/z 541.10 $[M+H]^+$.

[0964] *n*-Buthyllithium (1.6 M solution in THF, 1.93 mL, 3.10 mmol) was added to a solution of EtMgBr (1M solution in THF, 1.55 mL, 1.55 mmol) in THF (5 mL), which had been pre-cooled to 0°C. After 10 mins, the mixture was cooled to -78°C. A solution of **560-2** (841 mg, 1.55 mmol) in THF (4 mL) was added dropwise and the reaction was stirred at -78 °C for 20 min. The reaction was quenched with MeOH and diluted with EtOAc. The organic portion was washed with brine and the aqueous portion extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 30:70) afforded **560-3** as a white foam (580 mg, 90%).

[0965] Dess-Martin periodinane (1.19 g, 2.80 mmol) was added to a stirred solution of **560-3** (580 mg, 1.40 mmol) in DCM (10 mL). The reaction was stirred at r.t. for 1 h and quenched with a 1:1 mixture of 2M aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. After 20 mins vigorous stirring, the layers were separated. The aqueous portion was extracted with DCM. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 0:100) afforded **560-4** as a white foam (520 mg, 90%).

[0966] Trimethylsulfoxonium iodide (277 mg, 1.26 mmol) was added in one portion to a mixture of tBuOK (141 mg, 1.26 mmol) in CH_3CN (20 mL), which had been previously degassed. The mixture was further degassed and stirred at r.t. for 30 mins. The solution containing the ylide was filtered from the solid and added to a solution **560-4** (520 mg, 1.26 mmol) in CH_3CN (20 mL), which had been previously degassed. The reaction was stirred at room temp for 15 min. Volatiles were removed under reduced pressure.

Chromatography of the residue (cyclohexane:EtOAc, 80:20 to 50:50) afforded **560-5** as a colorless oil (311 mg, 58%). UPLC/MS(ES^+): m/z 427.28 $[M+H]^+$.

[0967] A solution of **560-5** (311 mg, 0.730 mmol) in 7M NH_3-MeOH (140 mL) was stirred at r.t. for 2 h. The volatiles were removed under reduced pressure to afford **560-6** (313 mg), which was directly progressed to the next step.

[0968] Method A: A mixture of **560-6** (155 mg, 0.350 mmol), acid (0.350 mmol), EDC (86.3 mg, 0.450 mmol), HOBT (61.4 mg, 0.450 mmol) and TEA (97 μL, 0.700 mmol) in DCM (5 mL) was stirred at r.t. for 2 h. Water was added and the mixture was stirred at r.t. for 10 mins. The layers were separated, and the organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc) afforded **560-7**.

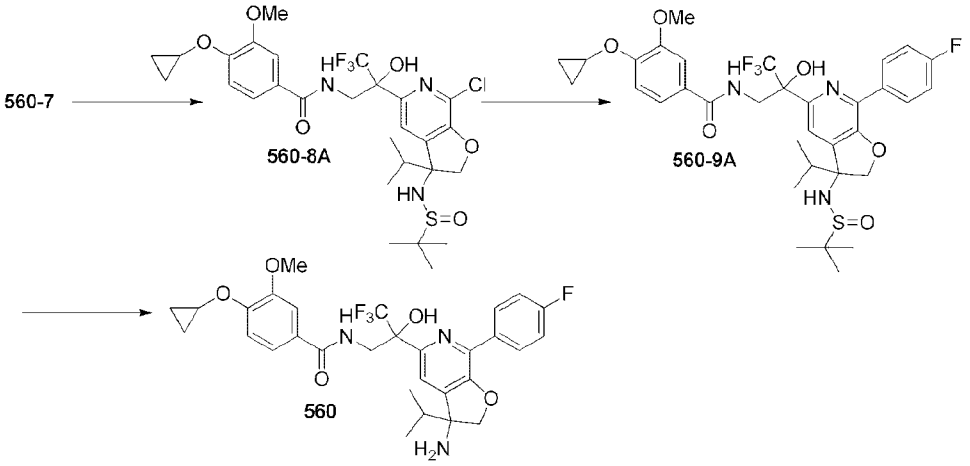
[0969] Method B: A mixture of acid (0.169 mmol), HATU (96.5 mg, 0.254 mmol), and DIPEA (59 uL, 0.338 mmol) in DMF (1 mL) was stirred at room temp for 30 min. A solution of aminol **560-6** (100 mg) in DMF (1 mL) was added and the reaction was stirred at room temp for 1h. EtOAc was added and the organic portion was washed twice with sat. aq. NH_4Cl solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **560-7**, which was directly progressed to the next step.

[0970] A mixture of **560-7** (0.250 mmol), 4-fluorophenylboronic acid (104 mg, 0.740 mmol), K_3PO_4 (106 mg, 0.500 mmol), KH_2PO_4 (68 mg, 0.500 mmol) and $Pd(dbpf)Cl_2$ (11 mg, 0.017 mmol) in a DME:EtOH:H_2O mixture (5:3:1, 18 mL) was degassed and warmed to 80 °C. After 3 h, EtOAc was added. The organic portion was washed with sat. aq. NH_4Cl solution, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc) afforded **560-8**.

[0971] Method A: Hydrochloric acid (4M solution in dioxane, 2 mL) was added to a solution of **560-8** (152 mg) in MeOH (4 mL). After 10 mins, the volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography to afford **560-9**.

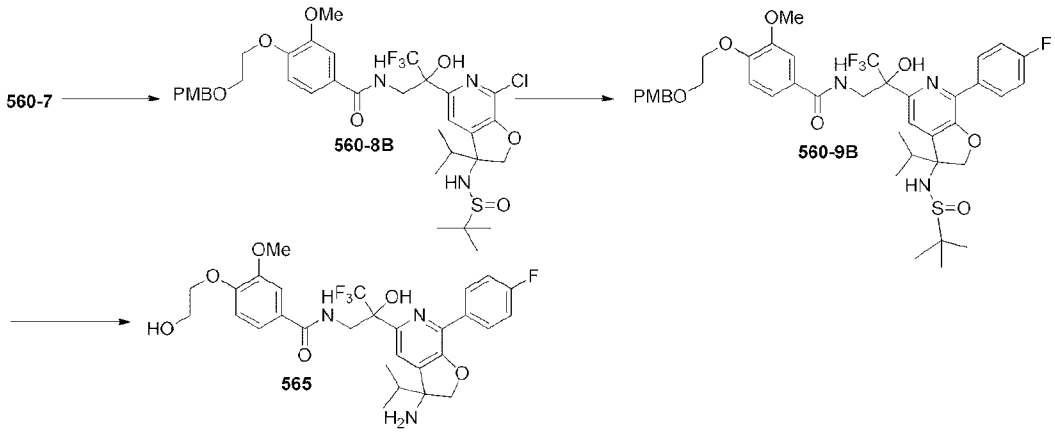
[0972] Method B: A solution of **560-8** (0.089 mmol) in 4M HCl-dioxane (4 mL) was stirred at r.t. for 40 mins. The volatiles were removed under reduced pressure. The

residue was purified by reverse phase chromatography (water-CH_3CN, 100:0 to 50:50) to afford **560-9**.



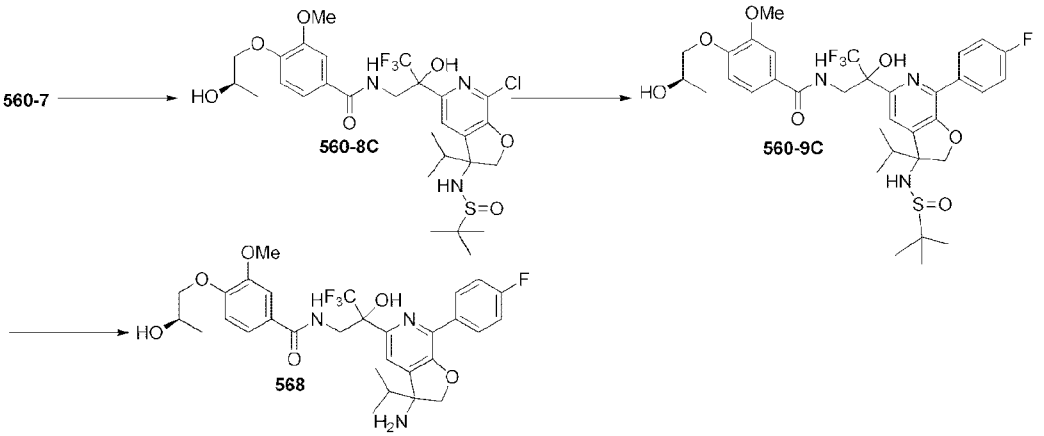
[0973] Coupling of **560-7** with 4-cyclopropoxy-3-methoxybenzoic acid according to Method A afforded **560-8A** (70%). UPLC/MS(ES^+): m/z 634.33 $[M+H]^+$.

[0974] Suzuki coupling of **560-8A** with 4-fluorophenylboronic acid followed by sulfinamide hydrolysis (Method A) afforded **560** as a white solid (43% over 2 steps). UPLC/MS(ES^+): m/z 590.40 $[M+H]^+$.



[0975] Coupling of **560-7** with 4-(2-(4-methoxybenzyloxy)ethoxy)-3-methoxybenzoic acid according to Method B afforded **560-8B** which was progressed to the next step without any purification.

[0976] Suzuki coupling of **560-8B** with 4-fluorophenylboronic acid followed by sulfinamide hydrolysis (Method B) afforded **565** as an off-white solid (13% overall). UPLC/MS(ES^+): m/z 594.40 $[M+H]^+$.

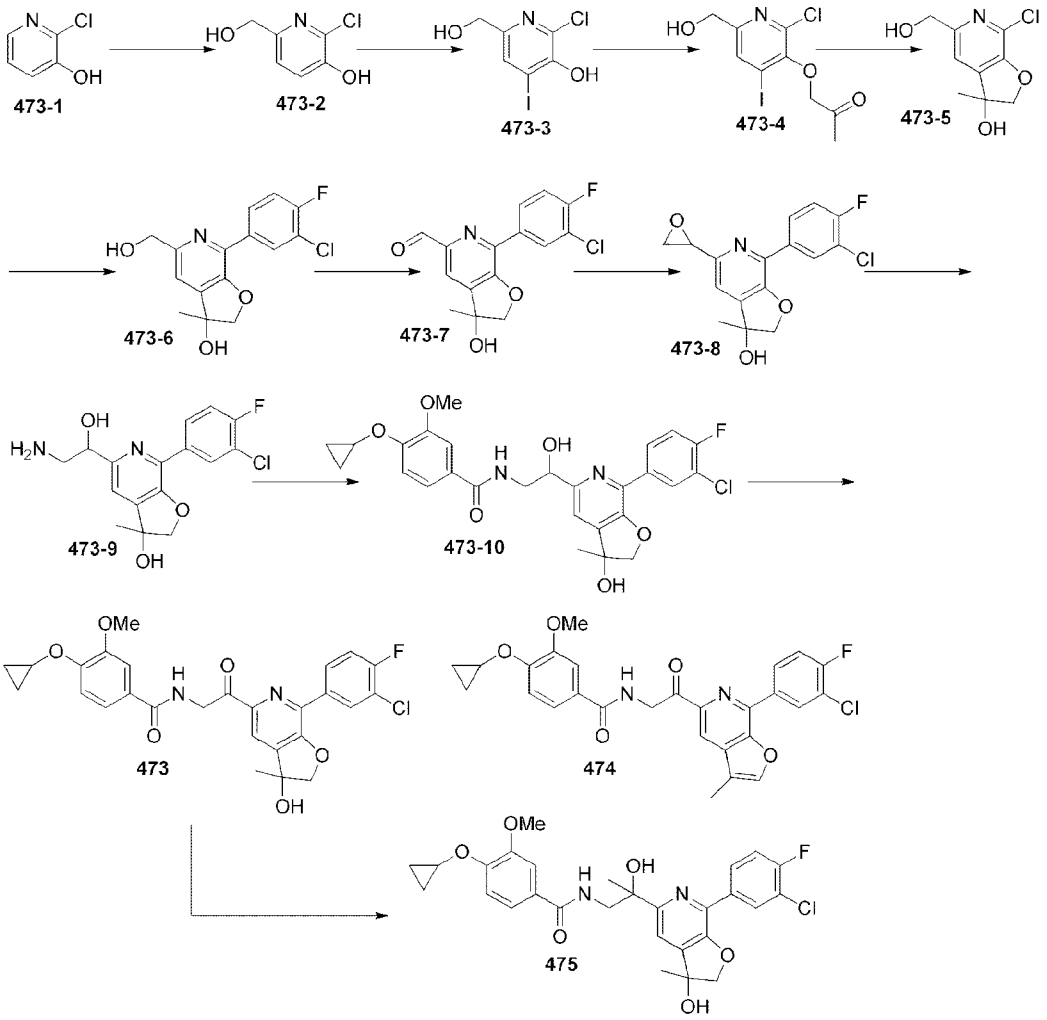


[0977] Coupling of **560-7** with 4-[(2R)-2-hydroxypropoxy]-3-methoxybenzoic acid according to Method A afforded **560-8C** (43%).

[0978] Suzuki coupling of **560-8C** with 4-fluorophenylboronic acid followed by sulfinamide hydrolysis (Method A) afforded **568** (52% overall). UPLC/MS(ES^+): m/z 608.50 $[M+H]^+$.

EXAMPLE 262

Preparation of Compounds 473, 474 and 475



[0979] Formaldehyde (37% aq. solution, 30.4 mL, 407 mmol) was added in 4 portions to a mixture of **473-1** (15.0 g, 116 mmol) and $NaHCO_3$ (14.6 g, 174 mmol) in water (120 mL) which had been pre-heated to 90°C. The reaction was stirred at 90 °C for 16 h. Additional formaldehyde (37% aq. solution, 232 mmol) was added and the reaction was stirred at 90°C for 1 h. After being cooled to r.t., the reaction was concentrated under reduced pressure. The crude **473-2** was directly used in the next step.

[0980] Iodine (25 g, 98.4 mmol) was added to a mixture of **473-2** (13 g) and K_2CO_3 (22.0 g, 159 mmol) in water (100 mL). The mixture was stirred at r.t. for 4 h. The reaction was poured in to a 1M aq. HCl solution, which had been pre-cooled to 0 °C. The

aqueous portion was extracted with EtOAc (3x). The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 0:100) afforded **473-3** as an off-white solid (5.4 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.41 (s, 2 H), 7.77 (s, 1 H), 10.37 (s, 1 H).

[0981] Chloroacetone (750 uL) was added to a mixture of **473-3** (2.41 g) and K_2CO_3 (1.69 g) in acetone (50 mL). The mixture was warmed to 50 °C and stirred at 50 °C for 16 h. The volatiles were removed under reduced pressure. The residue was partitioned between EtOAc and water. The layers were separated and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Trituration of the residue with DCM:cyclohexane afforded **473-4** as a white solid (2.33 g). UPLC/MS(ES$^+$): m/z 342.00 $[M+H]^+$.

[0982] EtMgBr (1M solution in 2-methyltetrahydrofuran, 4.39 mL, 4.39 mmol) was added to a solution of *n*-BuLi (1.6 M solution in hexane, 5.48 mL, 8.78 mmol) in THF (10 mL), which had been pre-cooled to 0 °C. After 10 mins, the mixture was cooled to -78 °C. A solution of **473-4** (1.35 g, 3.96 mmol) in THF (8 mL) was added dropwise and the reaction was stirred at -78 °C for 2 h. The reaction was quenched with MeOH and diluted with EtOAc. The organic portion was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 70:30 to 0:100) afforded **473-5** (619 mg, 72%). UPLC/MS(ES$^+$): m/z 216.10 $[M+H]^+$.

[0983] Alcohol **473-5** was split in 2 batches (2 x 305 mg) which were separately processed as described below. The 2 reactions were unified for work-up and purification procedures. A mixture of **473-5** (305 mg, 1.42 mmol), (3-chloro-4-fluorophenyl)boronic acid (617 mg, 3.54 mmol), $Pd(dppf)Cl_2$ (104 mg, 0.142 mmol) and sodium carbonate (2M aq. solution, 2.49 mL, 5.00 mmol) in DCE (10 mL) was degassed and stirred with heating to 100°C under microwave irradiation for 1.5 h. DCM and water were added. The layers were separated and the aqueous portion was extracted with DCM. The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 50:50 to 0:100) afforded **473-6** (315

mg, 35%) and some unreacted **473-5** (94 mg). **473-6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.74 (s, 3 H), 4.48 (d, *J*=10.3 Hz, 1 H), 4.66 (d, *J*=10.3 Hz, 1 H), 4.75 (d, *J*=14.1 Hz, 1 H), 4.79 (d, *J*=14.1 Hz, 1 H), 7.22 (s, 1 H), 7.23 (t, *J*=8.7 Hz, 1 H), 8.18 (ddd, *J*=8.7, 4.7, 2.3 Hz, 1 H), 8.36 (dd, *J*=7.3, 2.3 Hz, 1 H).

[0984] Dess-Martin periodinane (365 mg, 0.861 mmol) was added to a stirred solution of **473-6** (315 mg, 1.02 mmol) in DCM (5 mL). The reaction was stirred at r.t. for 1.5 h. A 1:1 1M aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$ mixture was added to the reaction and the mixture was stirred at r.t. for 20 mins. The layers were separated and the aqueous portion was extracted with DCM. The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 90:10 to 0:100) afforded **473-7** (266 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.57 (s, 3 H), 4.60 (d, *J*=10.3 Hz, 1 H), 4.82 (d, *J*=10.3 Hz, 1 H), 7.30 (t, *J*= 8.7 Hz, 1 H), 8.02 (s, 1 H), 8.32 (ddd, *J*=8.7, 4.6, 2.3 Hz, 1 H), 8.50 (dd, *J*=7.3, 2.3 Hz, 1 H), 10.11 (s, 1 H).

[0985] Trimethylsulfoxonium iodide (191 mg, 0.866 mmol) was added to a solution of tBuOK (97 mg, 0.866 mmol) in DMSO (3 mL). The mixture was stirred at r.t. for 30 mins. A solution of **473-7** (266 mg, 0.866 mmol) in DMSO (3 mL) was added and the mixture was stirred at r.t. for 30 mins. The reaction was diluted with EtOAc and water. The layers were separated and the aqueous portion was extracted with EtOAc. The combined organic portions were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 80:20 to 0:100) afforded **473-8** (81 mg, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.75 (2 x s, 3 H), 3.00-3.04 (m, 1 H), 3.24 (dd, *J*=5.1, 4.4 Hz, 1 H), 4.11- 4.15 (m, 1 H) 4.48 (d, *J*=10.0 Hz, 1 H), 4.68 (d, *J*=10.0 Hz, 1 H), 7.20 - 7.28 (m, 2 H), 8.21 - 8.28 (m, 1 H), 8.40 - 8.46 (m, 1 H).

[0986] A solution of **473-8** (81 mg, 0.252 mmol) in 7M NH_3-MeOH (50 mL) was stirred at r.t. for 20 h. The volatiles were removed under reduced pressure. Crude **473-9** was directly used in to the next step.

[0987] A mixture of 4-cyclopropoxy-3-methoxybenzoic acid (63 mg, 0.302 mmol), HATU (144 mg, 0.378 mmol) and DIPEA (88 uL, 0.504 mmol) in DMF (1 mL) was stirred at r.t. for 30 mins. A solution of **473-9** in DMF (2 mL) was added and the mixture

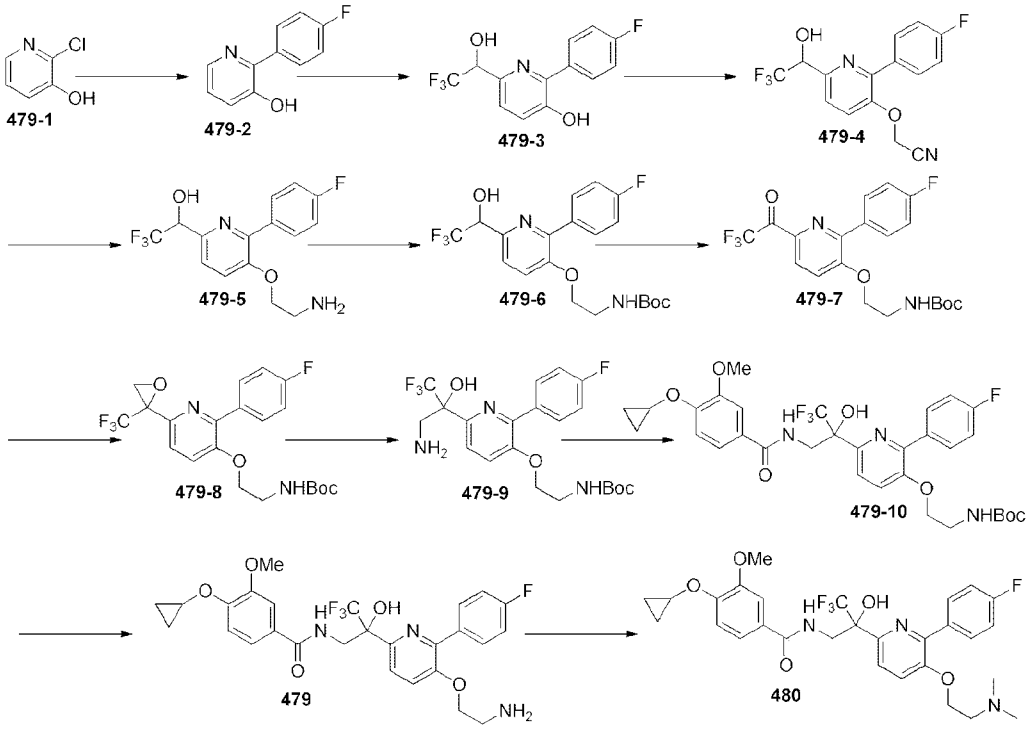
was stirred at r.t. for 1 h. EtOAc was added The organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc:MeOH, 100:0 to 80:20) afforded **473-10** (82 mg). UPLC/MS(ES^+): m/z 529.30 $[M+H]^+$.

[0988] Dess-Martin periodinane (65 mg, 1.57 mmol) was added to a solution of **473-10** (80 mg, 0.151 mmol) in DCM (5 mL). The reaction was stirred at r.t. for 10 mins. A 1:1 1M aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$ mixture was added. The mixture was stirred at r.t. for 20 mins. The layers were separated and the aqueous portion was extracted with DCM. The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 70:30 to 0:100) afforded **473** (24 mg, 18% over 3 steps) and **474** (19 mg, 15% over 3 steps). **473:** white solid; UPLC/MS(ES^+): m/z 527.30 $[M+H]^+$. **474:** off-white solid; UPLC/MS(ES^+): m/z 509.30 $[M+H]^+$.

[0989] MeMgBr (3M solution in Et_2O, 30 uL, 0.090 mmol) was added to a solution of **473** (16 mg, 0.030 mmol) in THF (2.5 mL). The reaction was stirred at r.t. under N_2 atmosphere for 30 mins. EtOAc and water were added. The layers were separated and the aqueous portion extracted with EtOAc. The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 30:70 to 0:100) afforded **475** as a white solid (6 mg, 37%). UPLC/MS(ES^+): m/z 543.30 $[M+H]^+$.

EXAMPLE 263

Preparation of Compounds 479 and 480



[0990] A mixture of **479-1** (1.00 g, 7.75 mmol), (4-fluorophenyl) boronic acid (2.17 g, 15.5 mmol), $Pd(dppf)Cl_2$ (566 mg, 0.775 mmol) and sodium carbonate (2M aq solution, 7.75 mL, 15.5 mmol) in DCE (70 mL) was degassed and stirred with heating to 85 °C overnight. Water and DCM were added. The layers were separated and the organic phase was concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **479-2** as a white solid (990 mg, 67%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.16 - 7.29 (m, 3 H), 7.34 (dd, *J*=8.2, 1.4 Hz, 1 H), 8.04 - 8.12 (m, 2 H), 8.15 (dd, *J*=4.4, 1.4 Hz, 1 H), 10.22 (s, 1 H).

[0991] Potassium carbonate (1.15 g, 8.34 mmol) and trifluoroacetaldehyde ethyl hemiacetal (740 uL, 6.26 mmol) were added to a suspension of **479-2** (790 mg, 4.17 mmol) in water (15 mL). The mixture was stirred at 100 °C overnight. Additional trifluoroacetaldehyde ethyl hemiacetal (327 uL, 2.70 mmol) was added and the reaction was stirred at 100 °C overnight. The reaction was cooled to 0°, neutralized with 1M aq HCl solution and extracted with EtOAc. The organic portion was dried with Na_2SO_4, filtered and

concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **479-3** as a white solid (1.08 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.00 - 5.14 (m, 1 H), 6.83 (d, *J*=6.3 Hz, 1 H), 7.23 - 7.30 (m, 2 H), 7.42 (s, 2 H), 8.07 - 8.15 (m, 2 H), 10.48 (s, 1 H).

[0992] NaH (195 mg, 4.87 mmol) was added to a stirred solution of **479-3** (1.08 g, 3.75 mmol) in DMF (11 mL), which had been pre-cooled to 0° C. The mixture was stirred at 0° C for 10 mins, then warmed to r.t. and stirred for 30 mins. The reaction was cooled to 0° C and chloroacetonitrile (260 uL, 4.13 mmol) was added dropwise. The mixture was allowed to gradually reach r.t. and stirring was continued for 20 h. EtOAc and sat. aq. NH_4Cl were added. The layers were separated. The organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **479-4** as a colorless wax (1.10 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.12 - 5.25 (m, 1 H), 5.33 (s, 2 H), 7.02 (d, *J*=6.0 Hz, 1 H), 7.30 - 7.37 (m, 2 H), 7.67 (d, *J*=8.7 Hz, 1 H), 7.83 (d, *J*=8.7 Hz, 1 H), 7.91 - 7.98 (m, 2 H).

[0993] $LiAlH_4$ (1M solution in THF, 3.17 mL, 3.17 mmol) was added dropwise to a stirred solution of **479-4** (940 mg, 2.80 mmol) in THF (20 mL) which had been pre-cooled to 0°C. The mixture was warmed to r.t. and stirred for 30 mins. The reaction was cooled to 0 °C. Water (3 mL) was slowly added, followed by 1N aq. NaOH solution (3 mL) and more water (9 mL). EtOAc was then added, and the layers were separated. The organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude **479-5** was directly used in the next step.

[0994] Di-tert-butyl dicarbonate (610 mg, 2.80 mmol) and DMAP (34.0 mg, 0.280 mmol) were added to a solution of **479-5** in DCM (10 mL). After 2 h, water was added and the layers were separated. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforted a di-protected compound. This di-protected compound was dissolved in CH_3CN (2 mL). A 1M aq. NaOH solution (2 mL) was added and the reaction was stirred at 50 °C for 1 h. Most of the solvents were removed under reduced pressure and the pH of the resulting solution was adjusted to 7 with 1M aq. HCl. The aqueous portion was extracted

with EtOAc. The organic layer was dried with Na_2SO_4, filtered and evaporated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **479-6** as a white solid (235 mg). UPLC/MS(ES^+): m/z 431.38 $[M+H]^+$.

[0995] Dess-Martin periodinane (274 mg, 0.640 mmol) was added to a stirred solution of **479-6** (235 mg, 0.540 mmol) in DCM (9 mL). The reaction was stirred at r.t. under N_2 atmosphere overnight and quenched with a 1:1 2M aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$ mixture. After 30 mins, the layers were separated. The organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **479-7** as a white solid (144 mg, 62%). UPLC/MS(ES^+): m/z 447.29 $[M+H_3O]^+$.

[0996] Trimethylsulfoxonium iodide (57.0 mg, 0.260 mmol) was added to a solution of tBuOK (29.0 mg, 0.260 mmol) in DMSO (3 mL). The mixture was stirred at r.t. for 30 mins. A solution of **479-7** (112 mg, 0.260 mmol) in THF (3 mL) was added, and the mixture was stirred at r.t. for 30 mins. The mixture was diluted with EtOAc and water, and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic portions were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **479-8** (44 mg) and unreacted **479-7** (53 mg). **479-8**: UPLC/MS(ES^+): m/z 443.29 $[M+H]^+$.

[0997] A solution of **479-8** (44 mg) in 7M NH_3-MeOH (2 mL) was stirred with heating to 45° C for 40 mins. The volatiles were removed under reduced pressure. Crude **479-9** (45 mg) was directly used in the next step.

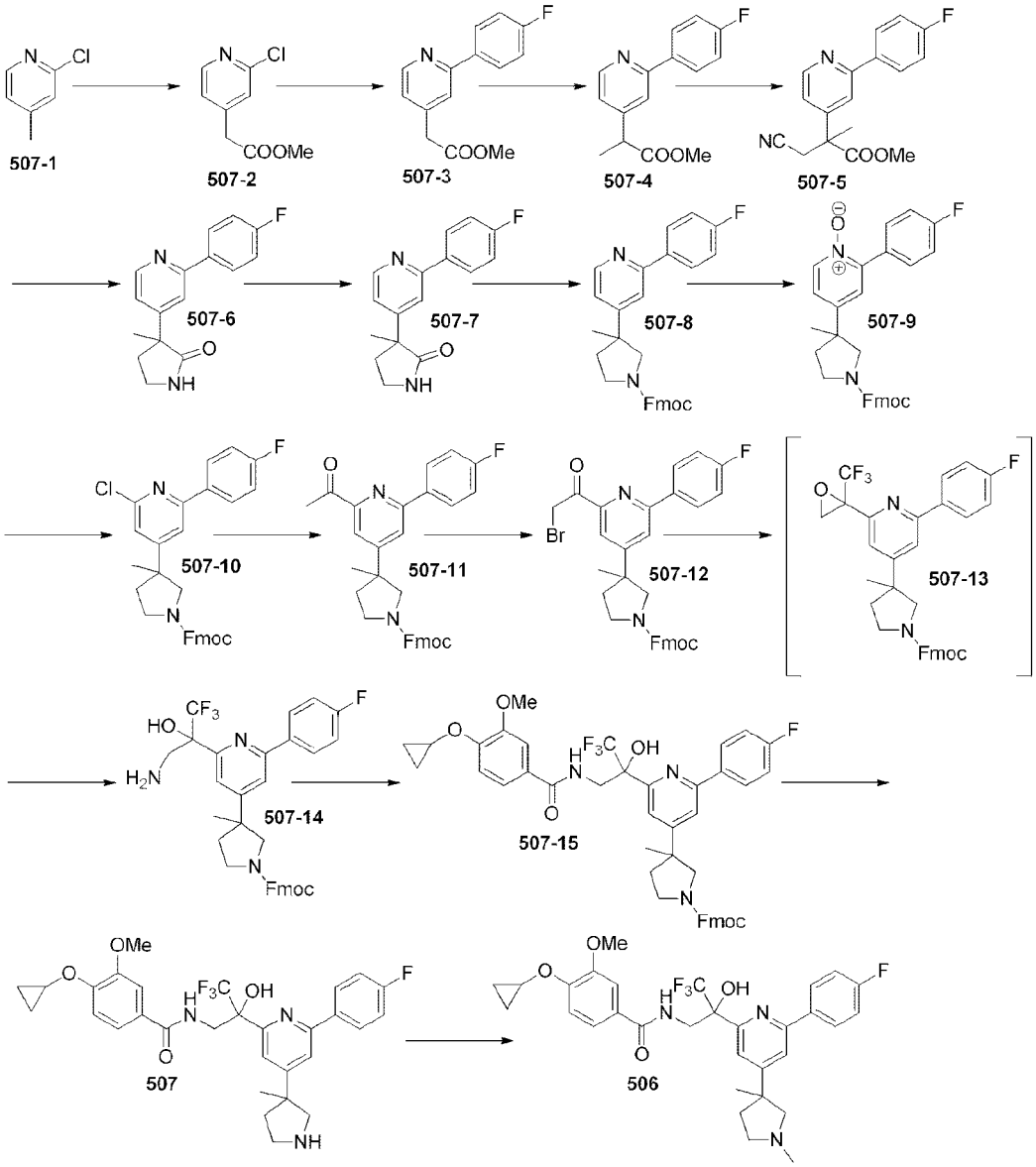
[0998] A mixture of **479-9** (45 mg), EDC (23 mg, 0.12 mmol), HOBT (17 mg, 0.12 mmol), TEA (33 uL, 0.24 mmol) and 4-cyclopropoxy-3-methoxybenzoic acid (20 mg, 0.098 mmol) in DCM (1 mL) was stirred at r.t. for 2 h. Water was added, and the mixture was stirred for 10 mins. The layers were separated. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (cyclohexane:EtOAc, 100:0 to 40:60) afforded **479-10** as a white solid (53 mg). UPLC/MS(ES^+): m/z 650.40 $[M+H]^+$.

[0999] TFA (350 uL) was added to a solution of **479-10** (53 mg, 0.081 mmol) in DCM (2 mL). The mixture was stirred at r.t. for 30 mins. Water was added, and the layers were separated. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water: CH_3CN, 100:0 to 40:60) to afford **479** (A/1587/35/1) as a white solid (30 mg, 67%). UPLC/MS(ES^+): m/z 550.32 $[M+H]^+$.

[1000] Formaldehyde (37% aq. solution, 3 uL) was added to a solution of **479** (17 mg, 0.030 mmol) in MeOH (200 uL). The mixture was stirred at r.t. for 3 h. Sodium cyanoborohydride (1.8 mg, 0.030 mmol) was added, and the reaction was stirred at r.t. for 10 mins. The solvents were removed under reduced pressure. Water and DCM were added. The layers were separated. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (DCM:MeOH, 100:0 to 90:10) afforded **480** as a white solid (2 mg, 10%). UPLC/MS(ES^+): m/z 578.40 $[M+H]^+$.

EXAMPLE 264

Preparation of Compounds 506 and 507



[1001] LDA (2M solution, 39.4 mL, 78.7 mmol) was added to a solution of **507-1** (5.00 g, 39.4 mmol) in dry THF (100 mL), which had been pre-cooled to -78° C. The mixture was stirred at -78 °C for 1 h. Dimethylcarbonate (8.0 mL, 95.0 mmol) was added, and the temperature was raised to 0 °C. The reaction was stirred at 0 °C for 30 mins and then partitioned between EtOAc and sat. aq. NH_4Cl solution. The organic phase was purified by

chromatography (cyclohexane:EtOAc, 100:0 to 80:20) to recover **507-2** as a yellow oil (4.8 g, 66%).

[1002] Tetrakis(triphenylphosphine)-palladium(0) (1.18 g, 1.03 mmol) was added to a mixture of **507-2** (3.8 g, 20.5 mmol), (4-fluorophenyl)boronic acid (4.30 g, 30.8 mmol) and Na_2CO_3 (5.4 g, 51.3 mmol) in 1:1 dioxane-H_2O (60 mL), which had been previously degassed by bubbling N_2. The reaction was stirred at 120 °C for 2 h. UPLC analysis of the reaction showed that Suzuki coupling was followed by hydrolysis of the methyl ester. The mixture was concentrated under reduced pressure. The residue was dissolved in MeOH and conc. H_2SO_4 was added. The reaction was warmed to 50 °C and stirred at 50 °C for 2 h. EtOAc was added. The mixture was cooled to 0 °C and quenched with a sat. aq. K_2CO_3 (final pH 8). The layers were separated, and the organic portion was concentrated under reduced pressure. Chromatography of the residue (DCM:cyclohexane, 50:50) afforded **507-3** (2.66 g, 53%). UPLC/MS(ES^+): m/z 246.20 $[M+H]^+$.

[1003] LHMDS (1M solution in THF, 11.9 mL, 11.9 mmol) was added dropwise to a solution of **507-3** (2.66 g, 10.8 mmol) in THF (40 mL), which had been pre-cooled to -78 °C. The mixture was stirred at -78 °C for 1 h. Methyl iodide (740 μL, 11.9 mmol) was added and the reaction was allowed to gradually reach r.t. After being stirred at r.t. for 16 h, the reaction was cooled to 0 °C and quenched with sat. aq. $NaHCO_3$ solution. The aqueous portion was extracted with EtOAc. The organic layer was concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 80:20) afforded **507-4** (1.70 g, 61%). UPLC/MS(ES^+): m/z 260.10 $[M+H]^+$.

[1004] LHMDS (1M solution in THF, 7.22 mL, 7.22 mmol) was added dropwise to a solution of **507-4** (1.70 g, 6.56 mmol) in THF (12 mL), which had been pre-cooled to -78 °C. The mixture was stirred at -78 °C for 1 h. A solution of bromoacetonitrile (503 uL, 7.22 mmol) in THF (12 mL) was added, and the reaction was allowed to gradually reach r.t. After being stirred at r.t. for 2 h, the reaction was cooled to 0 °C and quenched with sat. aq. NH_4Cl solution. The aqueous portion was extracted with EtOAc. The organic layer was concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 50:50) afforded **507-5** (1.91 g, 98%). ^1H NMR (400 MHz, DMSO-d_6) d ppm 1.76 (s, 3 H),

3.37 (d, *J*=17.0 Hz, 1 H), 3.44 (d, *J*=17.0 Hz, 1 H), 3.72 (s, 3 H), 7.31 - 7.40 (m, 3 H), 7.90 (d, *J*=1.5 Hz, 1 H), 8.15 - 8.23 (m, 2 H), 8.68 (d, *J*=5.3 Hz, 1 H).

[1005] Nickel Raney (0.600 mmol) was added to a solution of **507-5** (1.91 g, 6.40 mmol) in MeOH (50 mL). The reaction was stirred at 60 °C under H_2 atmosphere (5 bar) for 3 h. The reaction was filtered through a pad of celite and the solution was refluxed for 4 h. DIPEA (1 eq.) was added, and the mixture was refluxed for 30 mins. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc. The organic portion was washed with sat. aq. $NaHCO_3$ solution, dried and concentrated under reduced pressure. Chromatography of the residue (EtOAc:MeOH, 100:0 to 95:5) afforded **507-6** (870 mg, 50%). UPLC/MS(ES^+): m/z 271.20 $[M+H]^+$.

[1006] $LiAlH_4$ (2M solution in THF, 3.03 mL, 6.06 mmol) was added to a solution of **507-6** (820 mg, 3.03 mmol) in THF (18 mL), which had been pre-cooled to 0 °C. The reaction was stirred at r.t. for 1 h, then warmed to 70 °C and stirred at 70 °C for 30 mins. The reaction was cooled to 0 °C and Na_2SO_4•10 H_2O and Et_2O were added. The mixture was filtered through a pad of celite, and the solution concentrated under reduced pressure. Crude **507-7** (720 mg) was directly used in the next step.

[1007] A mixture of **507-7** (720 mg) and sat. aq. $NaHCO_3$ solution (16 mL) in dioxane (9 mL) was cooled to 0 °C. A solution of FmocCl (764 mg, 2.95 mmol) in dioxane (9 mL) was added, and the reaction was allowed to reach r.t. After 1 h, the reaction was diluted with EtOAc. The organic portion was washed with water and brine, dried and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 50:50) afforded **507-8** (1.10 g, 49% over 2 steps). UPLC/MS(ES^+): m/z 479.40 $[M+H]^+$.

[1008] *m*-Chloroperbenzoic acid (797 mg, 4.62 mmol) was added to a solution of **507-8** (1.10 g, 2.31 mmol) in DCM (30 mL). The reaction was stirred at r.t. overnight. EtOAc was added. The organic phase was washed with sat. aq. K_2CO_3 sol and concentrated under reduced pressure. Crude **507-9** (1.17 g) was directly used in the next step.

[1009] A mixture of **507-9** (1.17 g) and $POCl_3$ (50 mL) was stirred at 60 °C for 12 h. The volatiles were removed under reduced pressure. EtOAc and water were added, and the mixture was basified by adding sat. aq. $KHCO_3$ solution (final pH 8). The layers were separated, and the organic portion was concentrated under reduced pressure.

Chromatography of the residue (cyclohexane:EtOAc, 90:10 to 0:100, then EtOAc:MeOH, 80:20) afforded **507-10** (700 mg, 58%) and unreacted starting material **507-9** (300 mg). **507-10**: UPLC/MS(ES^+): m/z 513.27 $[M+H]^+$.

[1010] Tributyl[1-ethoxyethenyl]stannane (552 uL, 1.63 mmol) and $Pd(PPh_3)Cl_2$ (199 mg, 0.284 mmol) were sequentially added to a solution of **507-10** (700 mg, 1.36 mmol) in dioxane (4 mL), which had been previously degassed by bubbling N_2. The mixture was further degassed and stirred at 100 °C for 1 h. After being cooled to r.t., the mixture was partitioned between EtOAc and sat. aq. KF solution. The layers were separated. The organic portion was washed with 1M aq. HCl solution, dried and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 80:20) afforded **507-11** (670 mg, 95%). UPLC/MS(ES^+): m/z 521.32 $[M+H]^+$.

[1011] Hydrobromic acid (33% solution in AcOH, 377 uL, 2.08 mmol) and bromine (53 uL, 1.04 mmol) were added to a solution of **507-11** (541 mg, 1.04 mmol) in dioxane (10 mL), which had been pre-cooled to 0 °C. The reaction was stirred at r.t. for 2 h. Additional bromine (0.5 eq., 27 μL) was added and stirring was prolonged for 2 h. The reaction was quenched with water and neutralized with sat. aq. $NaHCO_3$ solution. The aqueous portion was extracted with DCM. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue (DCM:EtOAc, 60:40) afforded **507-12**.

[1012] $TMSCF_3$ (430 mg, 3.00 mmol) and CsF (91 mg) were sequentially added to a solution of **507-12** (90 mg) in THF (12 mL). The reaction was stirred at r.t. for 20 mins. The mixture was partitioned between EtOAc and 1M aq. HCl solution. The layers were separated, and the organic portion was concentrated under reduced pressure. Crude **507-13** was directly used in the next step.

[1013] A solution of **507-13** in ammonia (7M solution in MeOH, 5 mL) was stirred at r.t. for 1.5 h. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc-MeOH, 60:30:10) afforded **507-14** (44 mg). UPLC/MS(ES^+): m/z 606.40 $[M+H]^+$.

[1014] A solution of 4-cyclopropoxy-3-methoxybenzoic acid (20.0 mg, 0.095 mmol), DIPEA (50 uL, 0.270 mmol) and HATU (39.0 mg, 0.102 mmol) in DCM (4 mL) was

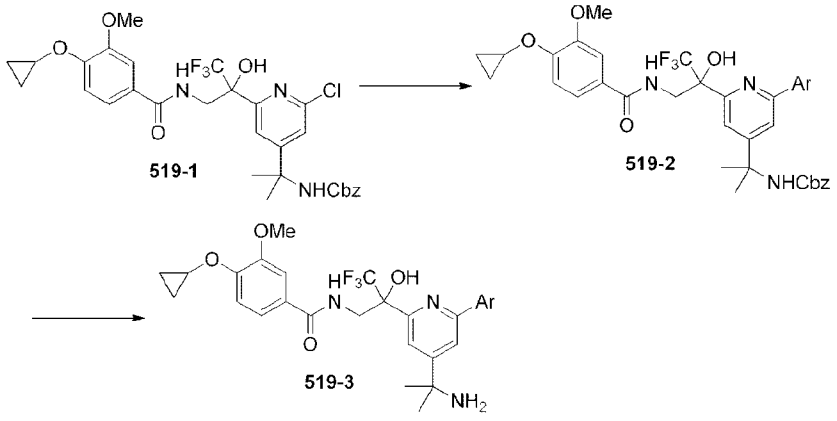
stirred at r.t. for 30 mins. A solution of **507-14** (41.0 mg, 0.068 mmol) in DCM (1 mL) was added. The reaction was stirred for 16 h, quenched with MeOH (10 mL) and stirred for 1 h. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 60:40) afforded **507-15** as a colorless oil (23 mg, 42%). UPLC/MS(ES^+): m/z 796.50 $[M+H]^+$.

[1015] Morpholine (1 mL) was added to a solution of **507-15** (23 mg, 0.029 mmol) in DMF (1 mL), and the solution was stirred for 1 h. The volatiles were removed under reduced pressure. Chromatography of the residue (NH-cartridge, cyclohexane:EtOAc:MeOH, 100:0:0 to 60:30:10) afforded **507** (10 mg, 60%). UPLC/MS(ES^+): m/z 574.30 $[M+H]^+$.

[1016] Formaldehyde (37% aq. solution, 30 uL, 0.350 mmol) and $NaBH(OAc)_3$ (22.0 mg, 0.105 mmol) were added to a solution of **507** (4.0 mg, 0.007mmol) in DCM (2 mL). The reaction was vigorously stirred overnight, quenched with 1M aq. NaOH solution and extracted with DCM. The volatiles were removed under reduced pressure. The residue was purified by SCX-chromatography to afford **506** as a colorless oil (2.4 mg, 58%). UPLC/MS(ES^+): m/z 588.50 $[M+H]^+$.

EXAMPLE 265

Preparation of Compounds 519, 520, 521, 527 and 523



General Suzuki coupling conditions

[1017] Method A: A mixture of **519-1** (70 mg, 0.112 mmol), boronate/boronic acid (0.170 mmol), KH_2PO_4 (15.3 mg, 0.112 mmol), K_3PO_4 (24.0 mg, 0.112 mmol) and $Pd(dbpf)Cl_2$ (7.5 mg, 0.011 mmol) in DME:H_2O:EtOH (1:0.5:0.3, 1.8 mL) was degassed and

heated to 50 °C for 24 h. The mixture was partitioned between Et_2O and water. The organic portion was concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc) afforded **519-2**.

[1018] Method B: A mixture of **519-1** (90 mg, 0.145 mmol), boronic acid (0.322 mmol), $Pd_2(dba)_3$ (15 mg, 0.016 mmol), PCy_3 (10 mg, 0.038 mmol) and K_3PO_4 (85 mg, 0.402 mmol) in dioxane (1 mL)- water (300 uL) was degassed and heated to 100 °C for 12 h. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc) afforded **519-2**.

Protecting group(s)-removal:

[1019] Method A: Aqueous HCl (6M solution, 4 mL) was added to a solution of **519-2** (0.056 mmol) in isopropanol (2.5 mL). The reaction was heated to 95 °C for 3 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography to afford **519-3**.

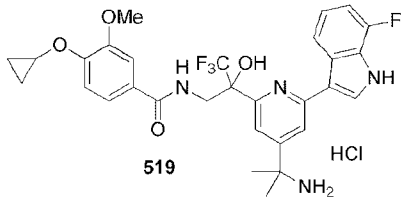
[1020] Method B: A mixture of **519-2** (0.047 mmol) and Pd/C (9 mg) in MeOH (4.7 mL) was stirred under H_2 atmosphere for 5 h. The mixture was filtered from the catalyst, and the solution was treated with 1M HCl solution in Et_2O. The volatiles were removed under reduced pressure. The residue was triturated with Et_2O to afford **519-3** as its hydrochloride salt.

[1021] Method C: TMSCl (32 uL) and NaI (39 mg) were sequentially added to a solution of **519-2** (0.089 mmol) in CH_3CN (4 mL). The reaction was stirred at r.t. for 1 h, warmed to 45 °C and stirred at that temp for 16 h. Additional TMSCl (64 uL) and NaI (80 mg) were added, and the reaction was stirred at 45 °C for 5 h. The volatiles were removed under reduced pressure. The residue was partitioned between EtOAc and a 1:1 mixture of 5% aq. $NaHCO_3$:1M aq. $Na_2S_2O_3$. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography to give **519-3**.

[1022] Method D: Hydrobromic acid (33% solution in AcOH, 30 uL) was added to a solution of **519-2** (20 mg) in 4M HCl-dioxane (2 mL). The reaction was warmed to 70 °C. When complete Cbz-removal was observed by UPLC, the reaction was concentrated

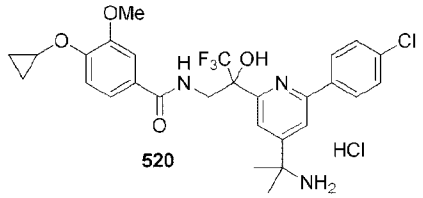
under reduced pressure. The residue purified by reverse phase chromatography to afford **519-3**.

[1023] Method E: A mixture of **519-2** (9.1 mg) in 4M HCl-dioxane (2 mL) was warmed to 70 °C (or 100 °C). When complete Cbz-removal was observed by UPLC, the reaction was concentrated under reduced pressure, and the residue purified by reverse phase chromatography to afford **519-3**.



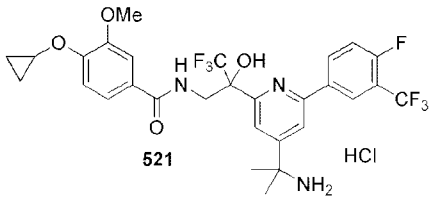
519

[1024] Suzuki coupling of **519-1** with 1-((2-(trimethylsilyl)ethoxy)methyl)-7-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (Method A) followed by protecting groups removal according to Method A afforded **519** as its hydrochloride salt (white solid, 16% overall). UPLC/MS(ES$^+$): m/z 587.36 [M+H]$^+$.



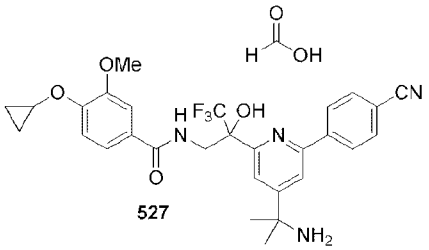
520

[1025] Suzuki coupling of **519-1** with 4-chlorophenylboronic acid (Method A) followed by Cbz-removal according to Method A afforded **520** as its hydrochloride salt (white solid, 24% overall). UPLC/MS(ES$^+$): m/z 564.30 [M+H]$^+$.



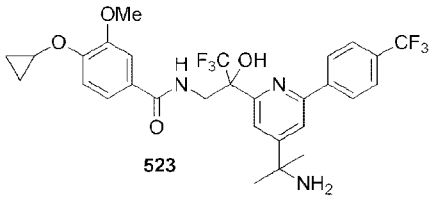
521

[1026] Suzuki coupling of **519-1** with 4-fluoro-3-(trifluoromethyl)phenylboronic acid (Method A) followed by Cbz-removal according to Method B afforded **521** as its hydrochloride salt (45% overall). UPLC/MS(ES$^+$): m/z 616.38 [M+H]$^+$.



527

[1027] Suzuki coupling of **519-1** with 4-cyanophenylboronic acid (Method A) followed by Cbz-removal according to Method C afforded **527** as its formic acid salt (white solid, 37% overall). UPLC/MS(ES$^+$): m/z 555.40 $[M+H]^+$.

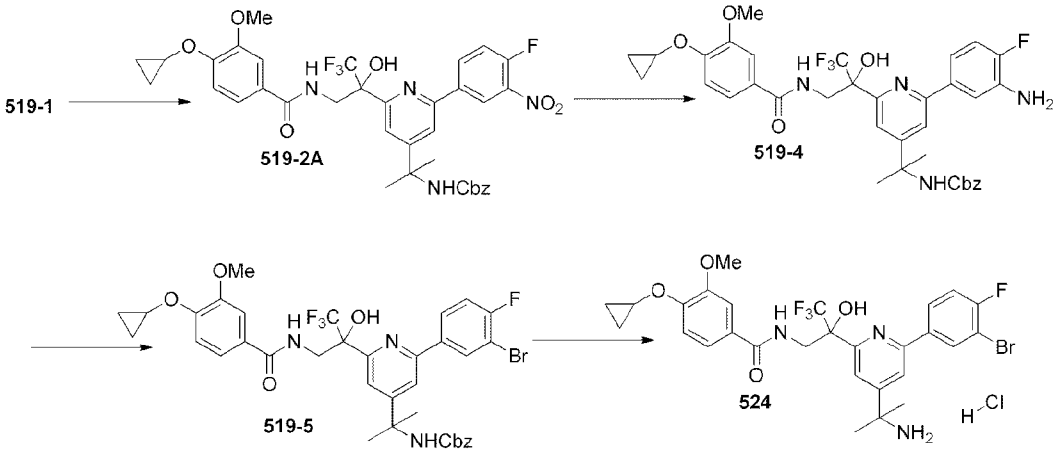


523

[1028] Suzuki coupling of **519-1** with 4-(trifluoromethyl)phenylboronic acid (Method A) followed by Cbz-removal according to Method B afforded **523** (5% overall). UPLC/MS(ES$^+$): m/z 598.30 $[M+H]^+$.

EXAMPLE 266

Preparation of Compound 524



[1029] Suzuki coupling of **519-1** (310 mg) with 2-(4-fluoro-3-nitrophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (Method A of Example 265) afforded **519-2A** (35 mg). UPLC/MS(ES$^+$): m/z 727.30 $[M+H]^+$.

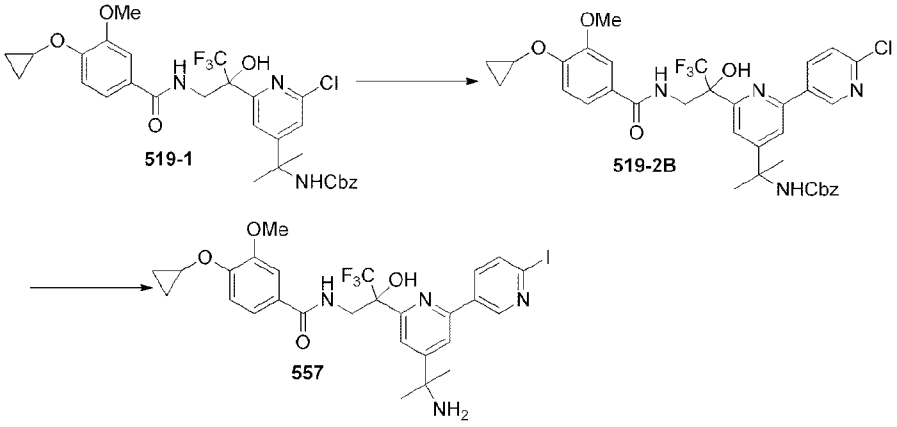
[1030] Iron powder (8 mg, 0.144 mmol) was added to a solution of **519-2A** (35 mg, 0.05 mmol) in 2:2:1 EtOH:AcOH-H_2O (2.5 mL). The mixture was heated to 80 °C for 1

h. The reaction was filtered through a pad of celite, and the volatiles were evaporated under reduced pressure. The crude was partitioned between EtOAc and aq. $NaHCO_3$ solution, and the organic portion was purified by chromatography to afford **519-4** (30 mg). UPLC/MS(ES^+): m/z 697.40 $[M+H]^+$.

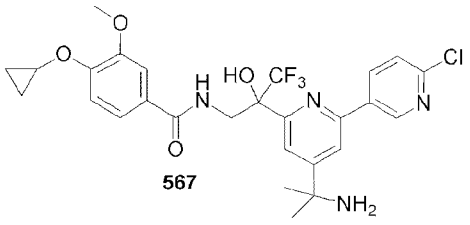
[1031] Aniline **519-4** (30 mg) was dissolved in CH_3CN (2 mL) under N_2 atmosphere. *t*-BuONO (14 mg, 0.129 mmol) was added. The mixture was stirred at r.t. for 30 mins. CuBr (6.2 mg, 0.043 mmol) was added, and the mixture was stirred for 2.5 h. The reaction was partitioned between DCM and sat. aq. NH_4Cl solution. The organic phase was purified by chromatography to recover **519-5** (12 mg).

[1032] Deprotection of **519-5** according to Method A of Example 265 afforded **524** as its hydrochloride salt (1.2 mg). UPLC/MS(ES^+): m/z 626.30 $[M+H]^+$.

EXAMPLE 267
Preparation of Compounds 557 and 567

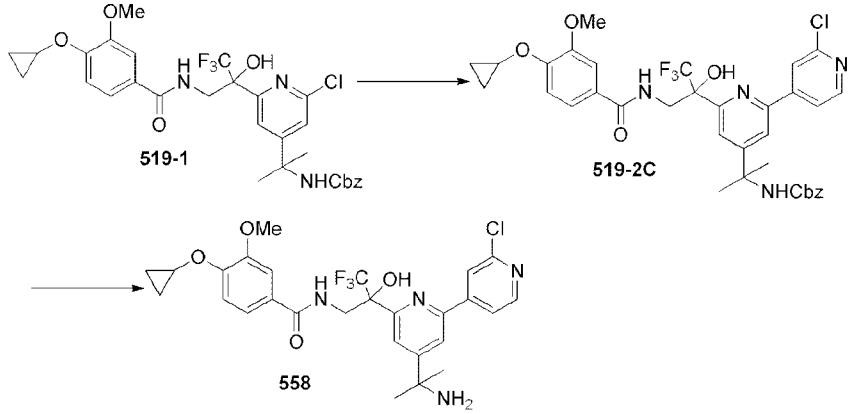


[1033] Suzuki coupling of **519-1** with 2-chloropyridine-5-boronic acid (Method B of Example 265) followed by treatment of the resulting Cbz-protected amine with TMSCl/NaI according to Method C of Example 265 afforded **557** (5% overall). UPLC/MS(ES+): m/z found 657.32 $[M+H]^+$.



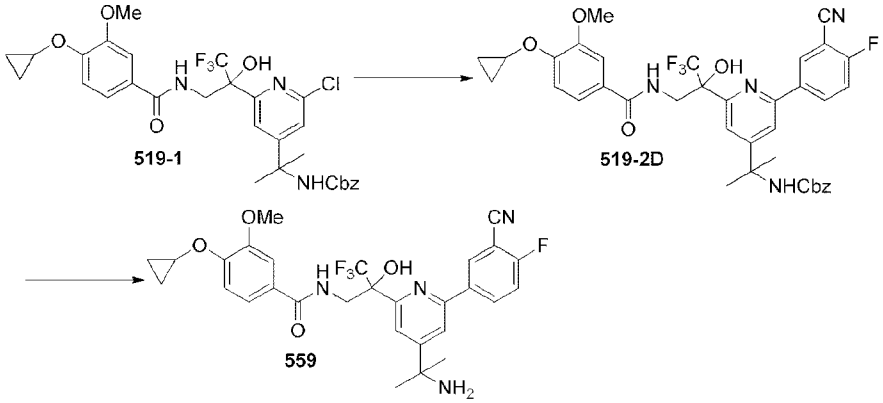
[1034] Deprotection of **519-2B** according to Method E of Example 265 afforded **567** (16%). UPLC/MS(ES^+): m/z 565.40 $[M+H]^+$.

EXAMPLE 268
Preparation of Compound 558



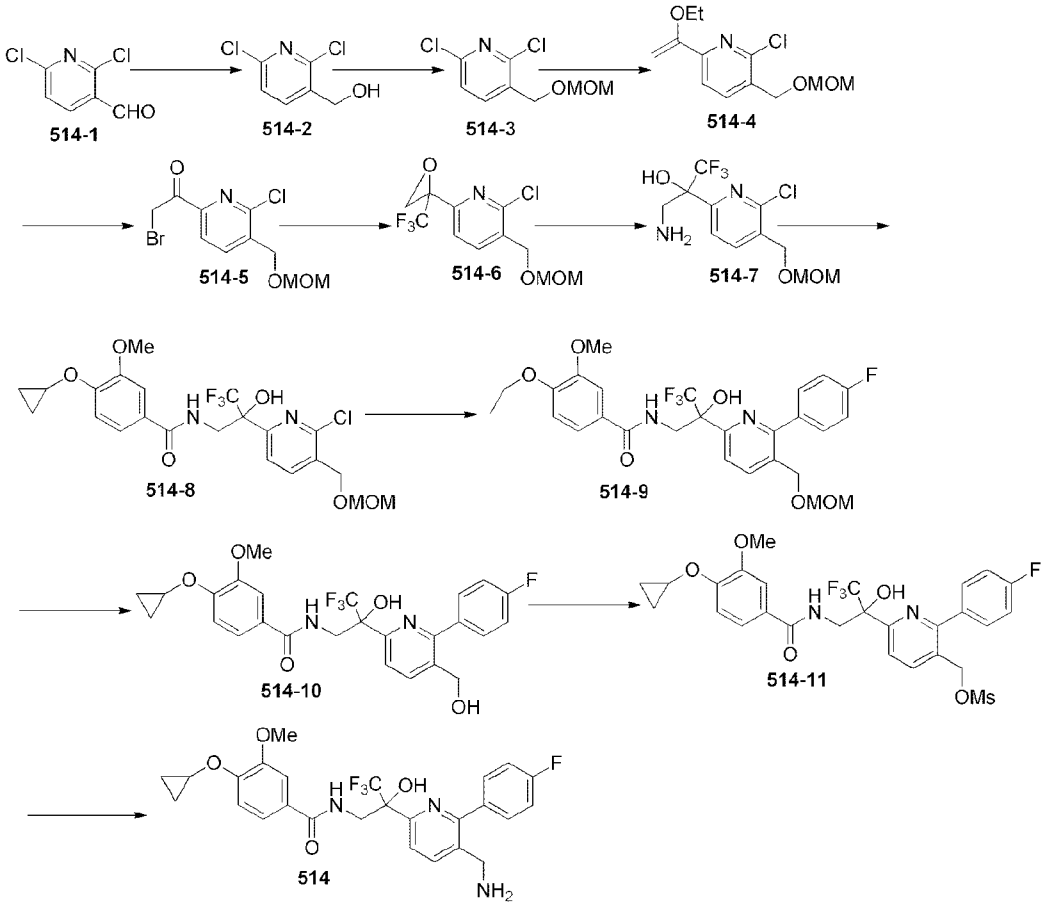
[1035] Suzuki coupling of **519-1** with 2-chloropyridine-4-boronic acid (Method B of Example 265) followed by Cbz-removal according to Method D of Example 265 afforded **558** (3% overall). UPLC/MS(ES^+): m/z 565.30 $[M+H]^+$.

EXAMPLE 269
Preparation of Compound 559



[1036] Suzuki coupling of **519-1** with 3-cyano-4-fluorophenylboronic acid (Method A of Example 265) followed by Cbz-removal according to Method D of Example 265 afforded **559** (10% overall). UPLC/MS(ES^+): m/z 573.42 $[M+H]^+$.

EXAMPLE 270
Preparation of Compound 514



[1037] $NaBH_4$ (808 mg, 21.3 mmol) was added to a solution of **514-1** (3.10 g, 17.7 mmol) in MeOH (22 mL), which had been pre-cooled to 0 °C. The mixture was allowed to reach r.t. and stirring was prolonged for 30 mins. 1M aq. HCl solution was added, and the organic solvent was removed under reduced pressure. The aqueous phase was extracted with DCM (3x). The combined organic portions were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure to afford **514-2** (3.01 g). UPLC/MS(ES^+): m/z 178.00 $[M+H]^+$.

[1038] Chloromethyl methyl ether (704 µL, 9.27 mmol) and TEA (1.75 mL, 12.6 mmol) were added to a solution of **514-2** (1.5 g) in DCM (12 mL). The reaction was warmed to 45 °C. When complete conversion was observed by UPLC, the reaction was cooled to r.t., diluted with DCM and washed with water. The organic portion was concentrated under

reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 70:30) afforded **514-3** (1.48 g). UPLC/MS(ES^+): m/z 222.00 $[M+H]^+$.

[1039] A mixture of **514-3** (1.38 g, 6.24 mmol), $Pd(PPh_3)Cl_2$ (438 mg, 0.624 mmol) and tributyl[1-ethoxyethenyl]stannane (2.11 mL, 6.24 mmol) in dioxane (40 mL) was degassed, warmed to 90 °C and stirred at that temp for 3 h. After being cooled to r.t., the reaction was diluted with EtOAc. The organic portion was washed with a sat. aq. KF solution and water, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **514-4**, which was directly used in the next step.

[1040] NBS (888 mg, 4.99 mmol) was added to a solution of **514-4** in THF (40 mL), which had been pre-cooled to 0 °C. The reaction was stirred at 0 °C for 1 h, then warmed to r.t., and stirred for 2 h. EtOAc was added. The organic portion was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 70:30) afforded **514-5** (1.11 g).

[1041] CF_3TMS (6 mL) was added to a solution of **514-5** (1.11 g) in THF (15 mL). CsF (2.74 g, 18.0 mmol) was added in 1 portion. After 1 h, the reaction was partitioned between EtOAc and sat. aq. NH_4Cl solution. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Crude **514-6** was directly used in the next step.

[1042] A solution of **514-6** and 7M NH_3-MeOH (50 mL) was stirred at r.t. for 16 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN, 100: 0 to 50:50) to afford **514-7** (214 mg). UPLC/MS(ES^+): m/z 315.30 $[M+H]^+$.

[1043] A mixture of **514-7** (291 mg, 0.928 mmol), EDC (212 mg, 1.11 mmol), HOBT (150 mg, 1.11 mmol), TEA (310 uL, 2.23 mmol) and 4-cyclopropoxy-3-methoxybenzoic acid (193 mg, 0.924 mmol) in DCM (6 mL) was stirred at r.t. for 2 h. A 1M aq. HCl solution was added, and the mixture was stirred for 2 mins. The layers were separated. The organic portion was washed with 1M aq. NaOH solution, and concentrated

under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 70:30) afforded **514-8** (140 mg, 30%). UPLC/MS(ES^+): m/z 505.20 $[M+H]^+$.

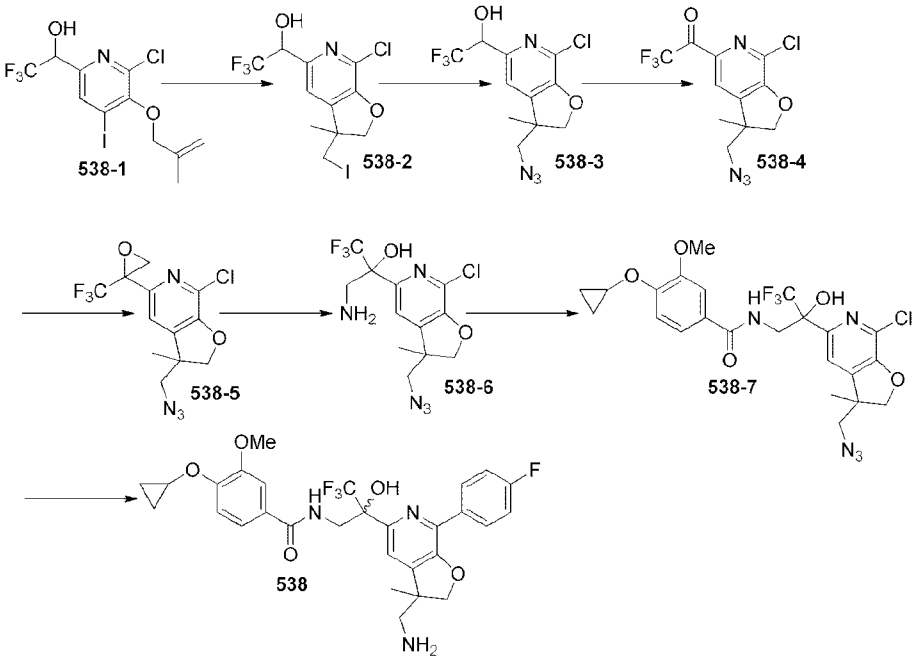
[1044] A mixture of **514-8** (67.6 mg, 0.134 mmol), 4-fluorophenylboronic acid (28 mg, 0.201 mmol), KH_2PO_4 (21 mg, 0.134 mmol), K_3PO_4 (29.0 mg, 0.134 mmol) and $Pd(dbpf)Cl_2$ (9 mg, 0.013 mmol) in DME-H_2O-EtOH (5:3:1, 5 mL) was degassed and heated to 50 °C for 48 h. The mixture was partitioned between DCM and water. The organic portion was concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 70:30) afforded **514-9** (50.7 mg). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.80-0.90 (m, 4 H), 3.36 (s, 3 H), 3.72 - 3.81 (m, 1 H), 3.85 (s, 3 H), 3.97 (dd, *J*=14.0, 3.5 Hz, 1 H), 4.58 (s, 2 H), 4.62-4.73 (m, 3 H), 6.43 (dd, *J*=7.9, 3.5 Hz, 1 H), 6.67 (s, 1 H), 7.08 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.14 - 7.22 (m, 3 H), 7.25 (d, *J*=1.8 Hz, 1 H), 7.53 - 7.61 (m, 2 H), 7.78 (d, *J*=8.1 Hz, 1 H), 8.05 (d, *J*=8.1 Hz, 1 H).

[1045] A solution of **514-9** (50.7 mg, 0.09 mmol) in 1:1 DCM-TFA (700 μL) was stirred at r.t. for 12 h. The reaction was diluted with DCM. The organic portion was washed with 2M aq. NaOH solution and concentrated under reduced pressure. Crude **514-10** (45 mg) was directly used in the next step. UPLC/MS(ES^+): m/z 521.30 $[M+H]^+$.

[1046] TEA (19 μL, 0.136 mmol) and MsCl (10 μL, 0.133 mL) were sequentially added to a solution of **514-10** (45 mg) in DCM (1 mL), which had been pre-cooled to 0 °C. The reaction was allowed to reach r.t., stirred for 12 h and diluted with DCM. The organic portion was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Crude **514-11** (36 mg) was directly used in the next step.

[1047] A solution of **514-11** (36 mg) in 7M NH_3-MeOH (1 mL) was stirred at r.t. for 12 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN, 100:0 to 67:33) to afford **514** (19.6 mg). UPLC/MS(ES^+): m/z 520.30 $[M+H]^+$.

EXAMPLE 271
Preparation of Compound 538



[1048] A 0.2 M solution of **538-1** (465 mg, 1.14 mmol) in toluene (5.7 mL) was degassed (mw vial). $Pd(Q\text{-}phos)_2$ (80 mg, 0.052 mmol) was added. The vial was sealed, purged with N_2 and heated to 100 °C for 6 h. Additional $Pd(Q\text{-}phos)_2$ (30 mg) was added. The vial was purged with N_2 and heated to 100 °C for 4 h. The mixture was directly purified by chromatography on silica gel (cyclohexane:EtOAc, 95:5 to 70:30) to afford **538-2** (414 mg, 96%). UPLC/MS(ES^+): m/z 408.10 $[M+H]^+$.

[1049] A mixture of **538-2** (340 mg) and NaN_3 (288 mg) in DMF (4 mL) was heated to 65 °C and stirred at that temp for 16 h. The volatiles were removed under reduced pressure. The crude residue was partitioned between EtOAc and sat. aq. NH_4Cl solution. The layers were separate. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford **538-3** (245 mg). UPLC/MS(ES^+): m/z 323.10 $[M+H]^+$.

[1050] Dess-Martin periodinane (484 mg, 1.14 mmol) was added to a solution of **538-3** (245 mg) in DCM (4 mL). The reaction was stirred at r.t. for 1 h and quenched with a 1:1 1M aq. $Na_2S_2O_3$:5% aq. $NaHCO_3$. The mixture was vigorously stirred for 1 h. The layers were separated, and the aqueous portion was extracted with DCM. The combined

organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc) afforded **538-4** (206 mg). UPLC/MS(ES^+): m/z 339.10 $[M+H_3O]^+$.

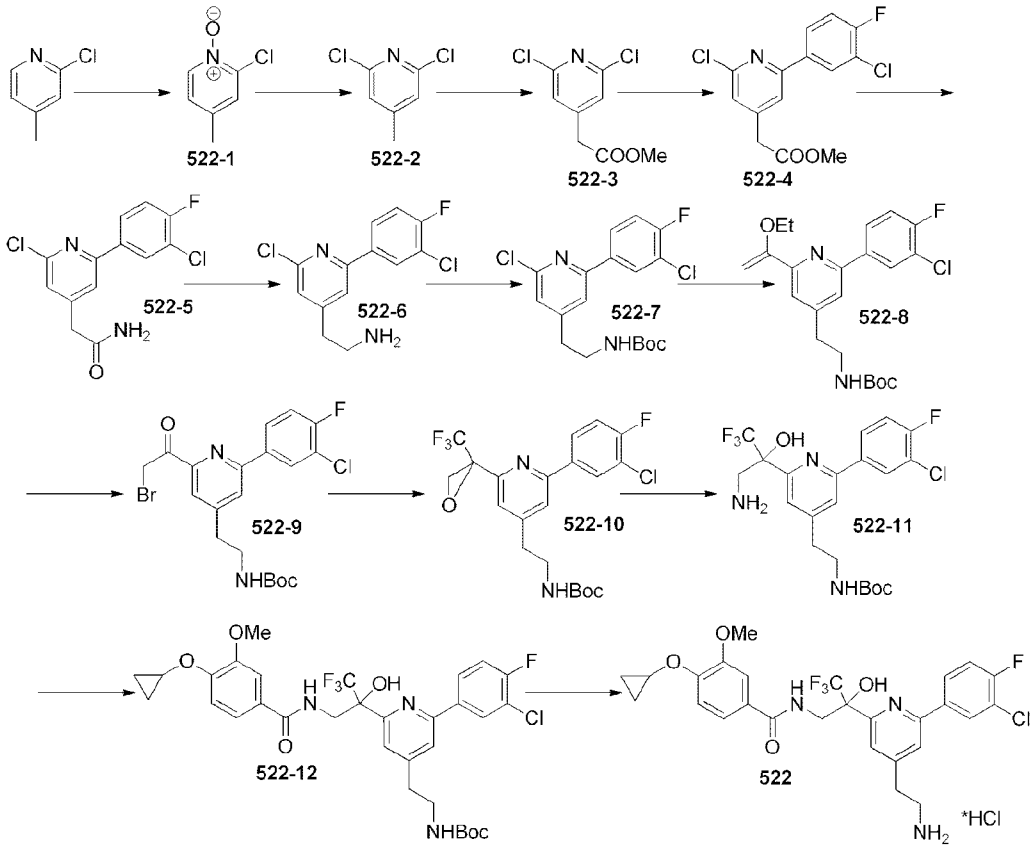
[1051] Trimethylsulfoxonium iodide (141 mg, 0.643 mmol) was added in one portion to a mixture of tBuOK (72 mg, 0.643 mg) in CH_3CN (4 mL), which had been previously degassed. After 20 mins, the solution was filtered from the solid and added to a solution of **538-4** (206 mg) in CH_3CN (4 mL), which had been previously degassed. The reaction was stirred at r.t. for 15 mins. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **538-5**. UPLC/MS(ES^+): m/z 335.10 $[M+H]^+$.

[1052] A solution of **538-5** (100 mg) in 7M NH_3-MeOH (60 mL) was stirred at r.t. for 1 h. The volatiles were removed under reduced pressure to afford crude **538-6** (108 mg), which was directly used in the next step. UPLC/MS(ES^+): m/z 352.10 $[M+H]^+$.

[1053] A mixture of **538-6** (108 mg), EDC (89 mg, 0.462 mmol), HOBT (63 mg, 0.462 mmol), 4-cyclopropoxy-3-methoxybenzoic acid (64 mg, 0.307 mmol) and TEA (86 uL, 0.616 mmol) in DCM (4 mL) was stirred at r.t. for 16 h. The reaction was diluted with DCM. The organic portion was washed with 1M aq. HCl solution (2x), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 50:50) afforded **538-7** (136 mg). UPLC/MS(ES^+): m/z 542.20 $[M+H]^+$.

[1054] $Pd(dbpf)Cl_2$ (16 mg, 0.025 mmol) was added to a mixture of **538-7** (136 mg), K_3PO_4 (107 mg, 0.503 mmol), KH_2PO_4 (68 mg, 0.503 mg) and 4-fluorophenylboronic acid (74 mg, 0.503 mmol) in 5:3:1 DME:EtOH:H_2O (2.7 mL), which had been previously degassed. The reaction was warmed to 65 °C and stirred at that temp for 10 h. The mixture was cooled to r.t. and stirred for 72 h. The reaction was diluted with EtOAc and washed with sat. aq. NH_4Cl solution. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water/0.1% HCOOH:CH_3CN/0.1% HCOOH, 100:0 to 50:50) to afford **538** as a white solid (formic acid salt, 33 mg, dr 1:1). UPLC/MS(ES^+): m/z 576.40 $[M+H]^+$.

EXAMPLE 272
Preparation of Compound 522



[1055] *meta*-Chloroperbenzoic acid (56.0 g, 328 mmol) was added in several portions to a solution of 2-chloro-4-methylpyridine (20.0 g, 156 mmol) in DCM (520 mL). The mixture was refluxed for 8 h and diluted with DCM. The organic portion was washed with sat. aq. K_2CO_3 solution. The aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (DCM:MeOH, 100:0 to 80:20) afforded **522-1** as a yellow oil (9.50 g, 42%). UPLC/MS(ES^+): m/z 144.00 $[M+H]^+$.

[1056] $POCl_3$ (130 mL) was added to a solution of **522-1** (9.50 g, 66.0 mmol) in toluene (20 mL). The reaction was heated to 70 °C and stirred at that temp for 20 h. The volatiles were removed under reduced pressure. The residue was poured into ice. The mixture neutralized with sat. aq. K_2CO_3 solution and extracted with DCM (3x). The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced

pressure. Chromatography of the residue afforded **522-2** (3.80 g, 36%). UPLC/MS(ES^+): m/z 162.10 $[M+H]^+$.

[1057] A freshly prepared solution of LDA solution (1M in THF-hexane, 44.6 mL, 44.6 mmol) was added to a solution of **522-2** (3.61 g, 22.3 mmol) in THF (110 mL), which had been pre-cooled to -78 °C. The reaction was stirred at -78 °C for 1 h. Dimethylcarbonate (4.5 mL, 53.5 mmol) was added. The reaction was allowed to reach 0 °C, stirred at that temp for 1 h and quenched with water. The volatiles removed under reduced pressure. The residue was taken up with EtOAc. The organic portion was washed with sat. aq. NH_4Cl solution, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 60:40) afforded **522-3** as a yellow oil (3.0 g, 61%). UPLC/MS(ES^+): m/z 220.0 $[M+H]^+$.

[1058] A mixture of **522-3** (450 mg, 2.00 mmol), 3-chloro-4-fluorophenylboronic acid (285 mg, 1.60 mmol), $NaHCO_3$ (515 mg, 6.10 mmol) and $Pd(PPh_3)_4$ (95 mg, 0.080 mmol) in 2:1 THF:water (9 mL) was degassed and heated to 50 °C. After 2 h, 3-chloro-4-fluorophenyl boronic acid (0.2 eq.) was added, and the mixture was stirred at 50 °C for 2 h. After being cooled to r.t., the reaction was diluted with DCM. The organic portion was washed with sat. aq. $NaHCO_3$ solution, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN, 70:30 to 10:90) to afford **522-4** as a yellow oil (180 mg, 29%). UPLC/MS(ES^+): m/z 314.10 $[M+H]^+$.

[1059] **522-4** (860 mg, 2.70 mmol) was dissolved in 7M NH_3-MeOH (14 mL) at 0 °C. The reaction was stirred at r.t. for 3 h and at 40 °C for 20 h. The volatiles were removed under reduced pressure to afford crude **522-5** (775 mg), which was directly used in the next step.

[1060] Borane-THF complex (1M solution in THF, 7.77 mL, 7.77 mmol) was added to a solution of **522-5** (775 mg) in THF (14 mL). The reaction was refluxed for 3 h. Additional borane-THF complex (4 eq., 2 aliquots) was added, and the mixture was refluxed overnight. The reaction was quenched with 2M aq. HCl solution, and the mixture was stirred for 30 mins . The aqueous portion was basified with sat. aq. $NaHCO_3$ solution and extracted with EtOAc. The organic portion was washed with brine, dried with Na_2SO_4, filtered and

concentrated under reduced pressure. The residue was loaded on to a SCX-column and eluted with 2M NH_3-MeOH to give **522-6** (610 mg, 82%). UPLC/MS(ES^+): m/z 285.10 $[M+H]^+$.

[1061] Triethylamine (590 uL, 4.26 mmol) and Boc_2O (700 mg, 3.20 mmol) were sequentially added to a solution of **522-6** (610 mg, 2.13 mmol) in DCM (11 mL). The reaction was stirred at r.t. for 1 h, diluted with DCM and washed with 0.5M aq. HCl solution. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 90:10 to 50:50) afforded **522-7** as a white solid (580 mg, 71%). UPLC/MS(ES^+): m/z 385.20 $[M+H]^+$.

[1062] A mixture of **522-7** (580 mg, 1.50 mmol), $Pd(PPh_3)Cl_2$ (105 mg, 0.150 mmol) and tributyl[1-ethoxyethenyl]stannane (560 uL, 1.65 mmol) in dioxane (8 mL) was degassed, warmed to 100 °C and stirred at that temp for 6 h. After being cooled to r.t., a sat. aq. KF solution was added. The mixture was stirred for 10 mins, and the aqueous portion was extracted with EtOAc. The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **522-8**, which was directly used in the next step.

[1063] *N*-Bromosuccinimide (293 mg, 1.65 mmol) was added to a solution of **522-8** in THF (8 mL), which had been pre-cooled to 0 °C. The reaction was stirred at 0 °C for 1 h, quenched with water and extracted with EtOAc. The organic portion was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 90:10 to 50:50) afforded **522-9** as a white solid (330 mg, 47% over 2 steps). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.45 (s, 9 H), 3.00 (t, *J*=6.5 Hz, 2 H), 3.50 (q, *J*=6.5 Hz, 2 H), 4.58 - 4.69 (m, 1 H), 4.95 (s, 2 H), 7.30 (t, *J*=8.0 Hz, 1 H), 7.79 (br. s., 1 H), 7.92 (s, 1 H), 7.95 - 8.02 (m, 1 H), 8.15 (dd, *J*=6.9, 2.1 Hz, 1 H).

[1064] CF_3TMS (1.03 mL, 7.00 mmol) was added to a solution of **522-9** (330 mg, 0.700 mmol) in THF (5 mL). CsF (531 mg, 3.50 mmol) was added in one portion. After 1 h, the reaction was partitioned between EtOAc and sat. aq. NH_4Cl solution. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude **522-10** was directly used in the next step.

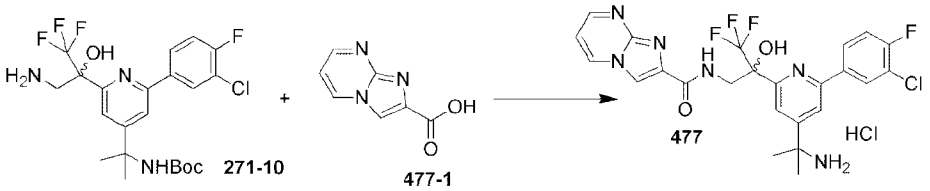
[1065] A solution of **522-10** and 7M NH_3-MeOH (10 mL) was stirred at r.t. for 3 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN, 95:5 to 30:70) to afford **522-11** (56 mg).

[1066] A mixture of 4-cyclopropoxy-3-methoxybenzoic acid (49.0 mg, 0.230 mmol), HATU (108 mg, 0.280 mmol) and DIPEA (122 uL, 0.700 mmol) in DCM (1 mL) was stirred at r.t. for 30 mins. A solution of **522-11** (56 mg) in DCM (1 mL) was added, and the reaction was stirred at r.t. for 2 h and quenched with water. EtOAc was added. The organic portion was washed with 1M aq. HCl solution, 2M aq. NaOH solution and brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 90:10 to 40:60) afforded **522-12** (65 mg).

[1067] A solution of **522-12** in 4M HCl-dioxane (1 mL) was stirred at 0 °C for 1 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water:CH_3CN, 95:5 to 40:60) to afford **522** (14 mg). UPLC/MS(ES^+): m/z 568.30 $[M+H]^+$.

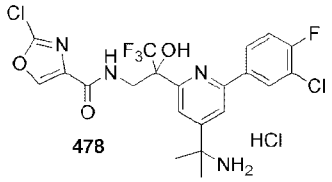
EXAMPLE 273

Preparation of Compound 477



[1068] A mixture of **271-10** (50 mg, 0.1 mmol), **477-1** (16 mg, 0.1 mmol) and TEA (1 mmol) was dissolved in anhydrous DCM (4 mL) with stirring. The mixture was treated with HATU (38 mg, 0.1 mmol) in 1 portion. After stirring at r.t. for 30 mins, TFA (1 mL) was added. The solution was stirred at r.t. for 2 h. The mixture was concentrated to dryness. The residue was purified by reverse prep-HPLC to afford **477** (28 mg, 48%) as a white solid. +ESI-MS: m/z 537.1 $[M+H]^+$.

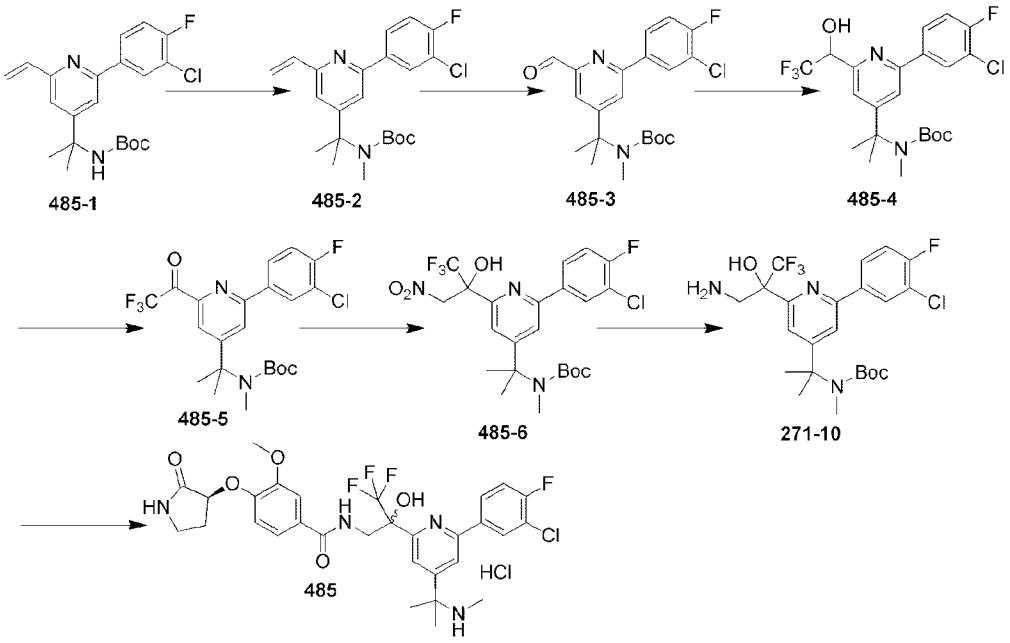
EXAMPLE 274
Preparation of Compound 478



478

[1069] Compound **478** was prepared following the general procedure for preparing **477** by using 2-chlorooxazole-4-carboxylic acid and **271-10**. Crude **478** was purified by prep-HPLC and obtained as a white solid (20 mg, 36%). +ESI-MS: m/z 520.9 $[M+H]^+$.

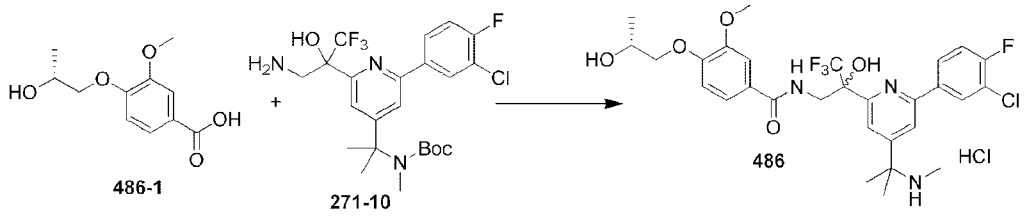
EXAMPLE 275
Preparation of Compound 485



[1070] To a solution of **485-1** (6 g, 15.4 mmol) in anhydrous DMF (95 mL) was added NaH (640 mg, 16 mmol, 60% in mineral oil) in small portions at r.t. After stirring for 10 mins, a solution of MeI (2.3 g, 16 mmol) in DMF (5 mL) was added dropwise, and the reaction was stirred for 1 h. After complete conversion of **485-1**, the mixture was quenched with water, and extracted with EtOAc (150 mL x 2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography using (PE:EtOAc: 100:0 to 80:20) to afford **485-2** (5.8 g, 93.5%).

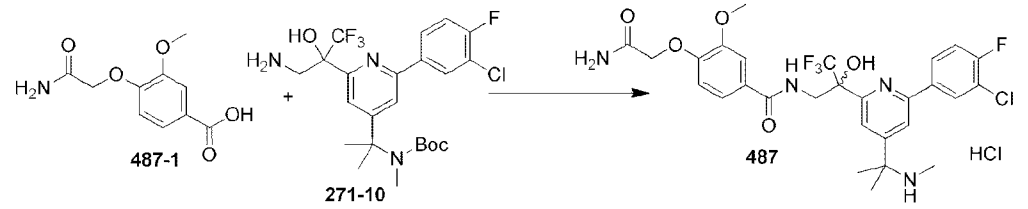
[1071] Compound **485** (white solid, 27 mg) was prepared following the general procedure for preparing **272** using **485-2** and (S)-3-methoxy-4-((2-oxopyrrolidin-3-yl)oxy)benzoic acid. +ESI-MS: m/z 639.1 $[M+H]^+$.

EXAMPLE 276
Preparation of Compound 486



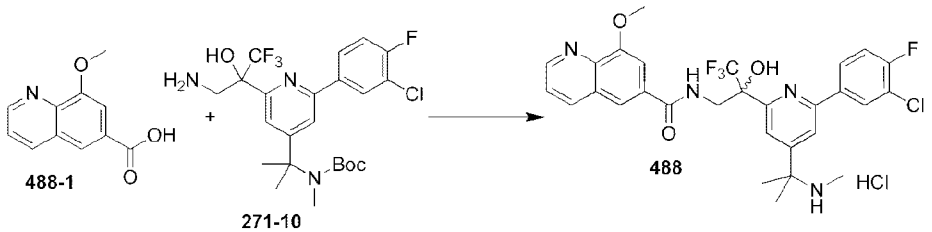
[1072] Compound **486** (white solid, 34 mg) was prepared following the general procedure for preparing **485** by using **486-1** and **271-10**. +ESI-MS: m/z 614.1 $[M+H]^+$.

EXAMPLE 277
Preparation of Compound 487



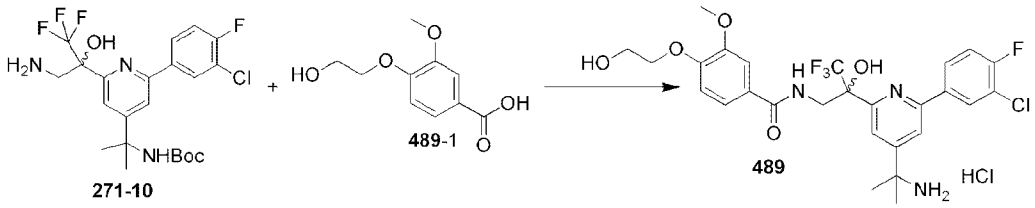
[1073] Compound **487** (white solid, 27.5 mg) was prepared following the general procedure for preparing **485** by using **487-1** and **271-10**. +ESI-MS: m/z 613.1 $[M+H]^+$.

EXAMPLE 278
Preparation of Compound 488



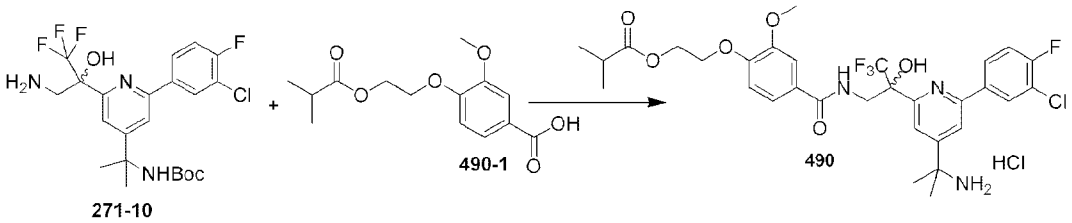
[1074] Compound **488** (white solid, 26 mg) was prepared following the general procedure for preparing **485** by using **488-1** and **271-10**. +ESI-MS: m/z 591.1 $[M+H]^+$.

EXAMPLE 279
Preparation of Compound 489



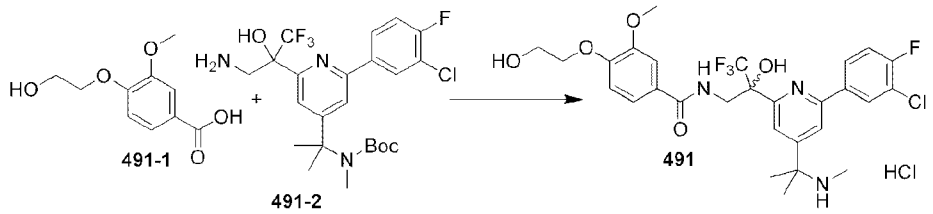
[1075] Compound **489** (white solid, 23 mg) was prepared following the general procedure for preparing **485** by using **489-1** and **271-10**. +ESI-MS: m/z 586.0 $[M+H]^+$.

EXAMPLE 280
Preparation of Compound 490



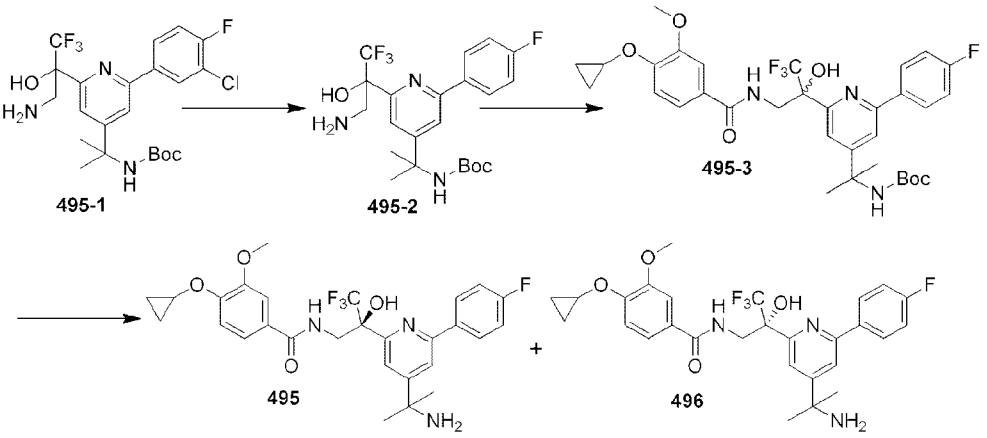
[1076] Compound **490** (white solid, 41 mg) was prepared following the general procedure for preparing **485** by using **490-1** and **271-10**. +ESI-MS: m/z 656.0 $[M+H]^+$.

EXAMPLE 281
Preparation of Compound 491



[1077] Compound **491** (white solid, 25 mg, 44 %) was prepared following the general procedure for preparing **485** by using **491-1** and **491-2**. +ESI-MS: m/z 600.1 $[M+H]^+$.

EXAMPLE 282
Preparation of Compounds 495 and 496



[1078] To a solution of **495-1** (850 mg, 1.73 mmol) in MeOH (50 mL) was added Pd/C (210 mg, 5%) under N_2 at r.t. The suspension was purged with hydrogen for several times. The mixture was stirred under hydrogen (15 psi) at r.t. for 12 h. After complete conversion of **495-1**, the mixture was filtered through a pad of Celite, and the filtrate was concentrated to dryness. The residue was **495-2** (750 mg, 94.6%), which was used directly without further purification. +ESI-MS: m/z 458.2 $[M+H]^+$.

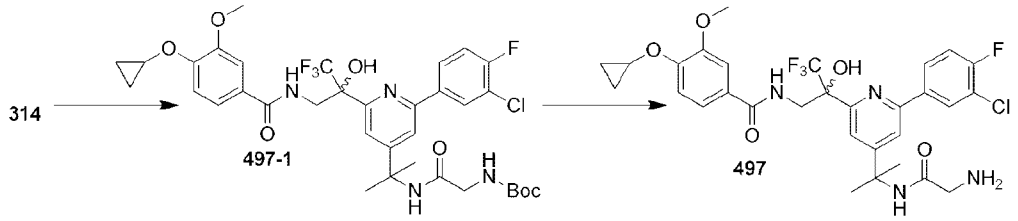
[1079] A mixture of **495-2** (750 mg, 1.64 mmol), carboxyl acid 3 (340 mg, 1.64 mmol) and TEA (1 mmol) is dissolved in anhydrous DMF (10 mL) with stirring. The solution was treated with HATU (623 mg, 1.64 mmol) in one portion. After stirring at r.t. for 1~2 h, the mixture was poured into cold water and extracted with EA (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=1:1 as the eluent to give **495-3** as an oil (910 mg, 86%). +ESI-MS: m/z 648.1 $[M+H]^+$.

[1080] To a stirring solution of **495-3** (910 mg, 1.41 mmol) in DCM (10 mL) was added TFA (5 mL) dropwise at r.t. The reaction was stirred for 30 mins and concentrated to dryness under reduced pressure. The residue was neutralized by sat. sodium carbonate solution and extracted with EA (15 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue

was purified by prep-HPLC and separated by SFC to give **495** (93 mg) and **496** (82 mg) as a white solid.

495: +ESI-MS: m/z 548.1 $[M+H]^+$; and **496**: +ESI-MS: m/z 548.1 $[M+H]^+$.

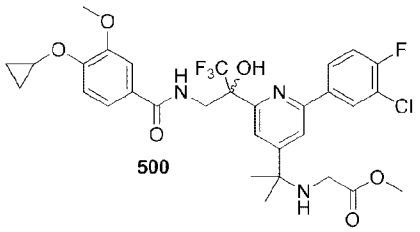
EXAMPLE 283
Preparation of Compound 497



[1081] To a stirring solution of **314** (116 mg, 0.2 mmol), 2-((tert-butoxycarbonyl)amino)acetic acid (35 mg, 0.20 mmol) and DIPEA (90 mg, 0.7 mmol) in anhydrous DCM (5 mL) was added HATU (76 mg, 0.2 mmol) in one portion at 25 °C. The solution was stirred for 1 h. The mixture was diluted with water and DCM. The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude **497-1** (110 mg), which used directly without purification. +ESI-MS: m/z 739.1 $[M+H]^+$.

[1082] To a stirring solution of crude **497-1** (110 mg) in EA (10 mL) was added HCl:EA (4 M, 5 mL) at r.t. The reaction was stirred for 30 mins with TLC monitoring. After conversion of **497-1**, the reaction was quenched with sat. sodium bicarbonate solution, and extracted with EA (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by prep-HPLC to give **497** (50 mg, 52.6%) as a white solid. +ESI-MS: m/z 639.2 $[M+H]^+$.

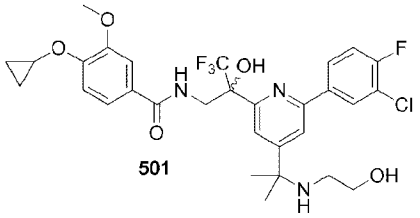
EXAMPLE 284
Preparation of Compound 500



[1083] To a solution of **314** (58 mg, 0.1 mmol) and K_2CO_3 (27 mg, 0.2 mmol) in DMF (1 mL) was added methyl 2-bromoacetate (23 mg, 0.15 mmol) at r.t. The mixture was

heated to 60 °C and stirred for 2 h. The reaction was cooled to r.t. and diluted with H_2O and EA. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **500** as a white solid (30 mg, 46.2%). +ESI-MS: m/z 654.1 $[M+H]^+$.

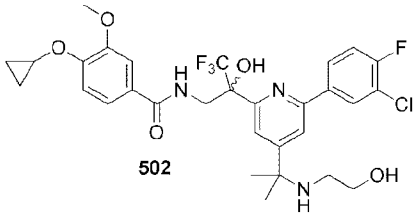
EXAMPLE 285
Preparation of Compound 501



501

[1084] To a solution of **500** (90 mg, 0.14 mmol) in MeOH (10 mL) was added NH_3:MeOH (7M, 10 mL). The vial was sealed and heated to 60 °C for 2 h. The reaction was cooled to r.t. and diluted with H_2O (20 mL) and EA (20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by prep-HPLC to give **501** as a white solid (49 mg, 54.7%). +ESI-MS: m/z 639.1 $[M+H]^+$.

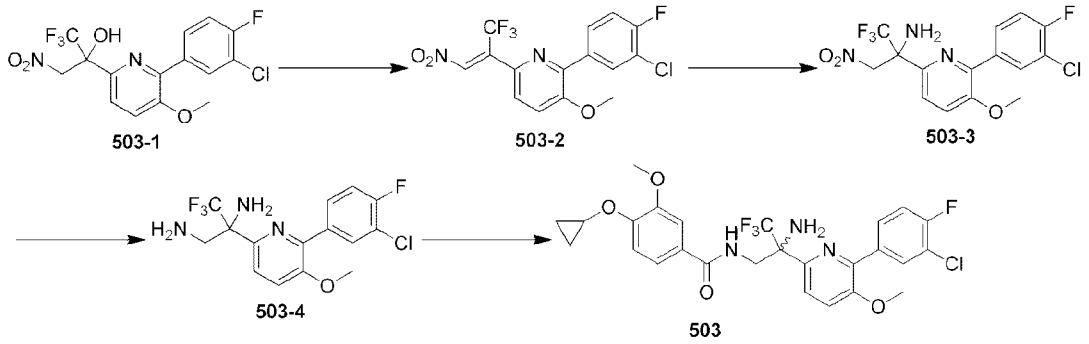
EXAMPLE 286
Preparation of Compound 502



502

[1085] To a solution of **500** (65 mg, 0.1 mmol) in co-solvent of THF (2 mL) and MeOH (2 mL) was added $LiBH_4$ (10 mg, 0.5 mmol) at r.t. The mixture was stirred at r.t. for 30 mins. The reaction was quenched with H_2O and extracted with EA (10 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness at low pressure. The residue was purified by prep-HPLC to give **502** as a white solid (40 mg, 64.5%). +ESI-MS: m/z 626.0 $[M+H]^+$.

EXAMPLE 287
Preparation of Compound 503



[1086] To a solution of **503-1** (1.0 g, 2.5 mmol) in toluene (8 mL) was added pyridine (590 mg, 7.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 mins and $SOCl_2$ (820 mg, 7.0 mmol) was added dropwise. After addition, the mixture was stirred at 0 °C for 30 mins. The reaction was quenched with H_2O and extracted with EA (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography using PE:EA=5:1 as the eluent to give **503-2** as a solid (0.8 g, 85.1%). +ESI-MS: m/z 377.1 $[M+H]^+$.

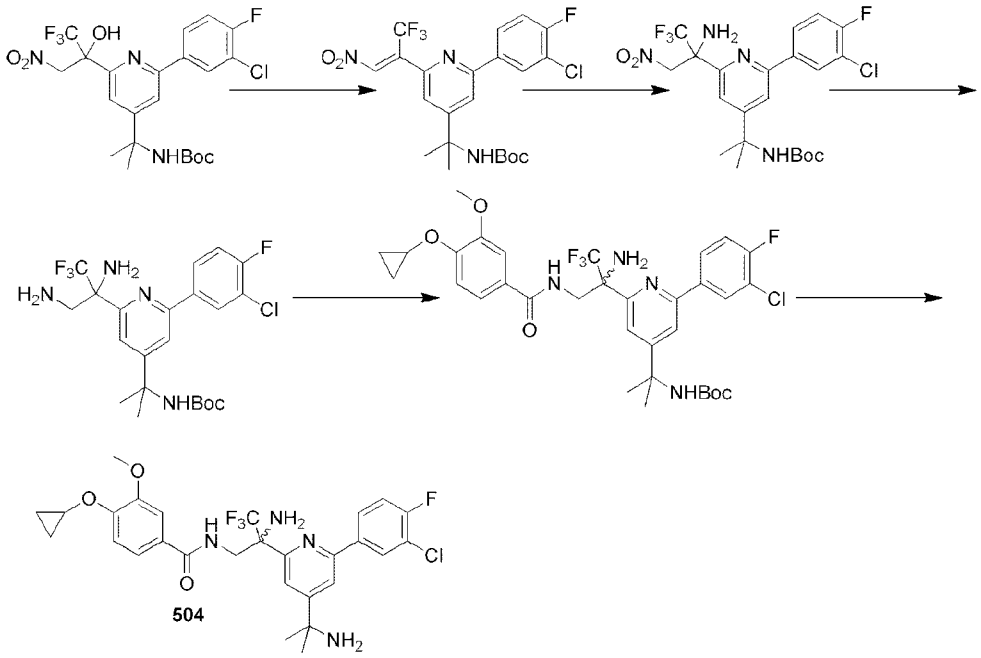
[1087] To a solution of **503-2** (0.8 g, 2.1 mmol) in DMSO (6 mL) was added ammonia water (1 mL) at 0 °C. The mixture was stirred at r.t. for 30 mins. The mixture was diluted with H_2O and extracted with EA (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography using PE:EA=3:1 as the eluent to give **503-3** as a solid (650 mg, 78.7%). +ESI-MS: m/z 394.1 $[M+H]^+$.

[1088] To a solution of **503-3** (650 mg, 1.7 mmol) in MeOH (10 mL) was added Raney Ni (0.7 g) under N_2. The suspension was degassed under vacuum and purged with H_2 for several times. The reaction was stirred under H_2 (balloon) at r.t. for 30 mins. The mixture was filtered through a pad of Celite, and the filtrate was concentrated to give **503-4** (550 mg), which was used directly without purification.

[1089] To a solution of **503-4** (37 mg, 0.10 mmol), 4-cyclopropoxy-3-methoxybenzoic acid (21 mg, 0.10 mmol) and DIPEA (39 mg, 0.3 mmol) in anhydrous DCM (3 mL) was added HATU (39 mg, 0.10 mmol) in one portion at 25 °C. The solution was

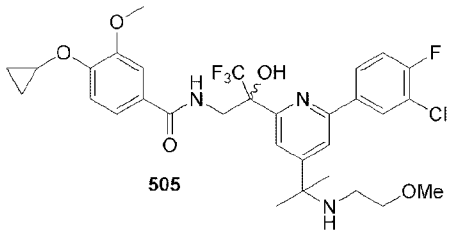
stirred at this temperature for 1 h. The reaction was diluted with H_2O and extracted with DCM (10 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness at low pressure. The residue was purified by prep-HPLC to give **503** as a white solid (35 mg, 63.6%). +ESI-MS: m/z 553.9 $[M+H]^+$.

EXAMPLE 288
Preparation of Compound 504



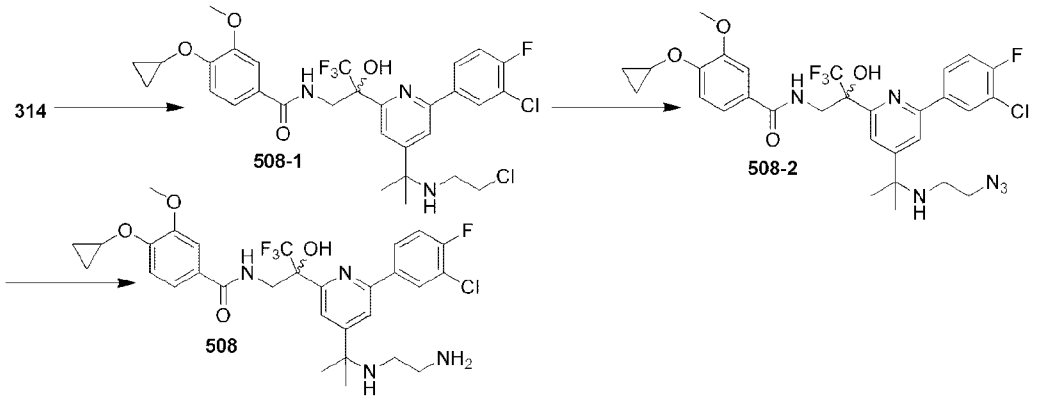
[1090] Compound **504** (white solid, 49 mg) was prepared following the general procedure for preparing **503** by using **503-1**. +ESI-MS: m/z 581.2 $[M+H]^+$.

EXAMPLE 289
Preparation of Compound 505



[1091] Compound **505** (white solid, 9 mg) was prepared following the general procedure for preparing **500** by using **314** and 1-bromo-2-methoxyethane as starting material. +ESI-MS: m/z 640.1 $[M+H]^+$.

EXAMPLE 290
Preparation of Compound 508

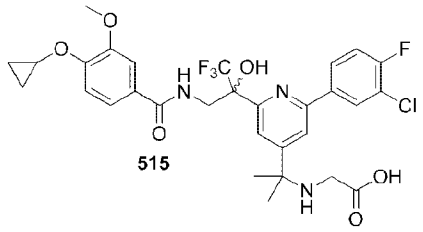


[1092] To a solution of **314** (290 mg, 0.5 mmol) in THF (5 mL) was added 2-chloroacetaldehyde (0.5 g, 40 % in H_2O) at r.t. The mixture was stirred for 30 mins and $NaBH_3CN$ (160 mg, 2.5 mmol) was added. The mixture was stirred at r.t. for 30 mins. The reaction was quenched with H_2O and extracted with EA (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography using PE:EA=1:1 as the eluent to give **508-1** as a solid (210 mg, 65.4%).

[1093] To a solution of **508-1** (210 mg, 0.33 mmol) in DMSO (5 mL) was added NaN_3 (60 mg, 0.92 mmol) at r.t. The mixture was stirred at 60 °C for 30 mins. The mixture was cooled to r.t. and diluted with H_2O and EA (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give crude **508-2** (190 mg) as a pale yellow solid, which was used directly without purification. +ESI-MS: m/z 651.1 $[M+H]^+$.

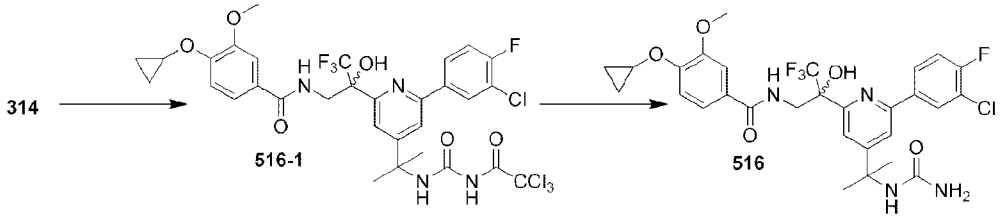
[1094] To a solution of **508-2** (190 mg, 0.29 mmol) in MeOH (15 mL) was added Pd/C (0.2 g) under N_2 at r.t. The suspension was degassed under vacuum and purged with H_2 for several times. The mixture was stirred under H_2 balloon for 30 mins at r.t. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to give **508** as a white solid (101 mg, 55.5%). +ESI-MS: m/z 625.0 $[M+H]^+$.

EXAMPLE 291
Preparation of Compound 515



[1095] To a solution of **500** (180 mg, 0.28 mmol) in MeOH (5 mL) was added a solution of NaOH (50 mg, 1.25 mmol) in H_2O (5 mL) at r.t. The mixture was stirred at 60 °C for 1 h. MeOH was evaporated, and the aqueous phase was acidified to pH = 1 by addition of 1 N HCl solution. The solution was extracted with EA (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by prep-HPLC to give **515** as a white solid (80 mg, 45.0%). +ESI-MS: m/z 640.0 $[M+H]^+$.

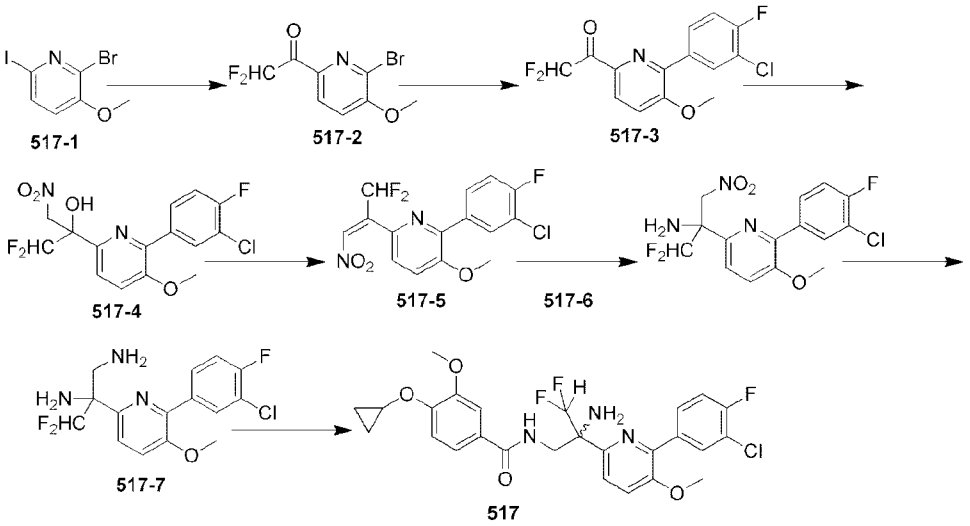
EXAMPLE 292
Preparation of Compound 516



[1096] To a solution of **314** (100 mg, 0.17 mmol) in DCM (2 mL) was added CCl_3CONCO (36 mg, 0.189 mmol) at 0 °C. The solution was stirred for 20 mins. The solution was diluted with DCM (10 mL) and H_2O (10 mL). The organic phase was separated and concentrated under reduced pressure to give crude **516-1** (78 mg, 60.0%), which was used directly without purification.

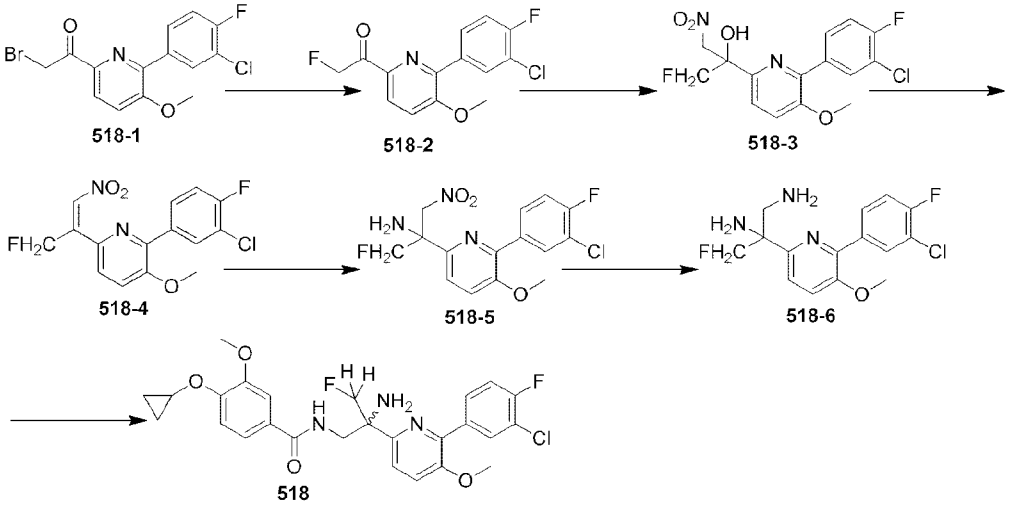
[1097] To a solution of **516-1** (78 mg, crude) in MeOH (1 mL) was added sat. $NaHCO_3$ solution (1 mL) and stirred at r.t. for 1 h. The mixture was extracted with EA (10mL x 3). The combined organic layers were washed by brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by prep-HPLC to give **516** (28 mg, 44.4%) as a white solid. +ESI-MS: m/z 625.1 $[M+H]^+$.

EXAMPLE 293
Preparation of Compound 517



[1098] Compound **517** (white solid, 87 mg, 35.3%) was prepared following the general procedure for preparing **232** and **504** by using **517-1** and ethyl 2,2-difluoroacetate. +ESI-MS: m/z 536.0 $[M+H]^+$.

EXAMPLE 294
Preparation of Compound 518



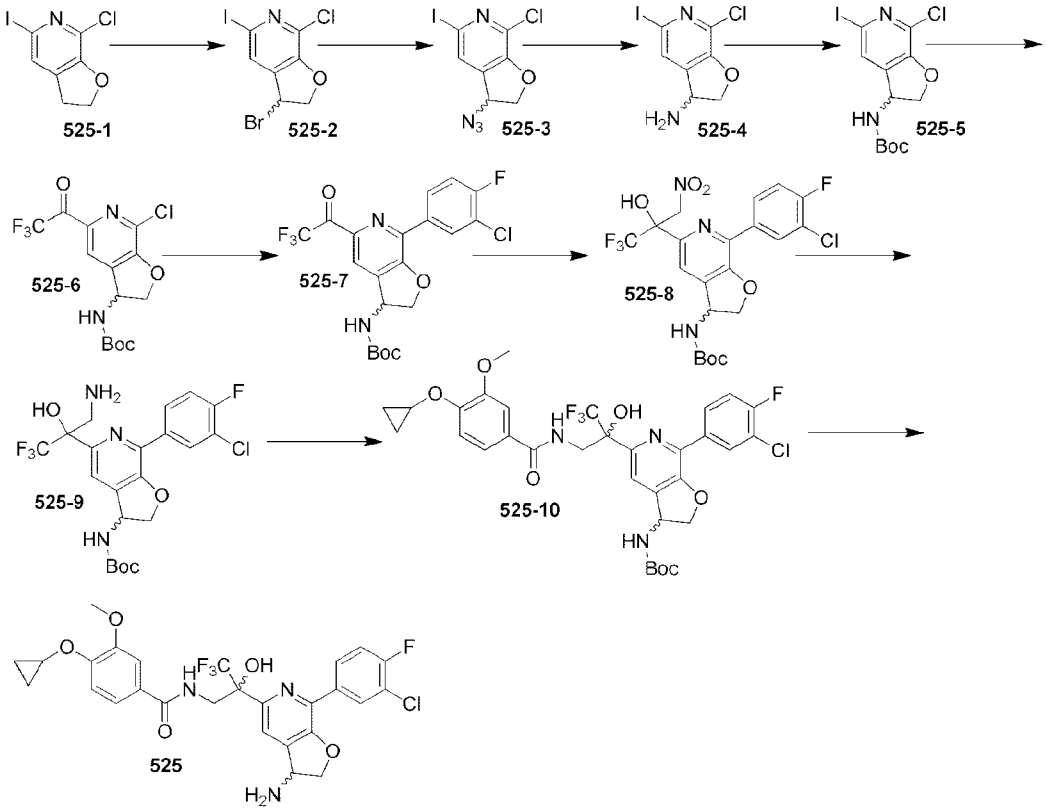
[1099] To a solution of **518-1** (3.56 g, 10.0 mmol) and CsF (3.0 g, 20.0 mmol) in MeCN (15 mL) was added 18-crown-6 (3.6 g, 13.6 mmol) at r.t. The mixture was heated to 100 °C and stirred at 100 °C for 5 h. The mixture was cooled to r.t., and the solid was removed by filtration. The filtrate was concentrated and purified by column chromatography

using PE:EA=5:1 as the eluent to give **518-2** as a solid (2.01 g, 67.3%). +ESI-MS: m/z 297.9 $[M+H]^+$.

[1100] Compound **518** (white solid, 21 mg, 45.3%) was prepared following the general procedure for preparing **503** by using **518-2**. +ESI-MS: m/z 518.0 $[M+H]^+$.

EXAMPLE 295

Preparation of Compound 525



[1101] To a solution of **525-1** (2.8 g, 10.0 mmol) and AIBN (168 mg, 1.0 mmol) in CCl_4 (20 mL) was added NBS (1.9 g, 10.7 mmol) at r.t. The mixture was heated to 70 °C and stirred for 3 h. The mixture was cooled to r.t. and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=15:1 as the eluent to give **525-2** as a solid (2.5 g, 69.8%). +ESI-MS: m/z 359.9 $[M+H]^+$.

[1102] To a solution of **525-2** (2.5 g, 7.0 mmol) in DMSO (15 mL) was added NaN_3 (1.1 g, 16.9 mmol) at r.t. The reaction was heated to 60 °C and stirred for 1 h. The reaction was cooled to r.t. The mixture was diluted with H_2O and extracted with EA (60 mL x 3). The organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced

pressure. The residue was purified by column chromatography using PE:EA=1:1 as the eluent to give **525-3** as a solid (1.8 g, 81.8%). +ESI-MS: m/z 322.8 $[M+H]^+$.

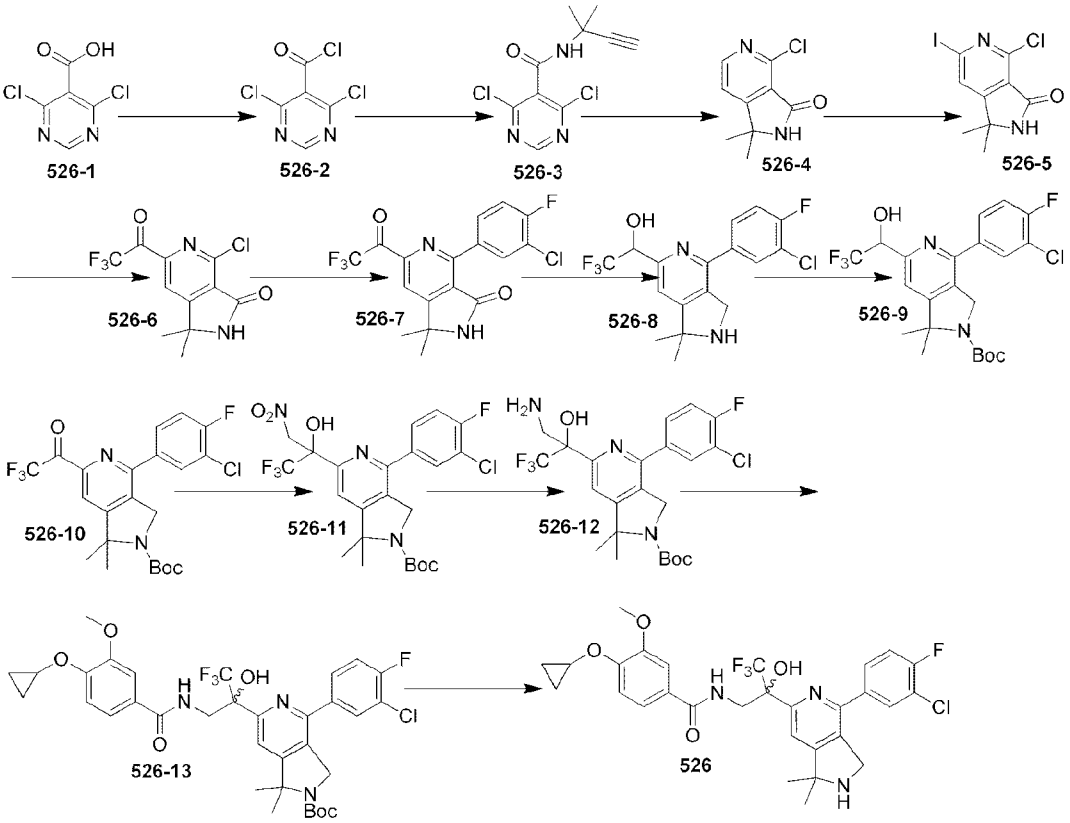
[1103] To a solution of **525-3** (1.8 g, 5.6 mmol) in MeOH (15 mL) was added $SnCl_2 \cdot 2H_2O$ (2.5 g, 11.1 mmol) at r.t. The mixture was stirred for 1 h with TLC monitoring. After **525-3** was consumed, the reaction was quenched with sat. $NaHCO_3$ and extracted with EA (30 mL x 2). The combined organic solution was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Crude **525-4** (1.0 g) was used directly without further purification.

[1104] To a solution of **525-4** (1.0 g, 3.4 mmol) in DCM (15 mL) was added Boc_2O (1.4 g, 6.4 mmol) at r.t. The mixture was stirred at r.t. for 3 h and then concentrated to dryness. The residue was purified by chromatography using PE:EA=5:1 as the eluent to give **525-5** as a solid (0.8 g, 61.5%).

[1105] To a solution of **525-5** (0.8 g, 2.0 mmol) and CF_3COOEt (1.7 g, 11.9 mmol) in THF (10 mL) was added isopropylmagnesium chloride (4 mL, 2.0 M in THF) dropwise at r.t. under N_2. The mixture was stirred at r.t. for 30 mins. The reaction was quenched with aq. NH_4Cl and extracted with EA (20 mL x 3). The combined organic solution was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Crude **525-6** (0.6 g) was used directly without purification.

[1106] Compound **525** (white solid, 130 mg) was prepared following the general procedure for preparing **272** using **525-6**. +ESI-MS: m/z 582.1 $[M+H]^+$.

EXAMPLE 296
Preparation of Compound 526



[1107] To a solution of **526-1** (10 g, 0.05 mol) in anhydrous DCM (100 mL) was added oxalyl dichloride (12.7 g, 0.1 mmol) and several drops of DMF. The mixture was stirred for 1 h and evaporated under reduced pressure to give **526-2**.

[1108] To a solution of 2-methylbut-3-yn-2-amine (4.4 g, 52.5 mmol) and Et_3N (10.1 g, 0.1 mmol) in anhydrous DCM (100 mL) was added a solution of crude **526-2** in DCM (50 mL) dropwise at r.t. The solution was stirred for 1 h, washed with water and brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated to give **526-3**. The residue was used directly without further purification.

[1109] **526-3** (2.58 g, 10 mmol) in $PhNO_2$ (10 mL) was put in a microwave tube. The solution was heated to 210 °C by microwave irradiation and stirred for 5 mins. The reaction was cooled to r.t. and concentrated at low pressure. The residue was purified by column chromatography using PE:EA=10:1~1:1 to give **526-4** (610 mg, 31.1%). +ESI-MS: m/z 197.1 $[M+H]^+$.

[1110] To a stirring solution of DMAE (1.068 g, 12 mmol) in THF (10 mL) was added n-BuLi (10 mL, 25 mmol) at -78 °C. After 5 mins, a solution of **526-4** (588 mg, 3 mmol) in anhydrous THF (3 mL) was added dropwise at -78 °C. The mixture was stirred for 10 mins and a solution of I_2 (6.35g, 25 mmol) in THF was added dropwise at -78 °C. After 20 mins, the reaction was quenched with sat. aq. Na_2SO_3. The solution was extracted with EA (50 mL x 2). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The organic phase was concentrated at low pressure, and the residue was purified by column chromatography using PE:EA=1:1 as the eluent to give **526-5** (650 mg, 51.0%). +ESI-MS: m/z 322.9 $[M+H]^+$.

[1111] To a solution of **526-5** (642 mg, 2 mmol) and CF_3COOEt (468 mg, 4 mmol) in anhydrous THF (5 mL) was added iPrMgCl (3 mL, 6 mmol) dropwise at r.t. The solution was stirred for 10 mins. The reaction was quenched with water and extracted with EA (20 mL x 2). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography using PE:EA=1:1 as the eluent to give **526-6** (302 mg, 51.3%).

[1112] To a solution of **526-6** (300 mg, 1.03 mmol) in DME/H_2O (4 mL/1 mL), Cs_2CO_3 (502 mg, 1.55 mmol), (3-chloro-4-fluorophenyl)boronic acid (270 mg, 1.87 mmol) and Pd(dppf)Cl_2 (50 mg, 65 mmol) were added at r.t. under N_2. The vial was sealed and heated to 100 °C for 40 mins by microwave irradiation. After cooling to r.t., the mixture was diluted with EA (10 mL) and brine (10 mL). The aqueous layer was extracted with EA (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=1:1 as the eluent to give **526-7** (310 mg, 73.7%). +ESI-MS: m/z 386.9 $[M+H]^+$.

[1113] To a solution of **526-7** (310 mg, 0.76 mmol) in dry THF (5 mL) was added $BH_3 \cdot Me_2S$ (1 mL, 10 mmol) at r.t. The solution was stirred in a pre-heated 80 °C oil bath for 2 h. The solution was cooled to r.t., and the reaction was quenched with H_2O. The mixture was extracted with EA (20 mL x 2). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was

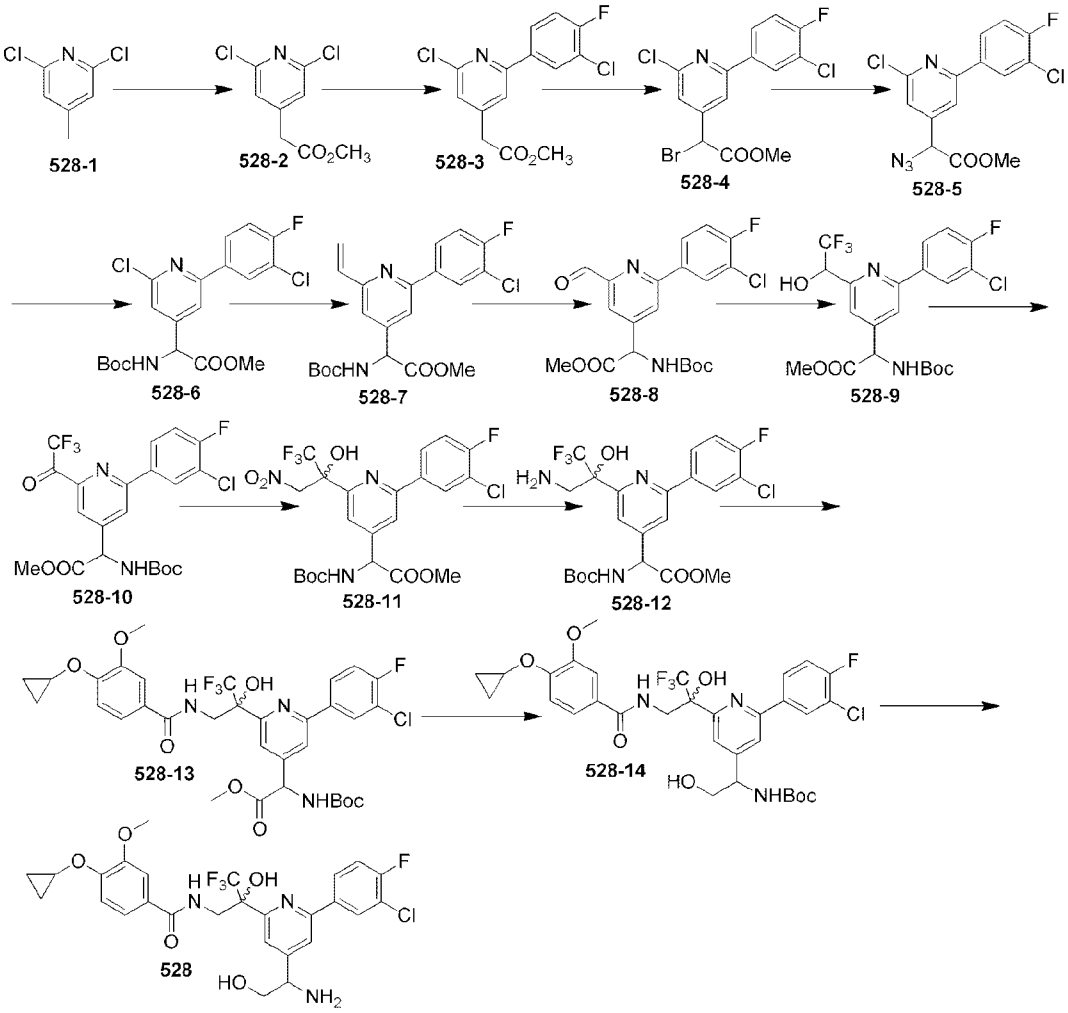
purified by column chromatography using EA as the eluent to give **526-8** (140 mg, 49.2%) as a gray solid.

[1114] To a solution of **526-8** (140 mg, 0.37 mmol) in toluene (3 mL) was added Et_3N (75 mg, 0.74 mmol) and Boc_2O (87 mg, 0.44 mmol) at r.t. The solution was stirred in a pre-heated 100 °C oil bath for 3 h. The solution was cooled to r.t. and diluted with EA (20 mL) and water (20 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=5:1 as the eluent to give **526-9** (90 mg, 51.0%). +ESI-MS: m/z 474.9 $[M+H]^+$.

[1115] To a stirred solution of **526-9** (90 mg, 0.189 mmol) in DMSO (2 mL) was added IBX (212 mg, 0.75 mmol) in one portion, and stirred at 40 °C for 2 h. The solution was poured into aq. $NaHCO_3$ and extracted with EA (10 mL x 2). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using 0~30% EA in PE as the eluent to give **526-10** (60 mg, 66.7%).

[1116] Compound **526** (white solid, 4 mg, 13.7%) was prepared following the general procedure for preparing **272** using **526-10**. +ESI-MS: m/z 594.1 $[M+H]^+$.

EXAMPLE 297
Preparation of Compound 528



[1117] To a stirred solution of **528-1** (50 g, 310 mmol) in anhydrous THF (1.2 L) was added LDA (310 mL, 620 mmol) at -78 °C slowly under N_2, and the mixture stirred at -78 °C for 0.5 h. A solution of dimethyl carbonate (67.1 g, 750 mmol) in dry THF (150 mL) was added dropwise. The solution was allowed to warm to 0 °C and stirred for 1 h below 0 °C. The reaction was quenched with aq. NH_4Cl (500 mL), and extracted with EA (500 mL x 3). The combined organic phase was washed with aqueous sodium bicarbonate, brine, and dried over anhydrous sodium sulfate. The organic layer was concentrated to dryness, and the residue was purified by column chromatography (PE:EA = 20:1) to give **528-2** (50 g, 73.5 %) as a colorless oil.

[1118] To a solution of crude **528-2** (50 g, 230 mmol) in dioxane:H_2O (6:1) (1 L) was added (3-chloro-4-fluorophenyl) boronic acid (40 g, 230 mmol), Cs_2CO_3 (223.3 g, 680 mmol) and $Pd(dppf)Cl_2$ (16.8 g, 23 mmol) under N_2. The mixture was degassed for 3 times and refilled with N_2. The reaction was stirred at 80 °C in a pre-heated oil bath for 4 h. After cooling to r.t., the mixture was diluted with water (1.5 L) and extracted with EA (1 L x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA=20:1~15:1) to yield **528-3** (42 g, 58.7%) as a light yellow solid.

[1119] To a solution of **528-3** (9.39 g, 30.00 mmol) in HOAc (100 mL) was added Br_2 (5.28 g, 33 mmol) dropwise at r.t. The mixture was heated at 60 °C for 5 h. The reaction was cooled to r.t. and concentrated under reduced pressure to dryness. The residue was used directly without further purification. +ESI-MS: m/z 393.7 $[M+H]^+$.

[1120] To a solution of crude **528-4** (10.0 g) in MeOH (100 mL) was added NaN_3 (3.3 g, 50.8 mmol) at 25 °C, and the mixture was stirred at 25°C for 1 h. The mixture was diluted with H_2O (150 mL), and extracted with and EA (150 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA =20:1~5:1 as the eluent to give **528-5** (8.02 g, 88%).

[1121] To a solution of **528-5** (8.02 g, 22.6 mmol) and Boc_2O (14.8 g, 67.77 mmol) in MeOH (100 mL) was added Pd/C (3.0 g, 10%) under N_2. The suspension was degassed and purged with H_2 for several times. The mixture was stirred under H_2 balloon at 25 °C for 3 h. TLC showed that the starting material was consumed completely. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=50:1~5:1) to give **528-6** (5.5 g). +ESI-MS: m/z 428.9 $[M+H]^+$.

[1122] **528-13** (white solid, 80 mg) was prepared following the general procedure for preparing **272** using **528-6**. +ESI-MS: m/z 712.1 $[M+H]^+$.

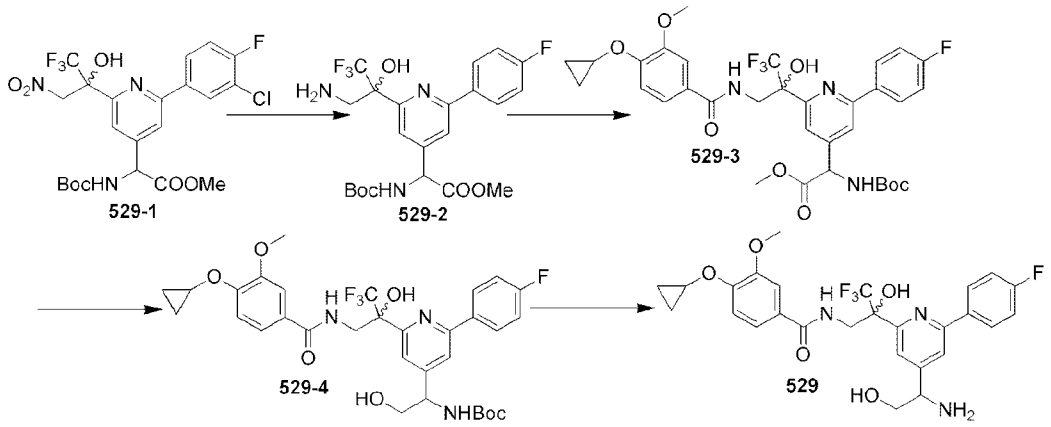
[1123] To a solution of **528-13** (80.00 mg crude) in a co-solvent of MeOH (5 mL) and THF (5 mL) was added $NaBH_4$ (40 mg, 1.05 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction was quenched by H_2O and extracted by EA (10 mL x 3). The combined

organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by prep-TLC to give **528-14** (51 mg). +ESI-MS: m/z 684.1 $[M+H]^+$.

[1124] Compound **528** (white solid, 18 mg, 39.9%) was prepared following the general procedure for preparing **272** using **528-14**. +ESI-MS: m/z 584.0 $[M+H]^+$.

EXAMPLE 298

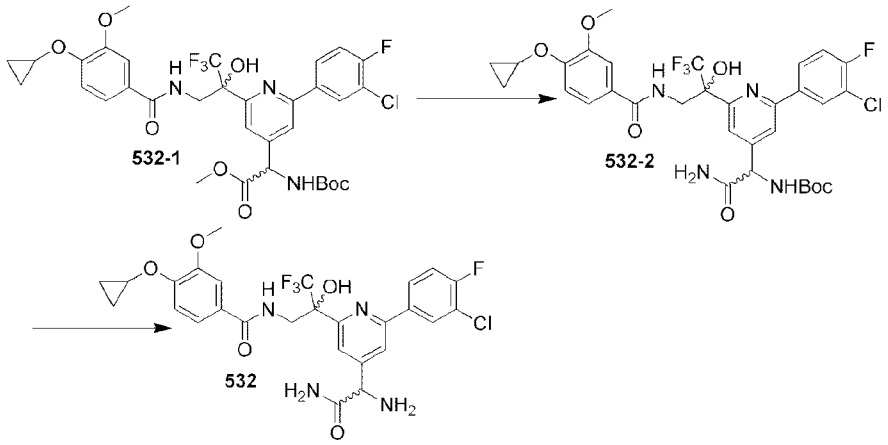
Preparation of Compound 529



[1125] To a solution of **529-1** (150.00 mg) in MeOH (50 mL) was added Ra-Ni (0.15 g) under N_2. The suspension was degassed and purged with H_2 for several times. The mixture was stirred under H_2 balloon at 25 °C for 2 H. TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was filtered, and the filtrate was concentrated to give **529-2** (90 mg, crude), which was used directly without further purification.

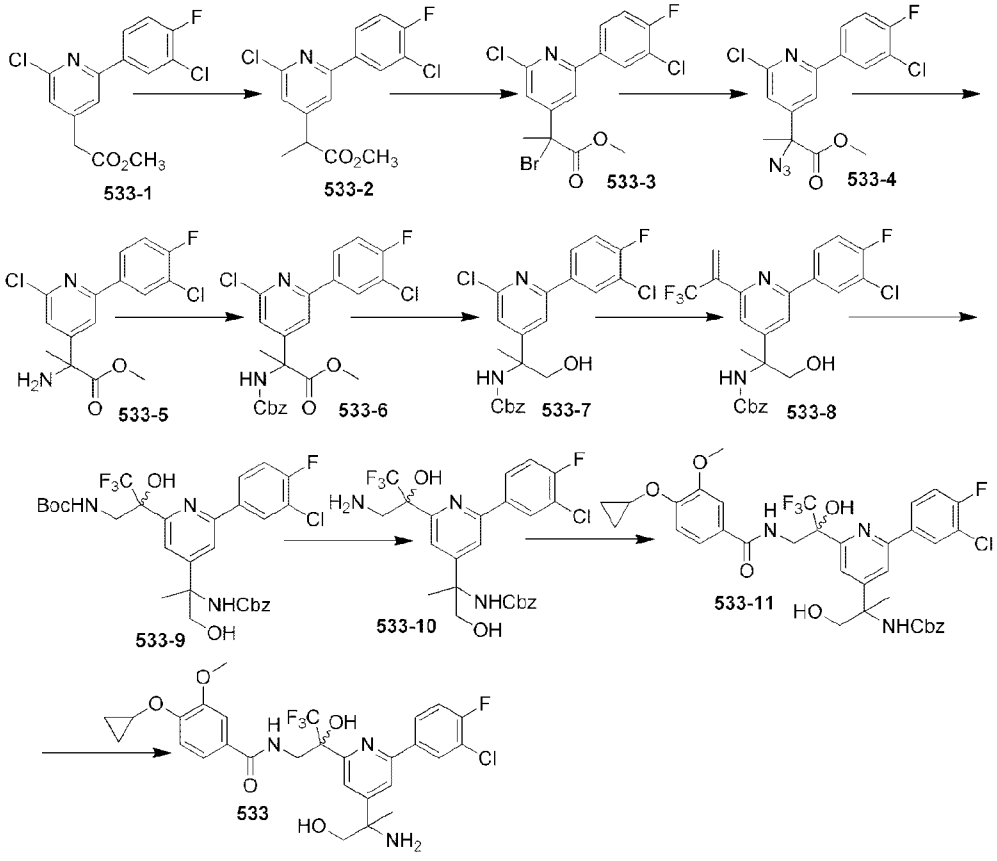
[1126] Compound **529** (white solid, 13 mg) was prepared following the general procedure for preparing **528** by using **529-2**. +ESI-MS: m/z 550.1 $[M+H]^+$.

EXAMPLE 299
Preparation of Compound 532



[1127] Compound **532** (white solid, 13 mg) was prepared following the general procedure for preparing **501** and **272** by using **532-1**. +ESI-MS: m/z 597.1 $[M+H]^+$.

EXAMPLE 300
Preparation of Compound 533



[1128] To a solution of **533-1** (10 g, 31.9 mmol) in anhydrous THF (100 mL) was added LiHMDS (63.9 mL, 63.9 mmol) dropwise, and stirred at -78 °C for 30 mins. A solution of MeI (9.07 g, 63.9 mmol) in dry THF (50 mL) was added dropwise. The mixture was warmed to 0 °C and stirred at 0 °C for 1 h. The reaction was quenched with water (100 mL) and extracted with EA (150 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuum to dryness. The residue was purified by column chromatography (PE:EA=10:1) to yield **533-2** (3.5 g, 32%) as a light yellow solid.

[1129] **533-4** (crude, yellow oil) was prepared following the general procedure for preparing **501** by using **2**. +ESI-MS: m/z 369.0 $[M+H]^+$.

[1130] To a solution of **533-4** (500.00 mg, 1.35 mmol) in MeOH (30 mL) was added $SnCl_2 \cdot 2H_2O$ (760.40 mg, 3.39 mmol) in one portion at r.t. under N_2, and the mixture was stirred for 2 h. TLC showed that the reaction was completed. The mixture was diluted with water (20 mL). The solution was extracted with EA (30 mL x 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was used in the next step without purification.

[1131] To a solution of **533-5** (0.5 g, 1.46 mmol) and CbzCl (745.56 mg, 4.37 mmol) in DCM (15 mL) was added $NaHCO_3$ (489.61 mg, 5.83 mmol) in one portion, and the mixture was stirred at r.t. for 1 h. The solution was poured into ice-water (15 mL) and stirred for 20 mins. The aqueous phase was extracted with EA (40 mL x 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA=30:1~10:1) to afford **533-6** (0.4 g) as a yellow solid. +ESI-MS: m/z 477.1 $[M+H]^+$.

[1132] To a solution of **533-6** (0.4 g, 0.84 mol) in THF (40 mL) was added $LiBH_4$ (55 mg, 2.5 mmol) in one portion, and the mixture stirred at r.t. for 1 h. TLC showed that the reaction was completed. The mixture was poured into ice-water (15 mL) and stirred for 20 mins. The aqueous phase was extracted with EA (40 mL x 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at low pressure. The residue was purified by column chromatography (PE:EA=30:1~2:1) to afford **533-7** (320.00 mg, 85%) as a yellow solid. +ESI-MS: m/z 448.6 $[M+H]^+$.

[1133] To a solution of **533-7** (320 mg, 0.71 mmol) in DME (5 mL) and H_2O (1 mL) were added 4,4,6-trimethyl-2-[1-(trifluoromethyl)vinyl]-1,3,2-dioxaborinane (320 mg, 1.42 mmol), Cs_2CO_3 (0.7 g, 2.13 mmol), and $Pd(dppf)Cl_2$ (52 mg, 0.07mol) under N_2. The reaction flask was sealed and stirred at 110 °C by microwave irradiation for 1 h. The reaction was cooled to r.t., and diluted with EA and water. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using 3-20% of EA in PE as the eluent to give **533-8** (220 mg, 60%). +ESI-MS: m/z 508.9 $[M+H]^+$.

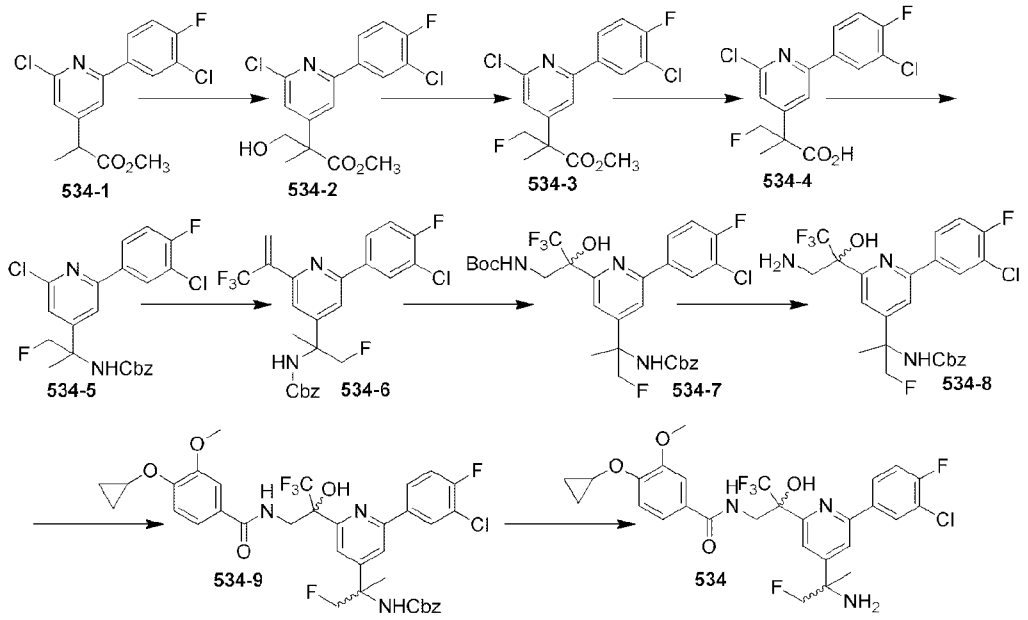
[1134] To a mixture of **533-8** (100.00 mg, 0.2 mmol) in t-BuOH (1.5 mL) and H_2O (0.5 mL), were added $K_2OsO_4H_2O$ (11 mg, 0.06 mmol) and BocHN-OTs (113 mg, 0.39 mmol), and the mixture was stirred at r.t. overnight. The mixture was poured into ice-water, stirred for 20 mins and extracted with EA (10 mL x 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=30:1~20:1 as the eluent to give **533-9** (50 mg, 40%) as a yellow solid. +ESI-MS: m/z 642.1 $[M+H]^+$.

[1135] To a solution of **533-9** (50.00 mg, 0.078 mmol) in DCM (2 mL) was added TFA (1 mL). The mixture was stirred at r.t. for 1 h. The solution was poured into ice-water (5 mL) and neutralized with sat. $NaHCO_3$ solution. The aqueous phase was extracted with EA (5 mL x 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using EA as the eluent to give **533-10** (30.00 mg, 71%) as a yellow solid. +ESI-MS: m/z 542.1 $[M+H]^+$.

[1136] **533-11** (yellow solid, 30 mg, 74%) was prepared following the general procedure for preparing **272** using **533-11**. +ESI-MS: m/z 732.3 $[M+H]^+$.

[1137] To a solution of **533-11** (30 mg) in CH_3CN (1 mL) was added one drop of TMSI at r.t. The mixture was stirred at r.t. for 10 mins. The mixture was poured into water, neutralized with sat. $NaHCO_3$ solution and extracted with EA (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **533** (23.00 mg) as a white solid. +ESI-MS: m/z 597.9 $[M+H]^+$.

EXAMPLE 301
Preparation of Compound 534



[1138] To a solution of **534-1** (6 g, 18.3 mmol) and TEA (18.5 g, 183 mmol) in THF (60 mL) was added aq. HCHO (15 g, 183 mmol) at 25 °C under N_2. The mixture was stirred at 25 °C for 2 h. TLC (PE:EA=5:1) showed that the reaction was completed. The mixture was diluted with water and extracted with EA (100 mL x 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=30:1~5:1 as the eluent to afford **534-2** (5.1 g, 77%) as a white oil. +ESI-MS: m/z 358.1 $[M+H]^+$.

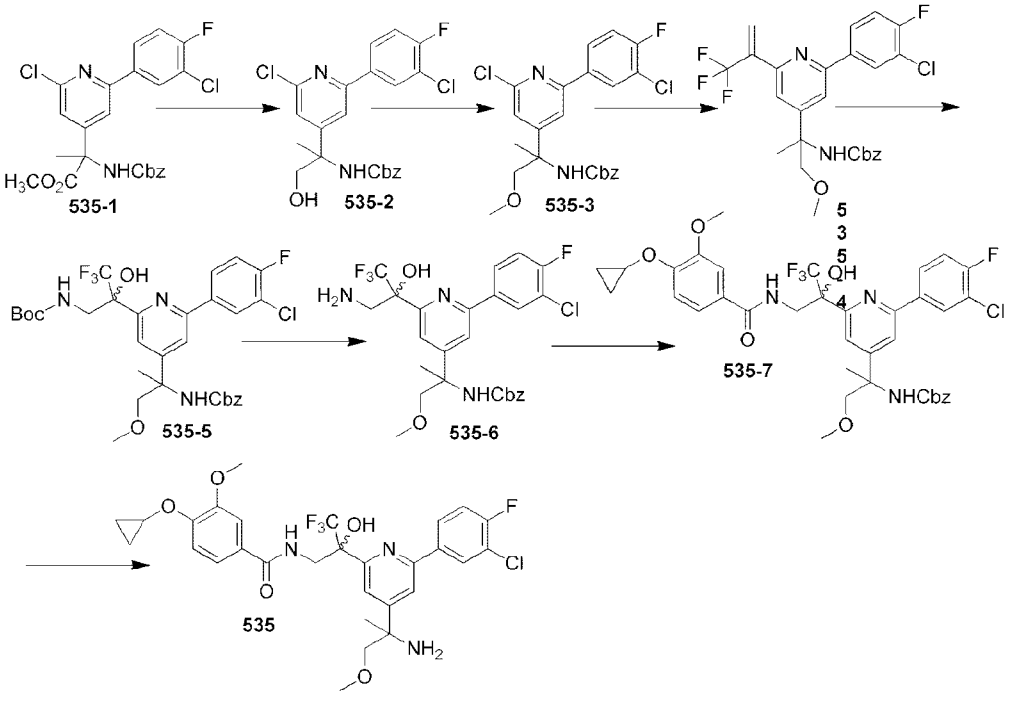
[1139] To a solution of **534-2** (1.76 g, 4.91 mmol) in DCM (20 mL) was added DAST (7.91 g, 49.10 mmol) dropwise at -78 °C under N_2. The mixture was slowly warmed to 25 °C, and stirred for 12 h. TLC (PE:EA=5:1) showed that the reaction was completed. The mixture was cooled to 0 °C and quenched with sat. $NaHCO_3$ solution. The aqueous phase was extracted with EA (20 mL x 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at low pressure. The residue was purified by column chromatography using PE:EA=100:1~ 60:1 as the eluent to afford **534-3** (0.6 g, 34%) as a white oil. +ESI-MS: m/z 360.1 $[M+H]^+$.

[1140] To a solution of **534-3** (590 mg, 1.64 mmol) in MeOH (6 mL) was added a solution of NaOH (260 mg, 6.6 mmol) in H_2O (6 mL) at r.t. The mixture was heated to 60 °C and stirred for 2 h. The mixture was cooled to r.t., and the organic solvent was removed under reduced pressure. The pH of aqueous phase was adjusted to ~3 using 2M HCl and extracted with EA (30 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give **534-4** (503 mg, 88%) as a white solid.

[1141] To a solution of **534-4** (438 mg, 1.27 mmol), DIPEA (655 mg, 5.07 mmol) and BnOH (274 mg, 2.53 mmol) in toluene (5 mL) was added DPPA (698 mg, 2.54 mmol) at r.t. under N_2. The mixture was heated to 80 °C and stirred for 12 h. The mixture was cooled to r.t. and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=30:1~5:1 as the eluent to afford **534-5** (450.00 mg, 78.52%) as a white solid.

[1142] Compound **534** (white solid, 21 mg, 45.9%) was prepared following the general procedure for preparing **533** using **534-5**. +ESI-MS: m/z 600.0 $[M+H]^+$.

EXAMPLE 302
Preparation of Compound 535



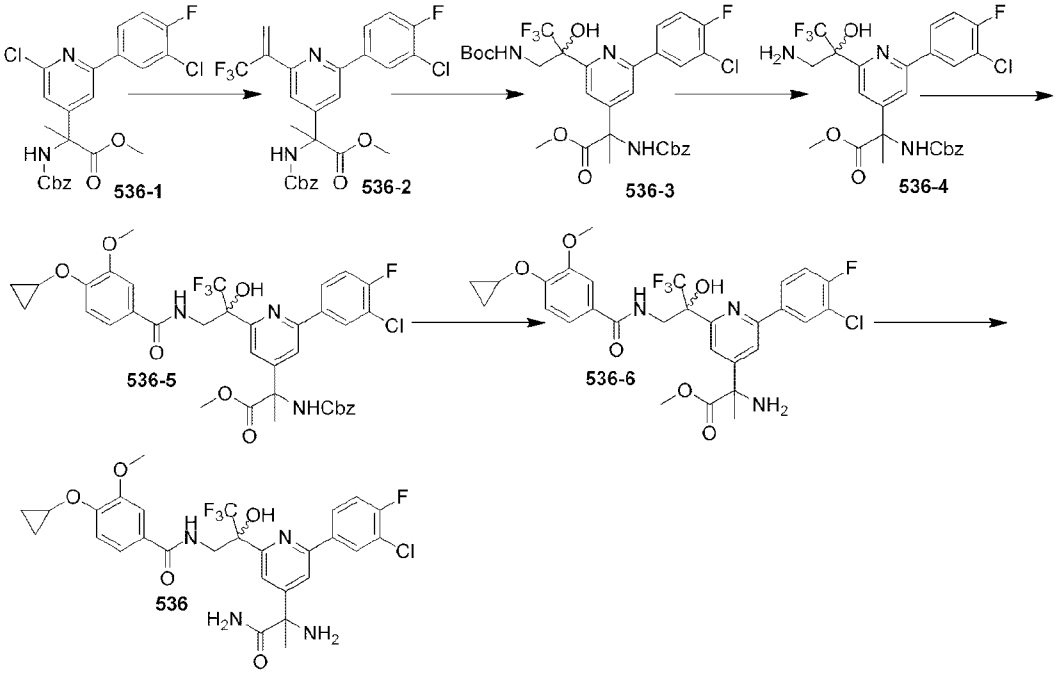
[1143] To a solution of **535-1** (2.0 g, 4.2 mmol) in MeOH (20 mL) was added $NaBH_4$ (476 mg, 12.6 mmol) at r.t. in small portions. The solution was stirred for 30 mins and quenched with H_2O. The mixture was extracted with EA (50 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography using PE:EA=1:1 to give **535-2** (1.6 g, 85%) as a white solid. +ESI-MS: m/z 449.1 $[M+H]^+$.

[1144] To a solution of **535-2** (1.40 g, 3.1 mmol) in THF (20 mL) were added Ag_2O (723 mg, 3.1 mmol) and MeI (1.77 g, 12.5 mmol) at r.t. The mixture was sealed and heated to 40 °C. The reaction was stirred overnight and concentrated to dryness at low pressure. The residue was purified by column chromatography using PE:EA=10:1 as the eluent to give **535-3** (450 mg, 31%). +ESI-MS: m/z 463.1 $[M+H]^+$.

[1145] Compound **535** (white solid, 11 mg, 22%) was prepared following the general procedure for preparing **533** using **535-3**. +ESI-MS: m/z 612.1 $[M+H]^+$.

EXAMPLE 303

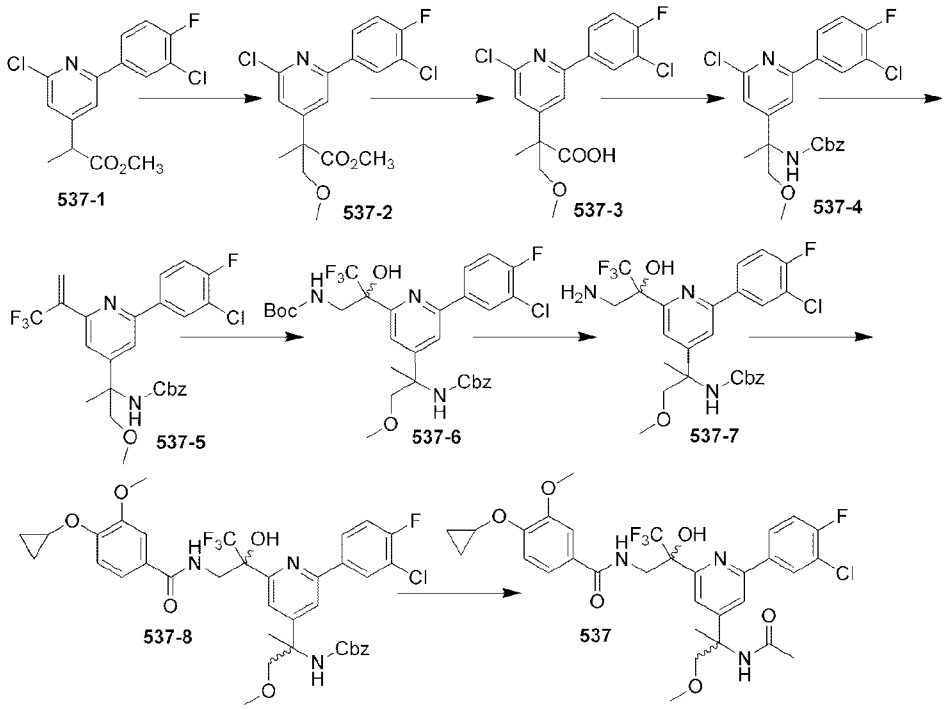
Preparation of Compound 536



[1146] Compound **536** (white solid, 65 mg, 83%) was prepared following the general procedure for preparing **533** and **501** using **536-1**. +ESI-MS: m/z 611.2 $[M+H]^+$.

EXAMPLE 304

Preparation of Compound 537



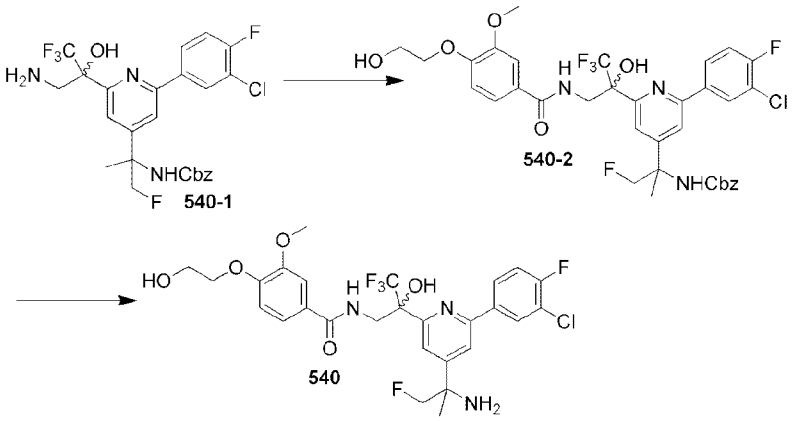
[1147] To a solution of **537-1** (0.7 g, 2.1 mmol) in THF (8 mL) was added LiHMDS (3.2 mL 1 M in THF) at -78 °C in a period of 1 minute under N_2. After stirring at -78°C for 10 minutes, a solution of MOMCl (340 mg, 4.2 mmol) in THF (2 mL) was added at -78 °C in a period of 1 min under N_2. The reaction mixture was warmed to room temperature and stirred for 20 minutes. LCMS showed that **537-1** was consumed completely. The reaction was quenched by water and extracted with EA (20 mL X 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **537-2** (720 mg, 82%) as colorless oil. +ESI-MS: m/z 372.1 $[M+H]^+$.

[1148] **537-8** (white solid, 45 mg, 78%) was prepared following the general procedure for preparing **533** using **537-2**. +ESI-MS: m/z 746.1 $[M+H]^+$.

[1149] To a solution of **537-8** (45 mg, 0.06 mmol) in TFA (1 mL) was added HBr/HOAc (1 mL, 40%) at r.t. The reaction mixture was stirred at room temperature until all starting material was consumed (followed by LCMS). The resulting mixture was concentrated under reduced pressure. The residue was neutralized with aqueous $NaHCO_3$ and

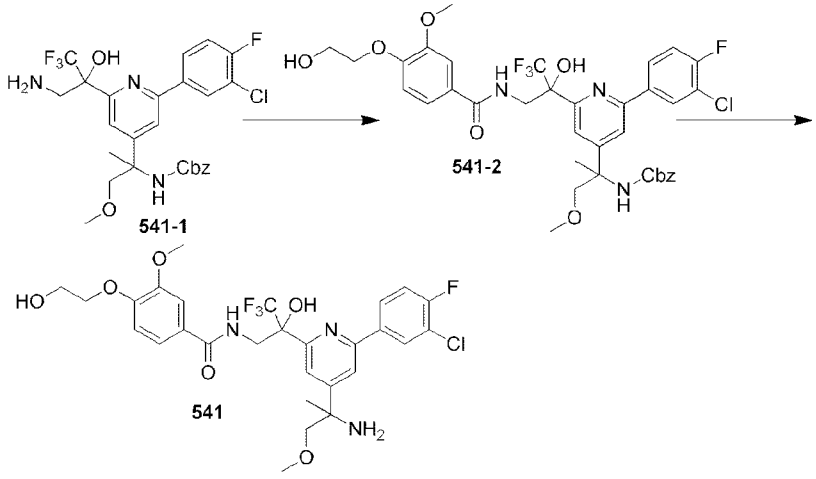
extracted with EA. The combined organic phase was concentrated under reduced pressure. The residue was purified by Pre-HPLC to afford **537** (9 mg, 16.3%) as a white solid. +ESI-MS: m/z 654.1 $[M+H]^+$.

EXAMPLE 305
Preparation of Compound 540



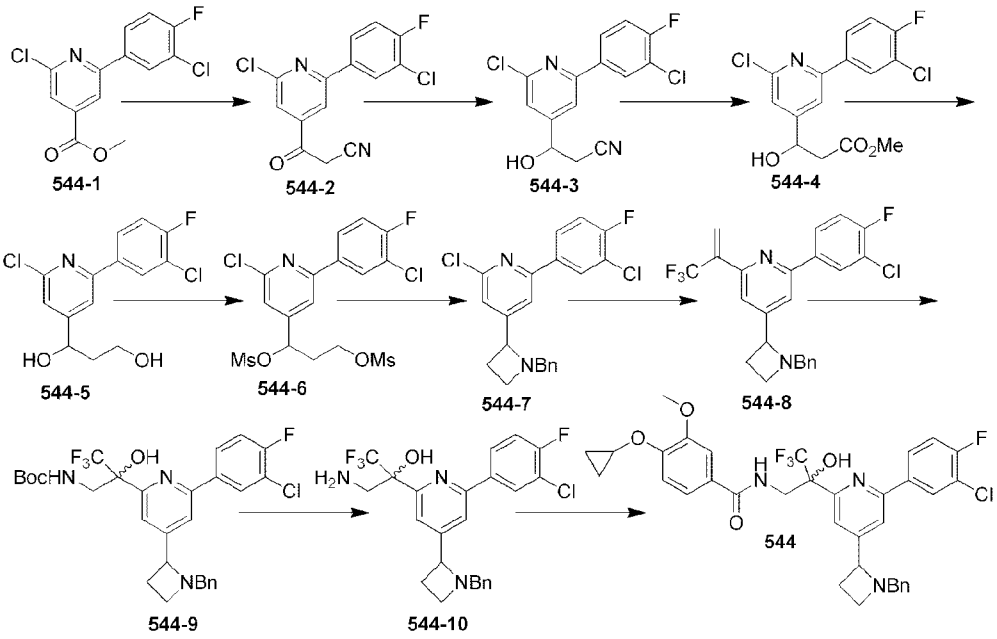
[1150] Compound **540** (white solid, 175 mg, 71%) was prepared following the general procedure for preparing **534** using **540-1**. +ESI-MS: m/z 604.1 $[M+H]^+$.

EXAMPLE 306
Preparation of Compound 541



[1151] Compound **541** (white solid, 13 mg, 18.4%) was prepared following the general procedure for preparing **537** and **528** using **541-1**. +ESI-MS: m/z 616.0 $[M+H]^+$.

EXAMPLE 307
Preparation of Compound 544



[1152] To a solution of CH_3CN (24.6 g, 600 mmol) in toluene (200 mL) was added n-BuLi (120 mL, 2.5 M in hexane) dropwise at -78°C under N_2. The mixture was stirred at -78 °C for 30 mins. The mixture was treated with a solution of **544-1** (36.0 g, 120 mmol) in toluene (200 mL). The mixture was warmed to r.t. and stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl, and extracted with EA (4 x 200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography to give **544-2** as a white solid (31.5 g, 85.0%). +ESI-MS: m/z 308.9 $[M+H]^+$.

[1153] To a solution of **544-2** (30.9 g, 100 mmol) in MeOH (600 mL) was added $NaBH_4$ (19 g, 500 mmol) in portions at 0 °C, and stirred at 0 °C for 4 h. The mixture was quenched with water, and extracted with EA (4 x 300 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was further purified by column chromatography to afford **544-3** as a light yellow solid (28.0 g, 90.0%). +ESI-MS: m/z 310.9 $[M+H]^+$.

[1154] To a solution of **544-3** (5 g, 16.08 mmol) in MeOH (100 mL) was added $SOCl_2$ (20 mL) at 0 °C dropwise. The mixture was heated to reflux and stirred for 48 h. The

mixture was cooled to r.t. The solution was neutralized with sat. aq. $NaHCO_3$, and extracted with EA (4 x 300 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to afford **544-4** as a light yellow solid (3.32 g, 60.0%).

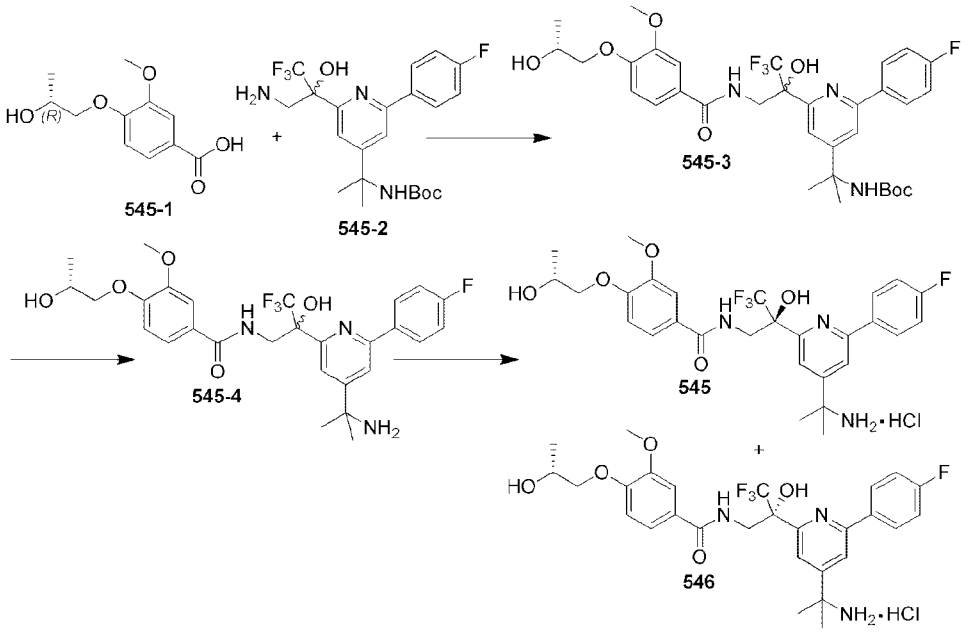
[1155] Compound **544-5** (light yellow solid, 2.65 g, 90%) was prepared was prepared following the general procedure for preparing **544-3** using **544-4**. +ESI-MS: m/z 315.7 $[M+H]^+$.

[1156] To a solution of **544-5** (2.65 g, 8.38 mmol) and TEA (2.54 g, 25.15 mmol) in DCM (20 mL) was added MsCl (2.88 g, 25.15 mmol) at 0 ^oC. The mixture was stirred at r.t. for 2 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with EA (4 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at low pressure. The residue was purified by column chromatography to afford **544-6** as a light yellow solid (3.2 g, 80.8 %).

[1157] To a solution of **544-6** (3.2 g, 8.4 mmol) in toluene (50 mL) were added $BnNH_2$ (5.4 g, 50.3 mmol), K_2CO_3 (6.9 g, 50.3 mmol), and KI (100 mg) at r.t. The mixture was stirred at 160 ^oC for 6 h. The mixture was cooled to r.t. and diluted with water. The solution was extracted with EA (4 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at low pressure. The residue was purified by column chromatography to afford **544-7** as a light yellow solid (1.1 g, 33.9%). +ESI-MS: m/z 386.9 $[M+H]^+$.

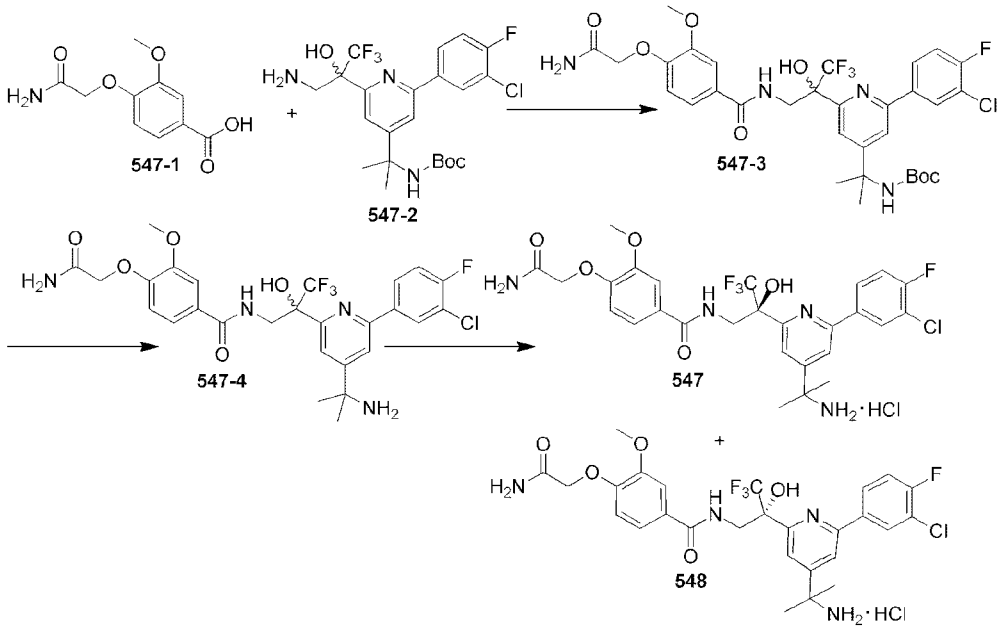
[1158] Compound **544** (white solid, 450 mg, 40.3%) was prepared was prepared following the general procedure for preparing **528** using **544-7**. +ESI-MS: m/z 670.3 $[M+H]^+$.

EXAMPLE 308
Preparation of Compounds 545 and 546



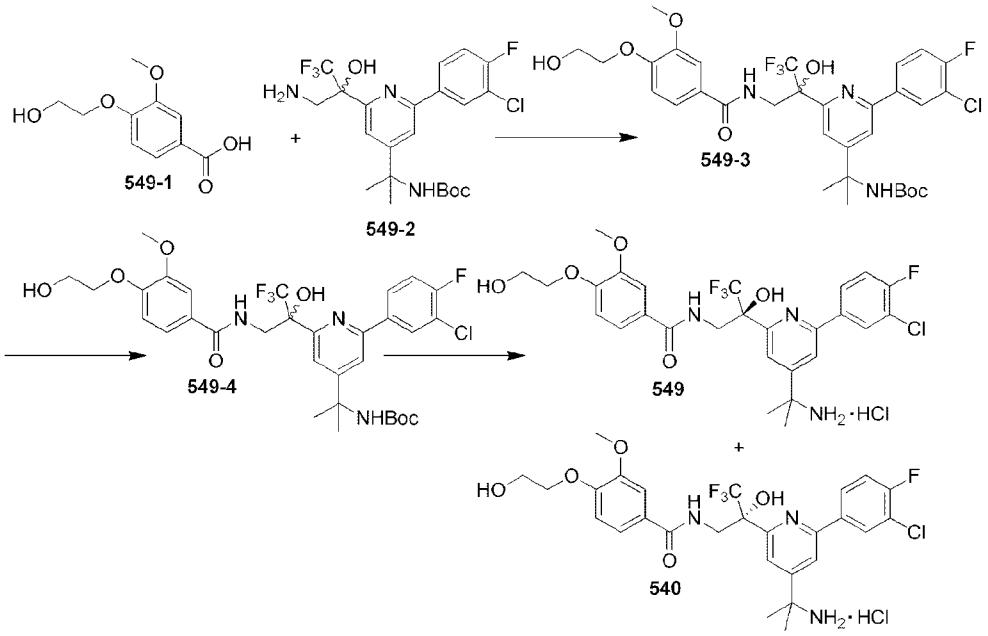
[1159] Compounds **545** (white solid, 112 mg) and **546** (white solid, 107 mg) was prepared following the general procedure for preparing **495** and **496** using **545-1** and **545-2**. **545**: +ESI-MS: m/z 566.2 $[M+H]^+$; and **546**: +ESI-MS: m/z 566.2 $[M+H]^+$.

EXAMPLE 309
Preparation of Compounds 547 and 548



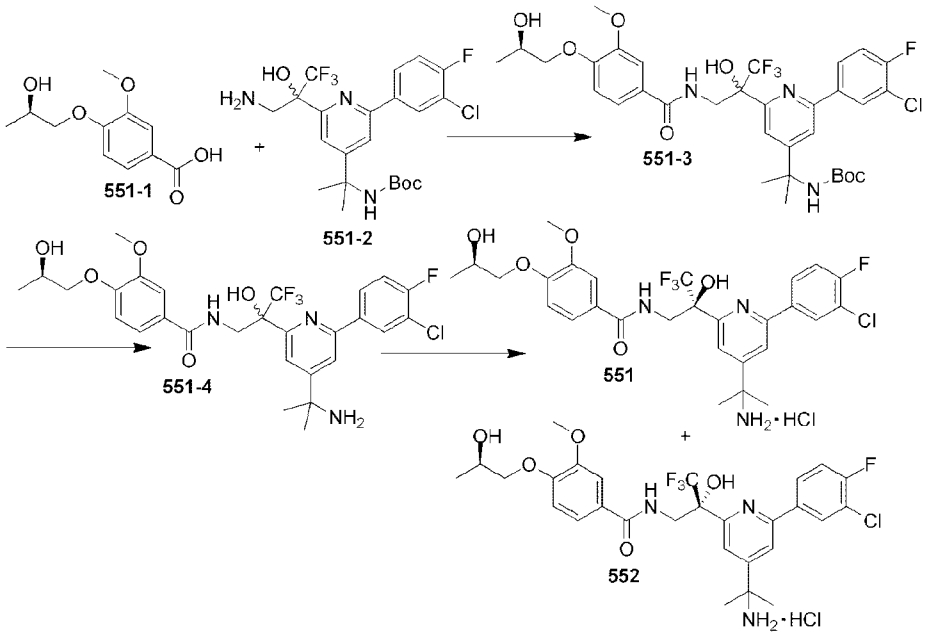
[1160] Compounds **547** (white solid, 45 mg) and **548** (white solid, 48 mg) was prepared following the general procedure for preparing **271** and **272** using **547-1** and **547-2**. **547**: +ESI-MS: m/z 599.1 $[M+H]^+$; and **548**: +ESI-MS: m/z 599.1 $[M+H]^+$.

EXAMPLE 310
Preparation of Compounds 549 and 550



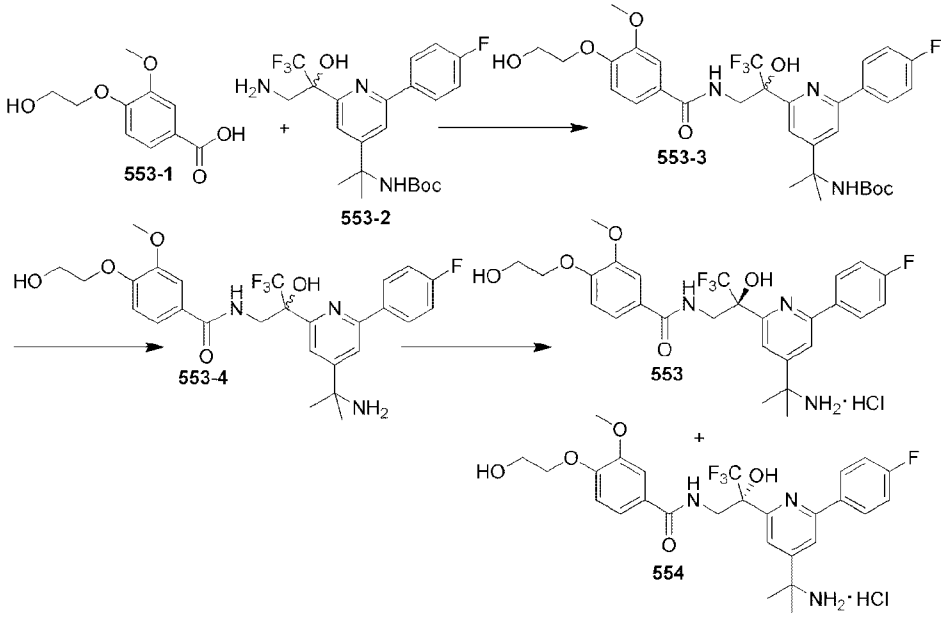
[1161] Compounds **549** (white solid, 102 mg) and **550** (white solid, 108 mg) was prepared following the general procedure for preparing **271** and **272** using **549-1** and **549-2**. **549**: +ESI-MS: m/z 585.9 $[M+H]^+$; and **550**: +ESI-MS: m/z 586.0 $[M+H]^+$.

EXAMPLE 311
Preparation of Compounds 551 and 552



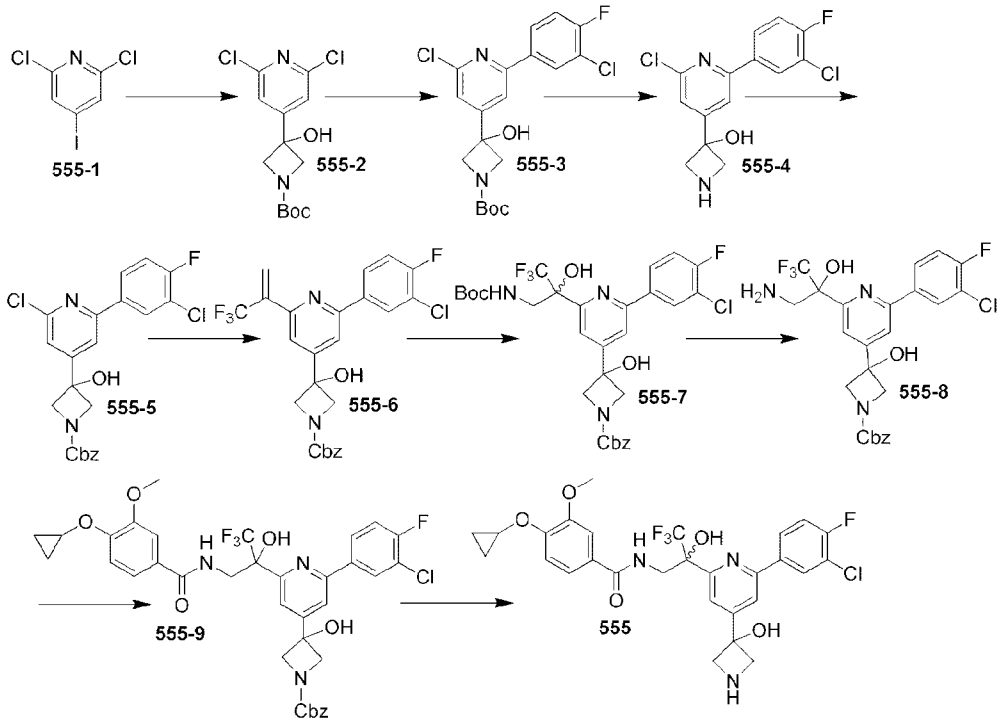
[1162] Compounds **551** (white solid, 78 mg) and **552** (white solid, 72 mg) was prepared following the general procedure for preparing **271** and **272** using **551-1** and **551-2**. **551**: +ESI-MS: m/z 600.2 $[M+H]^+$; and **552**: +ESI-MS: m/z 600.2 $[M+H]^+$.

EXAMPLE 312
Preparation of Compounds 553 and 554



[1163] Compounds **553** (white solid, 35 mg) and **554** (white solid, 45 mg) was prepared following the general procedure for preparing **495** and **496** using **553-1** and **553-2**. **553**: +ESI-MS: m/z 552.2 $[M+H]^+$; and **554**: +ESI-MS: m/z 552.1 $[M+H]^+$.

EXAMPLE 313
Preparation of Compound 555



[1164] To a solution of **555-1** (2.74 g, 10 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (4.8 mL, 2.5 M in hexane) dropwise at -78 °C under N_2. The mixture was stirred at -78 °C for 20 mins, and then treated with a solution of tert-butyl 3-oxoazetidine-1-carboxylate (1.71 g, 10.00 mmol) in anhydrous THF (5 mL) at -78 °C. The solution was stirred for 30 mins at -78 °C. The reaction was quenched with water and extracted with EA (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=9:1 as the eluent to afford **555-2** (1.05 g, 33%). +ESI-MS: m/z 319.1 $[M+H]^+$.

[1165] To a solution of **555-2** (0.8 g, 2.52 mmol) and (3-chloro-4-fluorophenyl) boronic acid (440 mg, 2.52 mmol) in dioxane:H_2O (10:1 mL) were added Cs_2CO_3 (1.23 g, 3.78 mmol) and $Pd(dppf)Cl_2$ (185.00 mg, 0.25 mmol) under N_2. The mixture was heated to

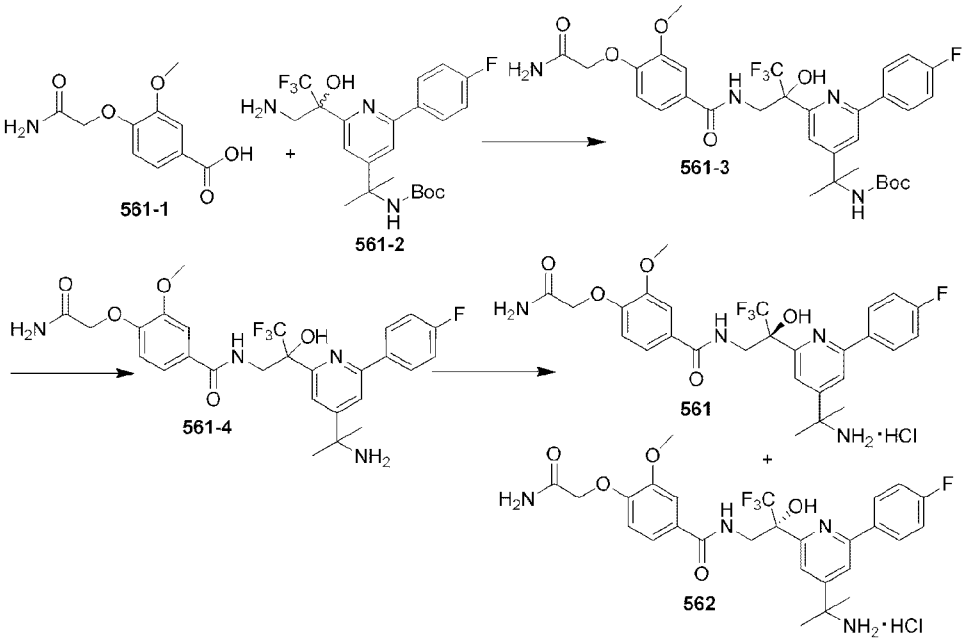
80 °C in an oil bath and stirred for 1 h. The mixture was cooled to r.t., poured into H_2O (20 mL) and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=9:1 as the eluent to afford **555-3** (780 mg). +ESI-MS: m/z 413.1 $[M+H]^+$.

[1166] To a solution of **555-3** (780 mg, 1.89 mmol) in DCM (8 mL) was added TFA (2 mL), and the mixture stirred at r.t. for 30 mins. The mixture was concentrated under reduced pressure, and the residue was dissolved in DCM (10 mL) and Et_3N (572 mg, 5.65 mmol). CbzCl (643 mg, 3.77 mmol) was added slowly at r.t., and the mixture was stirred for 2 h. The solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduce pressure. The residue was purified by column chromatography using PE:EA=4:1 as the eluent to give **555-5** (720.00 mg). +ESI-MS: m/z 447.1 $[M+H]^+$.

[1167] Compound **555** (white solid, 3.5 mg, 16.3%) was prepared following the general procedure for preparing **533** using **555-5**. +ESI-MS: m/z 595.9$[M+H]^+$.

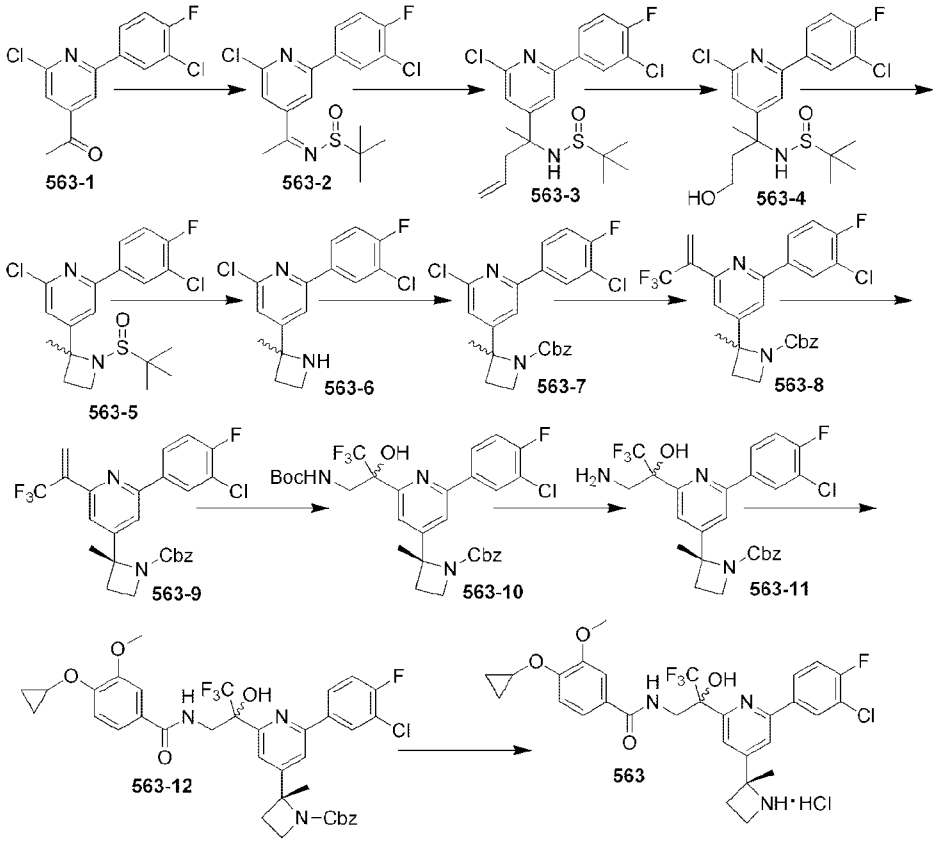
EXAMPLE 314

Preparation of Compounds 561 and 562



[1168] Compounds **561** (white solid, 50 mg) and **562** (white solid, 48 mg) was prepared following the general procedure for preparing **495** and **496** using **561-1** and **561-2**. **561**: +ESI-MS: m/z 565.1 $[M+H]^+$; and **562**: +ESI-MS: m/z 565.1 $[M+H]^+$.

EXAMPLE 315
Preparation of Compound 563



[1169] A solution of **563-1** (3.00 g, 10.56 mmol) and tetraethoxytitanium (7.23 g, 31.68 mmol) in anhydrous THF (60 mL) was stirred for 5 mins. The solution was treated with 2-methylpropane-2-sulfinamide (1.92 g, 15.84 mmol) and stirred at 70 °C for 5 h. The mixture was cooled to r.t., and the reaction was quenched with sat. aq. $NaHCO_3$ until white titanium salts precipitate was formed. The suspension was filtered through a pad of Celite, and the cake was washed with EA. The aqueous was extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give **563-2** (3.50 g, 85.6%). +ESI-MS: m/z 387.0 $[M+H]^+$.

[1170] To a solution of **563-2** (3.50 g, 9.0 mmol) in anhydrous THF (15 mL) was added allylmagnesium bromide (13.6 mL, 1.0 M in THF) at -78 °C under N_2, and the mixture was stirred at -78 °C for 1 h. The mixture was allowed to warm to 25 °C and stirred for another 1 h. The reaction was quenched with aq. NH_4Cl solution and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified column chromatography to afford **563-3** (1.20 g, 31%) as a yellow solid. +ESI-MS: m/z 429.1 $[M+H]^+$.

[1171] Ozone was bubbled into a solution of **563-3** (1.2 g, 2.8 mmol) in anhydrous MeOH (30 mL) at -78 °C for 10 mins. After excess O_3 was purged by nitrogen, $NaBH_4$ (420 mg 11.2 mmol) was added at 25 °C in portions. The solution was stirred for 30 mins at r.t. The reaction was quenched with H_2O and extracted with EA (3 x 60 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA = 2:1 as the eluent to give **563-4** (1.02 g, 83%) as a solid. +ESI-MS: m/z 433.1 $[M+H]^+$.

[1172] To a solution of **563-4** (1.01 g, 2.5 mmol) and PPh_3 (1.0 g, 3.8 mmol) in anhydrous THF (20 mL) was added DIAD (870 mg, 4.3 mmol) dropwise at 25 °C under N_2. The mixture was heated to 70 °C and stirred for 4 h. The mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by column chromatography to afford **563-5** (902 mg, 85%) as a solid.

[1173] To a solution of **563-5** (902 mg 2.2 mmol) in dioxane (8 mL) was added conc. HCl (1 mL, 12 M) in one portion, and stirred at 25 °C for 1 h. The mixture was concentrated to give **563-6** (750 mg), which was used for the next step without further purification.

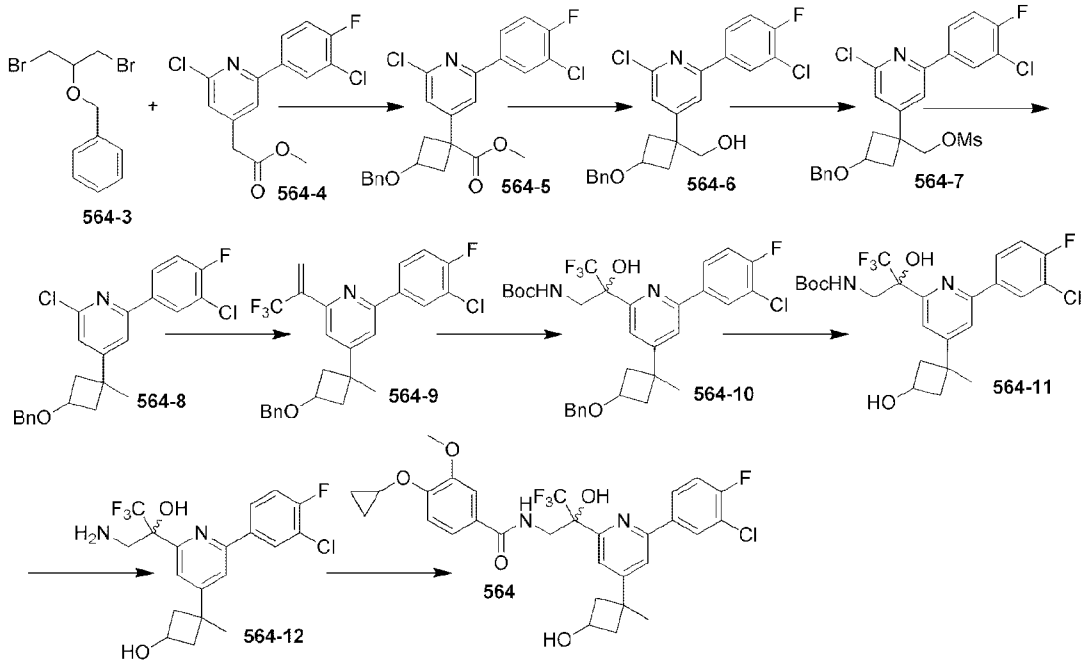
[1174] **563-6** (750mg) and $NaHCO_3$ (607 mg, 7.2mmol) were dissolved in DCM (10 mL) and H_2O (1 mL). The solution was treated with CbzCl (617 mg 3.6 mmol) at r.t. The mixture was stirred at r.t. for 1 h. The mixture was diluted with water and extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous

Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to afford **563-7** (990 mg, 93%). +ESI-MS: m/z 444.9 $[M+H]^+$.

[1175] **563-8** (white solid, 1.1 g, 16.3%) was prepared following the general procedure for preparing **533** using **563-7**. +ESI-MS: m/z 595.9 $[M+H]^+$. **563-9** (402 mg) was obtained by SFC separation of **563-8** (1.1 g).

[1176] Compound **563** (white solid, 20 mg, 33%) was prepared following the general procedure for preparing **533** using **563-9**. +ESI-MS: m/z 593.9 $[M+H]^+$.

EXAMPLE 316
Preparation of Compound 564



[1177] **564-3** was prepared as described in Franck, D. et al., Bioorganic & Medicinal Chemistry (2013) 21(3):643-652.

[1178] To a solution of **564-4** (11.22 g, 35.7 mmol) in anhydrous THF (200 mL) was added LiHMDS (286 mL 1 M in THF) in portions at -78 °C under N_2. The mixture was stirred at -78 °C for 30 mins. The mixture was treated with a solution of **564-3** (22 g, 71.4 mmol) in anhydrous THF (50 mL) dropwise. The mixture was warmed to r.t. and stirred for 3 h. The reaction was quenched with ice-water (150 mL). The aqueous phase was extracted with EA (3 x 200 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified

by column chromatography using PE:EA=30:1~10:1 as the eluent to afford **564-5** (11.0 g, 70% purity) as a light yellow oil. +ESI-MS: m/z 460.0 $[M+H]^+$.

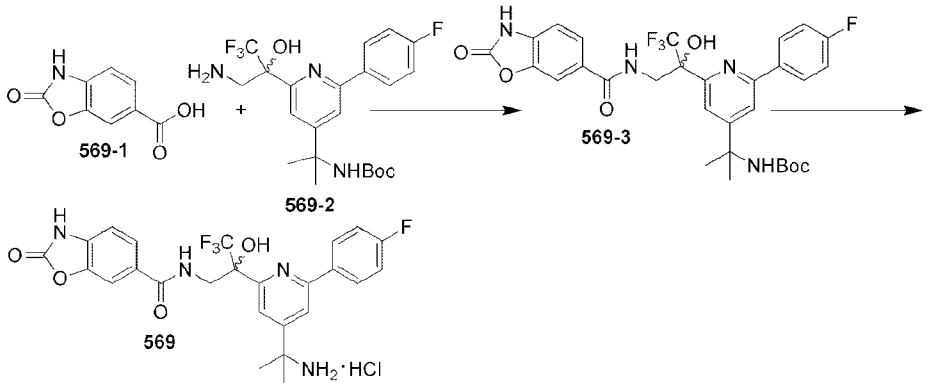
[1179] To a solution of **564-5** (11.0 g, 23.9 mmol) in anhydrous THF (60 mL) was added $LiAlH_4$ (907 mg, 23.9 mmol) in portions at 0 °C under N_2. The mixture was stirred at 0 °C for 30 mins. The reaction was quenched by ice-water and filtered via a pad of Celite. The filtrate was extracted with EA (3 x 100 mL). The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=30:1~20:1 as the eluent to afford **564-6** (3.8 g, 28% yield, 81% purity) as a light yellow oil. +ESI-MS: m/z 432.1 $[M+H]^+$.

[1180] To a solution of **564-6** (0.8 g, 2.34 mmol) and TEA (0.71 g, 7.01 mmol) in DCM (10 mL) was added MSCl (270 mg, 2.34 mmol) dropwise at 0 °C, and the mixture was stirred at 20 °C for 30 mins. The mixture was poured into ice-water (50 mL) and extracted with EA (3 x 20 mL). The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **564-7** (0.6 g, crude) as a yellow oil, which was used for next step directly. +ESI-MS: m/z 509.9 $[M+H]^+$.

[1181] To a solution of crude **564-7** (0.6 g, 1.43 mmol,) in DMSO (6 mL) was added $NaBH_4$ (270 mg, 7.14 mmol) in one portion at r.t. under N_2. The mixture was stirred at 50-60 °C for 12 h. The reaction was cooled to r.t., quenched with ice-water and extracted with EA (3 x 20 mL). The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=30:1~8:1 as the eluent to afford **564-8** (0.3 g, 78% purity) as a yellow solid. +ESI-MS: m/z 415.9 $[M+H]^+$.

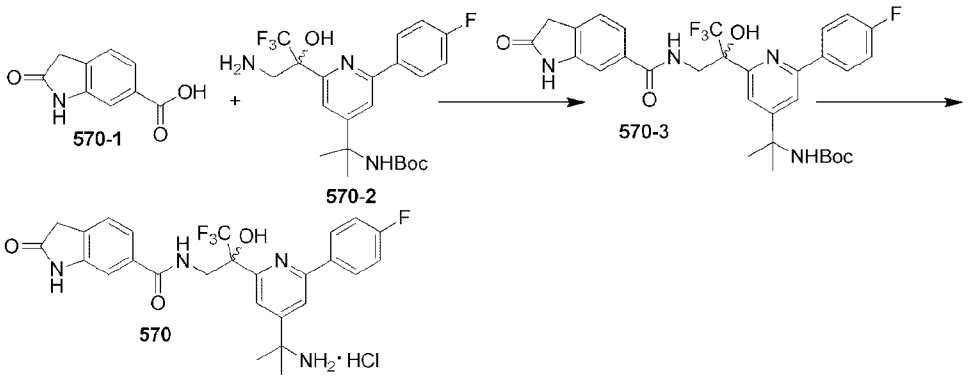
[1182] Compound **564** (white solid, 2.7 mg) was prepared following the general procedure for preparing **533** using **564-8**. +ESI-MS: m/z 609.1 $[M+H]^+$.

EXAMPLE 317
Preparation of Compound 569



[1183] Compound **569** (white solid, 53 mg, 74%) was prepared following the general procedure for preparing **495** using **569-1** and **569-2**. +ESI-MS: m/z 519.1 $[M+H]^+$.

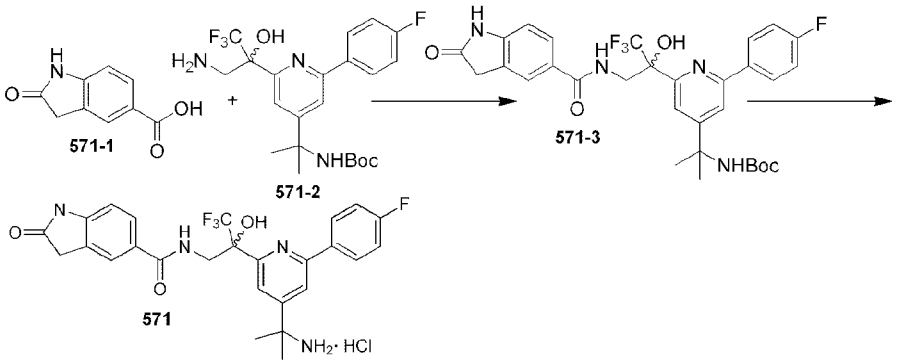
EXAMPLE 318
Preparation of Compound 570



[1184] Compound **570** (white solid, 25 mg, 32%) was prepared following the general procedure for preparing **495** using **570-1** and **570-2**. +ESI-MS: m/z 517.1 $[M+H]^+$.

EXAMPLE 319

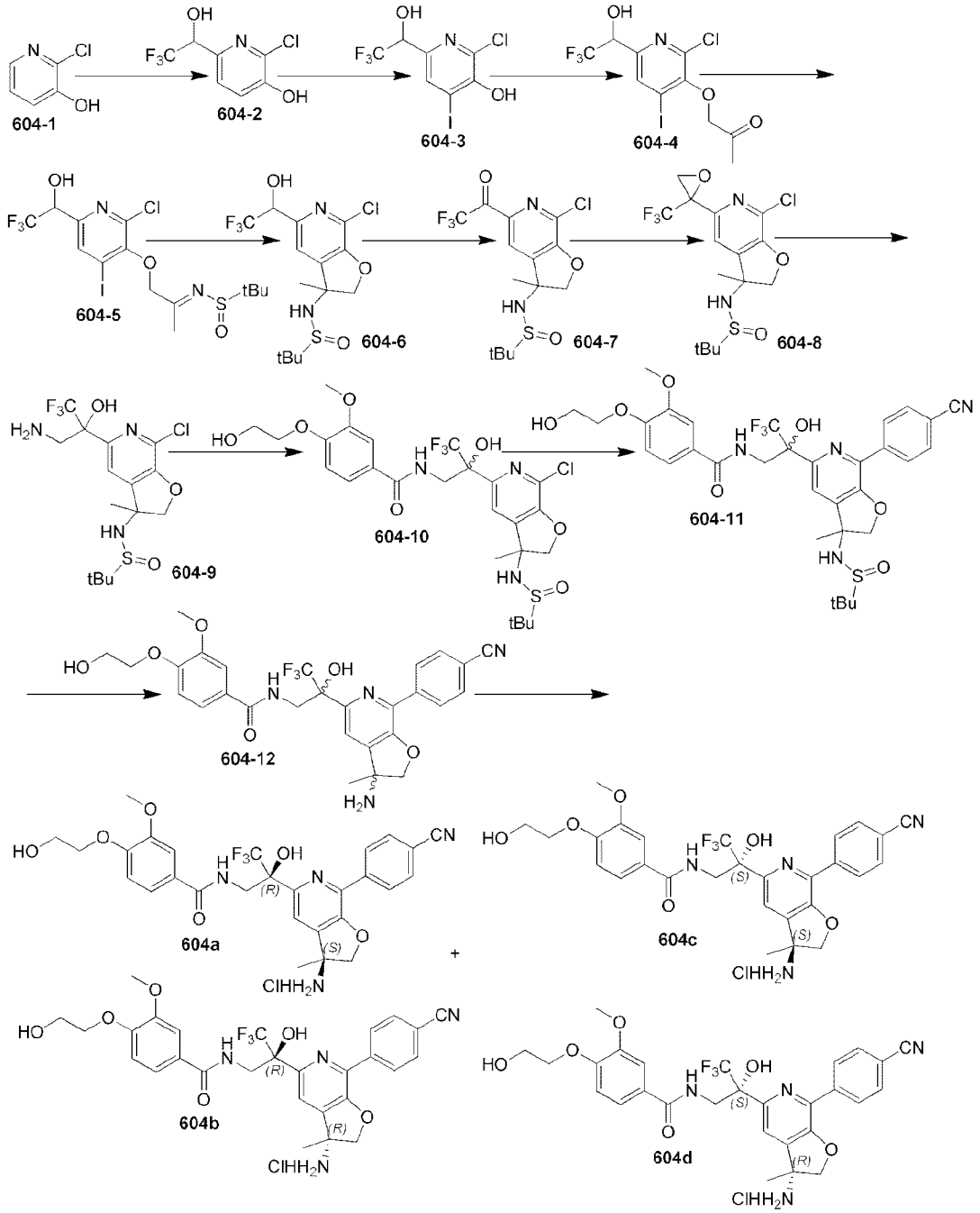
Preparation of Compound 571



[1185] Compound **571** (white solid, 21 mg, 23%) was prepared following the general procedure for preparing **495** using **571-1** and **571-2**. +ESI-MS: m/z 517.1 $[M+H]^+$.

EXAMPLE 320

Preparation of Compounds 604a-d



[1186] To a mixture of **604-1** (12.0 g, 92.6 mmol) and 2,2,2-trifluoroethane-1,1-diol (32.3 g, 277.9 mmol) in H_2O (25 mL) was added K_2CO_3 (25.6 g, 185.2 mmol, 2.00 eq.) in one portion at r.t. The flask was sealed, heated to 125°C and stirred for 16 h. The mixture

was cooled to 0 °C, neutralized with 1M HCl solution, and extracted with EA (3 x 100 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was washed with DCM and PE to afford **604-2** (17.0 g, 81%) as a white solid.

[1187] To a stirring solution of **604-2** (130 g, 571.2 mmol) and Na_2CO_3 (121 g, 1.1 mol) in H_2O (800 mL) was added I_2 (174 g, 685.5 mmol) in portions. The mixture was stirred at 25 °C for 48 h. A sat. sodium sulfite solution (500 mL) was used to quench the reaction. The mixture was acidified with 3M HCl 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 Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography by using PE:EA=1:1 as the eluent to afford **604-3** (180 g, 89%) as a white solid.

[1188] To a solution of **604-3** (88 g, 249 mmol) and 1-chloropropan-2-one (55.9 g, 605.0 mmol) in DMF (200 mL) was added $NaHCO_3$ (62.7 g, 746.1 mmol) in one portion at r.t. under N_2. The mixture was stirred at 25 °C for 25 h, and the solid was removed by filtration. The filtrate was concentrated to dryness under reduced pressure, and the residue was dissolved in DCM and triturated with PE to afford **604-4** (66 g, 65%) as a white solid.

[1189] A mixture of **604-4** (9.0 g, 22 mmol), 2-methylpropane-2-sulfinamide (S-configuration, 2.66 g, 22 mmol) and titanium(IV) ethoxide (10.5 g, 46.1 mmol) in anhydrous THF (18.00 mL) was heated to 80 °C (sealed vial, degassed and purged with N_2) and stirred for 1 h. EA (150 mL) and water (10 mL) were added with stirring. The mixture was stirred for 5 mins and filtered through a pad of celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel using EA:DCM=1:9 as the eluent to afford **604-5** (6.8 g, 60%).

[1190] To a solution of EtMgBr (4.4 mL, 13.2 mmol, 3 M in ether) in dry THF (50 mL) was added *n*-BuLi (10.6 mL, 26.5 mmol, 2.5 M in hexane), and the mixture was stirred at 0 °C. After stirring for 10 mins, the mixture was cooled down to -78 °C. A solution of **604-5** (6.8 g, 13.26 mmol) in dry THF (50 mL) was added dropwise, and the reaction was stirred at -78 °C for 15 mins. The reaction was quenched with H_2O (50 mL) and extracted with EA (2 x 100 mL). The combined organic phase was washed with brine, dried

over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 0~10% EA in DCM) to afford **604-6** (3.10 g, 60%).

[1191] To a stirring solution of **604-6** (6.8, 17.6 mmol) in DCM (50 mL) was added Dess-Martin reagent (8.95 g, 21.1 mmol), and the mixture was stirred at r.t. under N_2 for 1 h. The reaction was quenched with sat. aq. Na_2SO_3 solution and sat. aq. $NaHCO_3$ solution. After 30 mins of stirring vigorously, the organic layers were separated, and the aqueous layer was extracted with EA (2 x 100 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 0~10% EA in DCM) to afford **604-7** (5.1 g 75.4%).

[1192] To a solution of *t*-BuOK (1.64 g, 14.58 mmol) in CH_3CN (150 mL) was added Me_3SOI (3.21 g, 14.58 mmol). The mixture was degassed and stirred at r.t. for 30 mins. The solution containing the ylide was filtered from the solid and added to a solution of **604-7** (5.1 g, 13.25 mmol) in CH_3CN (150 mL), which had been previously degassed. The reaction was stirred at r.t. for 1 h. The volatiles were removed under reduced pressure. The residue was purified by column chromatography using DCM:EA=9:1 as the eluent to give **604-8** (3.2 g, 60.5%).

[1193] To a solution of **604-8** (3.2 g, 8.02 mmol) in MeOH (300 mL) was added ammonia water (10 mL) in one portion. The solution was stirred at 25 °C for 18 h. The volatiles were removed under reduced pressure to afford crude **604-9** (3.1 g, 93%).

[1194] To a solution of 4-(2-hydroxyethoxy)-3-methoxybenzoic acid (460 mg, 2.17 mmol) in DCM (6 mL) was added HATU (985 mg, 2.59 mmol) and DIPEA (558 mg, 4.32 mmol) in one portion at r.t. After stirring for 10 mins, **604-9** (900 mg, 2.16 mmol) was added. The mixture was stirred for 1 h at r.t. The solution was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 10~100% EA in PE) to give **604-10** (890 mg, 67.5%).

[1195] **604-10** (300 mg, 0.49 mmol), (4-cyanophenyl)boronic acid (88 mg, 0.6 mmol) and Cs_2CO_3 (240 mg, 0.74 mmol) were taken up into a microwave tube in co-solvent

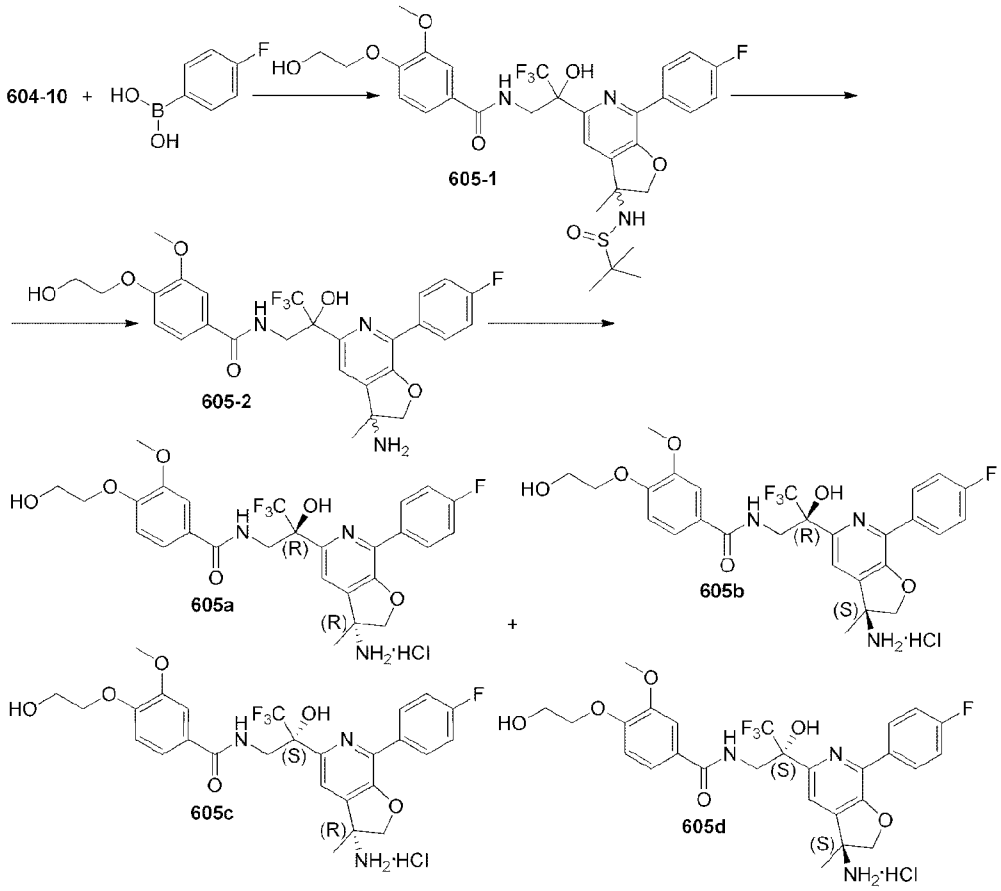
DME:H_2O (12 mL, v:v=5:1). The solution was degassed and $Pd(PPh_3)_4$ (57 mg, 0.05 mmol, 0.10 eq.) was added. The sealed tube was heated to 110 °C by microwave irradiation and stirred for 1 h. The solution was cooled to r.t. and poured into water. The mixture was extracted with EA (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using EA as the eluent to give **604-11** (320 mg, 96.2%).

[1196] To a solution of **604-11** (300 mg, 0.44 mmol) in dioxane (3 mL) was added HCl/dioxane (1 mL, 4M) at r.t. The mixture was stirred at r.t. until all the starting material was consumed. The mixture was concentrated under reduced pressure. The residue was dissolved in EA, and basified by a sat. $NaHCO_3$ solution. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **604-12** (~200 mg, 71% yield, 90% purity).

[1197] **604-12** (~200.00 mg, 90% purity) was separated by SFC ("Column: Chiralcel OJ-H 250×4.6mm I.D., 5um Mobile phase: methanol (0.05% DEA) in CO2 from5% to 40% Flow rate: 2.35mL/min Wavelength: 220nm") to give peak 1, peak 2, peak 3 and peak 4. The solution of peak 1 in CH_3CN and water was treated with HCl (2 M, 0.2 mL) and lyophilized to give **604a** (25 mg). +ESI-MS: m/z 573.1 $[M+H]^+$. The solution of peak 2 in CH_3CN and water was treated with HCl (2 M, 0.2 mL) and lyophilized to give **604b** (25 mg). +ESI-MS: m/z 573.1 $[M+H]^+$. The solution of peak 3 in CH_3CN and water was treated with HCl (2 M, 0.2 mL) and lyophilized to give **604c** (19 mg). +ESI-MS: m/z 573.1 $[M+H]^+$. The solution of peak 4 in CH_3CN and water was treated with HCl (2 M, 0.2 mL) and lyophilized to give **604d** (22 mg). +ESI-MS: m/z 573.3 $[M+H]^+$.

EXAMPLE 321

Preparation of Compounds 605a-d

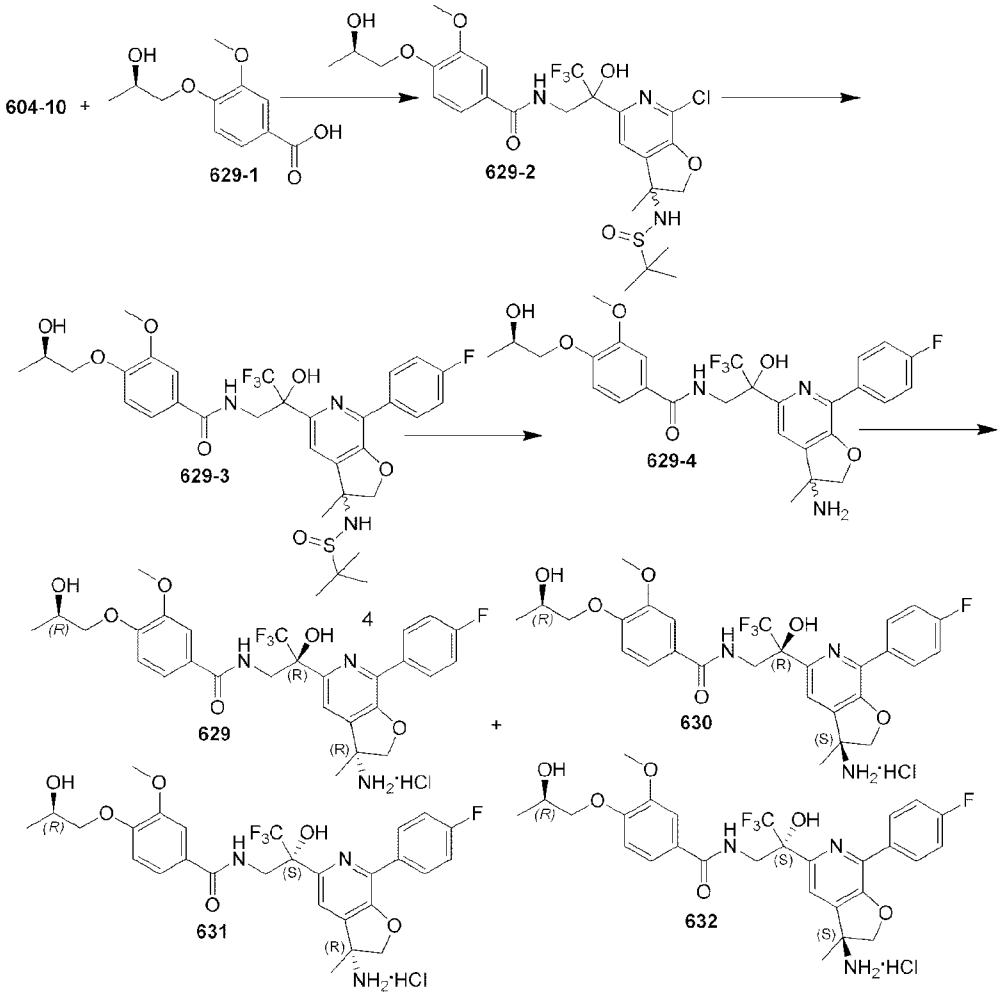


[1198] To a solution of **604-10** (400 mg, 0.66 mmol) and (4-fluorophenyl)boronic acid (138 mg, 984 mmol) in DME (3 mL) and H_2O (1 mL) was added $Pd(dppf)Cl_2$ (24 mg, 0.033 mmol) and Cs_2CO_3 (641 mg, 2.0 mmol) in a microwave tube under N_2. The reaction mixture was heated to 100 °C and stirred for 1 hour. After cooling to room temperature, the reaction mixture was poured into water (30 mL) and stirred for 5 mins. The aqueous phase was extracted with EA (30 mL X 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using EA as eluent to give **605-1** (310 mg) as a white solid. +ESI-MS: m/z 670.1 $[M+H]^+$.

[1199] Compounds **605a, 605b, 605c** and **605d** was prepared following the general procedure for preparing **605a** using **605-1**. The crude was purified by prep-HPLC

and SFC separation. **605a** (white solid, 20 mg): m/z 566.2 $[M+H]^+$, **605b** (white solid, 18 mg): m/z 566.1 $[M+H]^+$, **605c** (white solid, 12.8 mg): m/z 566.1 $[M+H]^+$ and **605d** (white solid, 12.7 mg): m/z 566.2 $[M+H]^+$.

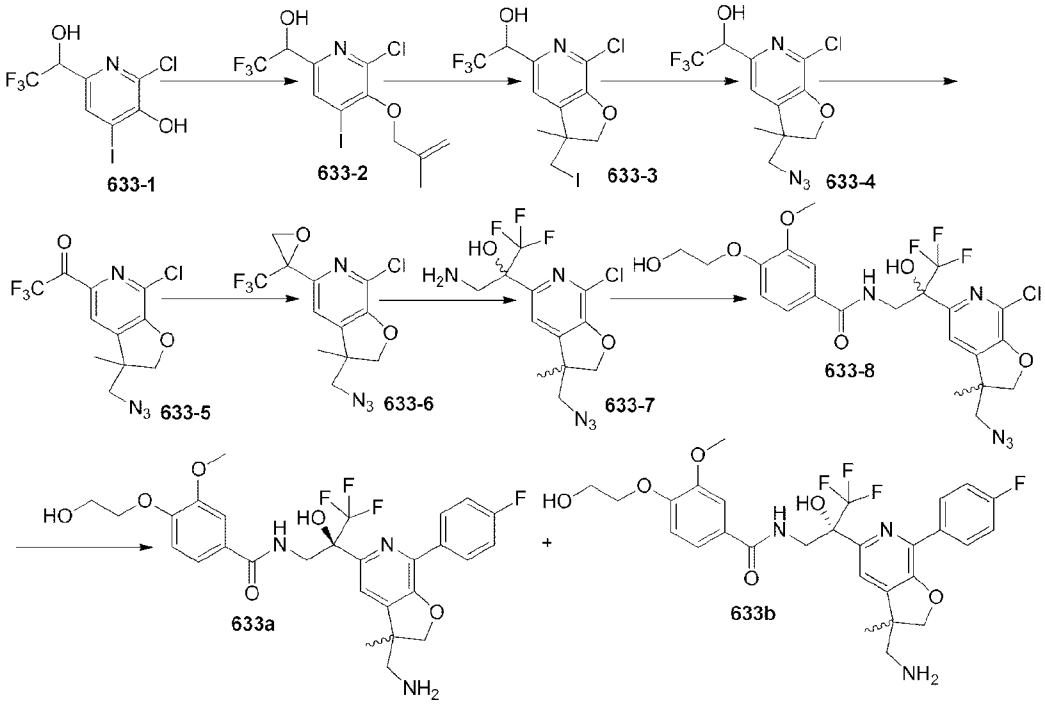
EXAMPLE 322
Preparation of Compounds 629-632



[1200] Compounds **629**, **630**, **631** and **632** was prepared following the general procedure for preparing **605d** using **604-10**, **629-1** and (4-fluorophenyl)boronic acid. **629** (white solid, 14.1 mg): m/z 580.1 $[M+H]^+$, **630** (white solid, 18.6 mg): m/z 580.1 $[M+H]^+$, **631** (white solid, 25.8 mg): m/z 580.1 $[M+H]^+$ and **632** (white solid, 34.5 mg): m/z 580.1 $[M+H]^+$.

EXAMPLE 323

Preparation of Compounds 633a-633b



[1201] **633-1** (9.0 g, 25.5 mmol) and $NaHCO_3$ (6.4 g, 76.4 mmol) were dissolved in DMF (80 mL). 3-bromo-2-methylprop-1-ene (4.5 g, 33.1 mmol) was added by syringe, and the mixture was heated to 70 °C for 3 h. After cooling to r.t, the reaction was quenched with H_2O and extracted with EA. The organic phase was washed with brine, dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent: PE:EA = 30:1~8:1) to give **633-2** (8.02 g, 77%) as a white solid. +ESI-MS: m/z 407.8 $[M+H]^+$.

[1202] A sealed tube was charged with a solution of **633-2** (7.0 g, 17.2 mmol) in toluene (50 mL). $Pd_2(dba)_3$ (580.0 mg, 1.0 mmol) and Q-phos (1.0 g, 1.4 mmol) was added under N_2. The sealed tube was stirred at 100 °C in an oil bath. After stirring for 7 h, the mixture was cooled to r.t. and concentrated at low pressure. The residue was purified by flash chromatography using 2~5% EA in PE as the eluent to afford **633-3** (3.5 g, 50%) as a solid.

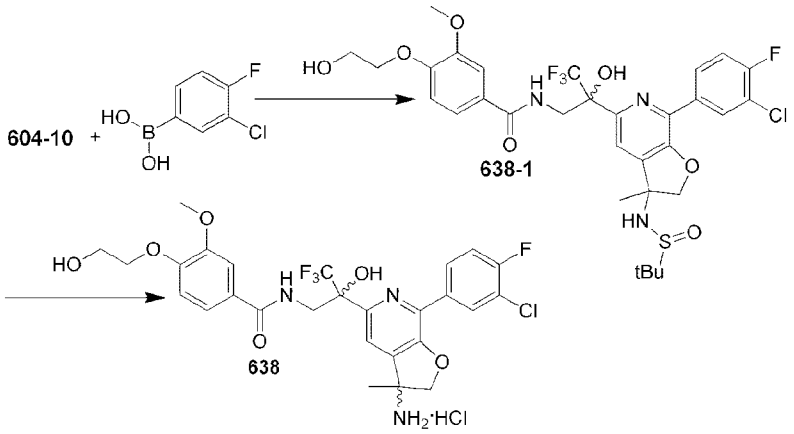
[1203] To a solution of **633-3** (3.5 g, 8.6 mmol) in DMF (50 mL) was added NaN_3 (12.4 g, 190.7 mmol) at r.t. The solution was heated to 70 °C and stirred for 16 h. The

mixture was cooled to r.t. and quenched by pouring into water. The mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using 5~12% EA in PE as the eluent to give **633-4** (2.4 g, 86.6%) as an oil. +ESI-MS: m/z 322.9 $[M+H]^+$.

[1204] **633-8** was prepared following the general procedure for preparing **604a** using **633-4**.

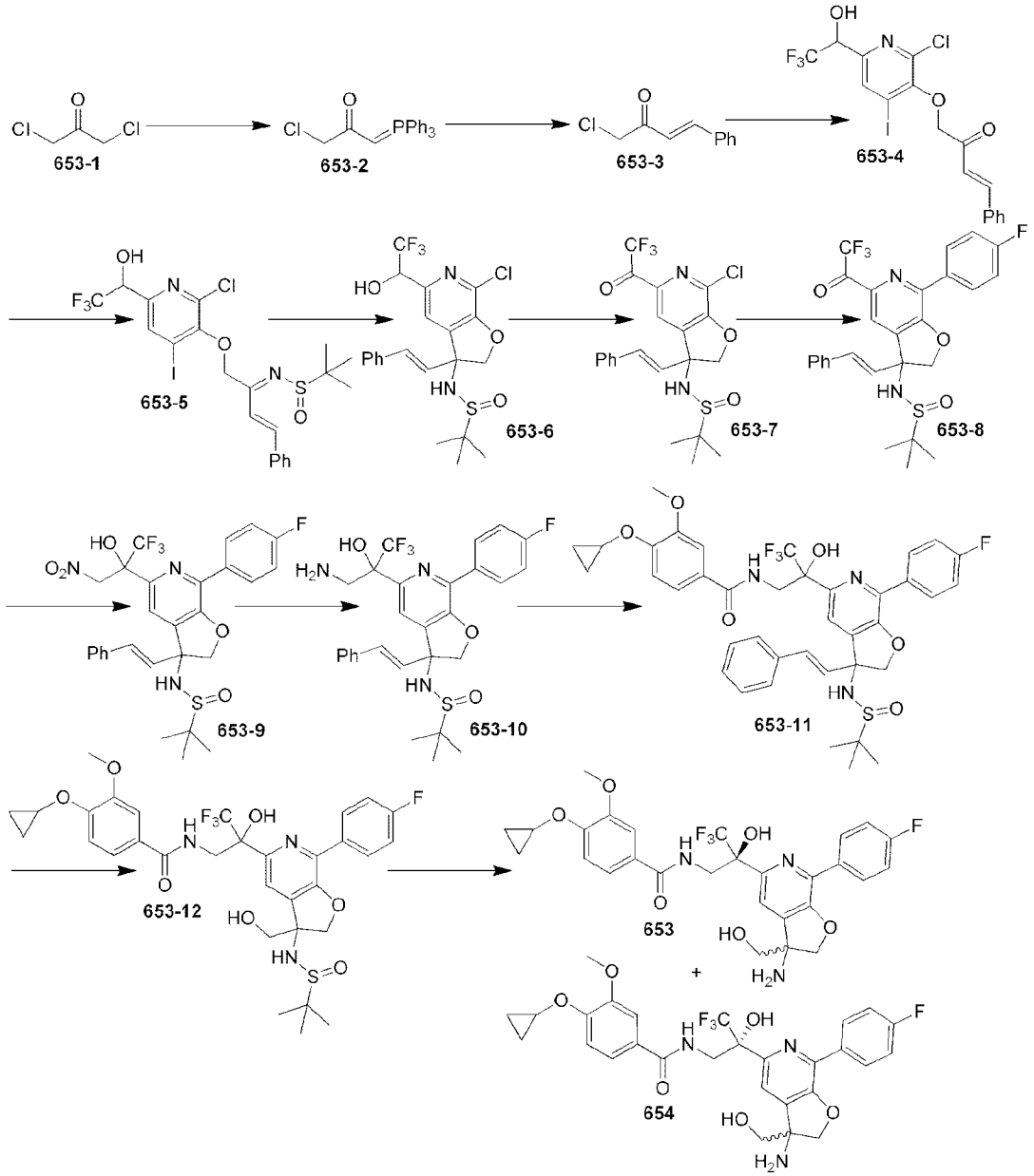
[1205] **633-8** (500 mg, 0.92 mmol), (4-fluorophenyl)boronic acid (167 mg, 1.2 mmol), Cs_2CO_3 (450 mg, 1.4 mmol) and $Pd(PPh_3)_4$ (106 mg, 0.092 mmol) were taken up into a microwave tube in a co-solvent of dioxane (15 mL) and H_2O (3 mL). The sealed tube was heated at 110 °C by microwave irradiation and stirred for 1 h. LCMS showed that ~30% of the desired product was formed. The solution was concentrated under reduced pressure, and the residue was purified by TLC and further purified by prep-HPLC to give pure **633a** (~80 mg) and **633b** (~70 mg). **633a:** +ESI-MS: m/z 580.2 $[M+H]^+$ and **633b:** +ESI-MS: m/z 580.1 $[M+H]^+$.

EXAMPLE 324
Preparation of Compound 638



[1206] Compound **638** (white solid, 15 mg) was prepared following the general procedure for preparing **604a** using **604-10** and (3-chloro-4-fluorophenyl)boronic acid. +ESI-MS: m/z 600.1 $[M+H]^+$.

EXAMPLE 325
Preparation of Compounds 653 and 654



[1207] 2-chloro-4-iodo-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-ol was prepared as provided in Hénichart, J. et al., *J. Het. Chem.* (1986), 23(5):1531-1533.

[1208] To a solution of 2-chloro-4-iodo-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-ol (16 g, 45.3 mmol) in CH_3CN (150 mL) was added K_2CO_3 (12.5 g, 90.5 mmol) in one portion. After stirring at r.t. for 5 mins, a solution of **653-3** (9.8 g, 54.3

mmol) in CH_3CN (10 mL) was added slowly under N_2. The mixture was stirred at 90 °C for 1 h in a pre-heated oil bath. After cooling to r.t., 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 Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography using 2~5% EA in PE as the eluent to afford **653-4** (10.9 g, 49%) as a yellow solid.

[1209] **653-8** was prepared following the general procedure for preparing **604a** using **653-4**.

[1210] To a solution of **653-8** (1.0 g, 1.9 mmol) in CH_3NO_2 (15 mL) was added TEA (2.0 mL) in one portion at r.t. The reaction 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 **653-9** (0.8 g, 72%) as a yellow solid. +ESI-MS: m/z 593.9 $[M+H]^+$.

[1211] To a solution of **653-9** (400 mg, 0.67 mmol) in EtOH (10 mL) and H_2O (10 mL) was added Fe (188 mg, 3.4 mmol) powder and NH_4Cl (180 mg, 3.4 mmol) in one portion. The mixture was stirred at 80 °C for 2 h. After cooling to r.t., the mixture was poured into water (20 mL) and extracted with EA (3 x 10 mL). The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography using EA as the eluent to afford **653-10** (250 mg, 66%) as a yellow solid. +ESI-MS: m/z 564.1 $[M+H]^+$.

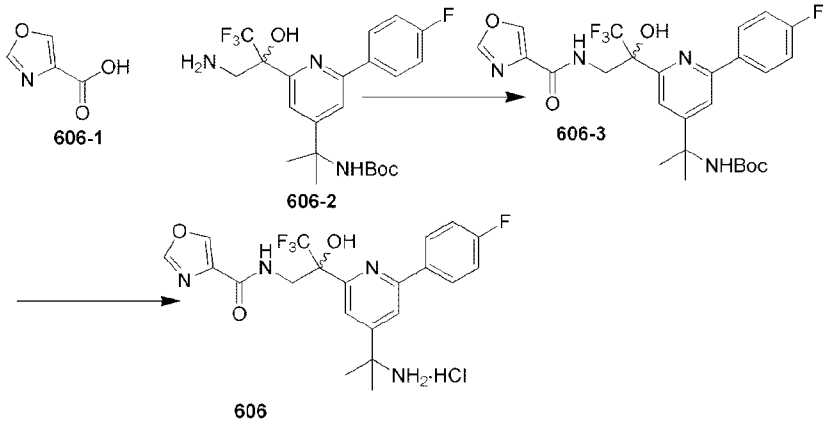
[1212] To a solution of 4-cyclopropoxy-3-methoxybenzoic acid (75 mg, 0.36 mmol) in DMF (6.0 mL) was added HATU (137 mg, 0.36 mmol) and DIPEA (47 mg, 0.36 mmol). After stirring at r.t. for 5 mins, **653-10** (203 mg, 0.36 mmol) was added. The mixture was stirred for 1 h and then poured into water. The mixture was extracted with EA (2 x 10 mL). The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography using EA as the eluent to afford **653-11** (120 mg, 44.2 %) as a yellow solid. +ESI-MS: m/z 754.2 $[M+H]^+$.

[1213] Ozone was bubbled into a solution of **653-11** (120 mg, 0.16 mmol) in anhydrous MeOH (10 mL) at -78 °C for 6 mins. After excess O_3 was purged by N_2, $NaBH_4$

(18.1 mg, 0.48 mmol) was added at r.t. The reaction was stirred for 0.5 h and quenched with water. The mixture was extracted with EA (2 x 10 mL), dried over sodium sulfate, concentrated to give the crude product. The residue was purified by column chromatography using EA as the eluent to afford **653-12** (70 mg, 65%) as a yellow solid. +ESI-MS: m/z 682.1 $[M+H]^+$.

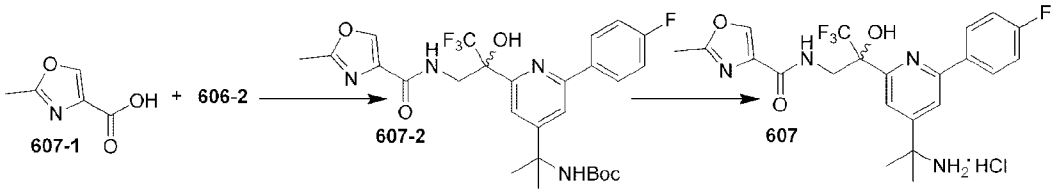
[1214] To a solution of **653-12** (70 mg, 0.1 mmol) in MeOH (10 mL) was added HCl/dioxane (3 mL, 4 M). The mixture was stirred at r.t. for 20 mins. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford **653** (12 mg) and **654** (18 mg) as white solids. **653:** +ESI-MS: m/z 578.1 $[M+H]^+$ and **654:** +ESI-MS: m/z 578.1 $[M+H]^+$.

EXAMPLE 326
Preparation of Compound 606



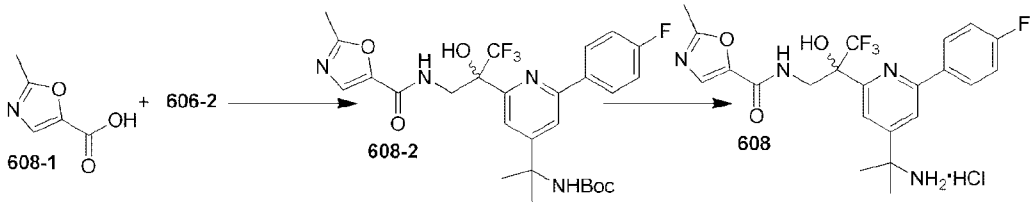
[1215] A mixture of **606-2** (45 mg, 0.1 mmol), **606-1** (16 mg, 0.1 mmol) and TEA (1 mmol) is dissolved in anhydrous DCM (4 mL) with stirring. The solution was treated with HATU (38 mg, 0.1 mmol) in one portion. After stirring at r.t. for 30 mins, TFA (1 mL) was added. The solution was stirred at r.t. for 2 h. The mixture was concentrated to dryness. The residue was isolated by acidic prep-HPLC to afford **606** (26 mg, 45%) as a white solid. +ESI-MS: m/z 452.0 $[M+H]^+$.

EXAMPLE 327
Preparation of Compound 607



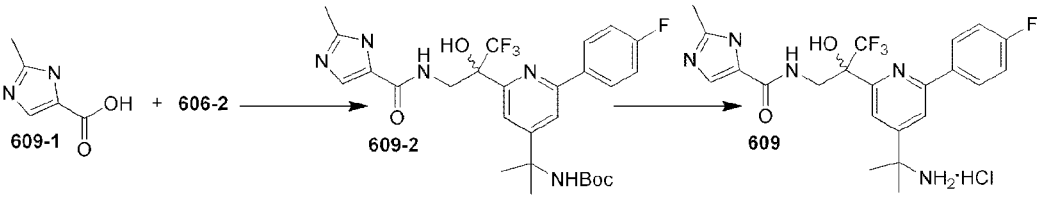
[1216] Compound **607** was prepared following the general procedure for preparing **606** using **607-1** and **606-2**. The crude product was purified by prep-HPLC to give **607** (66 mg, 75%) as a white solid (66 mg, 75%). +ESI-MS: m/z 466.9 $[M+H]^+$.

EXAMPLE 328
Preparation of Compound 608



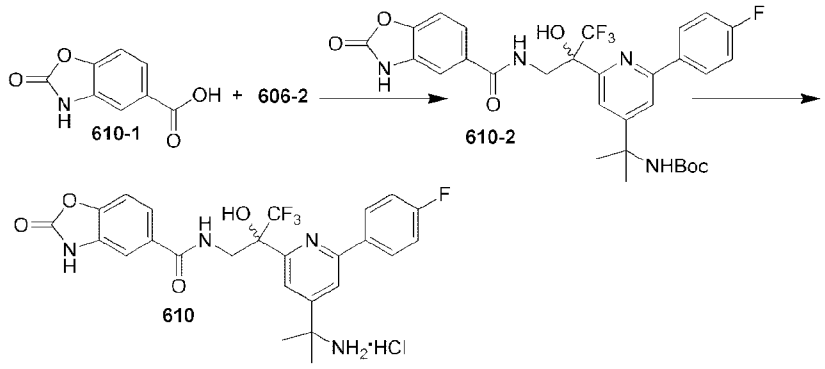
[1217] Compound **608** was prepared following the general procedure for preparing **606** using **608-1** and **606-2**. The crude product was purified by prep-HPLC to give **608** (46.5 mg, 84%) as a white solid. +ESI-MS: m/z 466.9 $[M+H]^+$.

EXAMPLE 329
Preparation of Compound 609



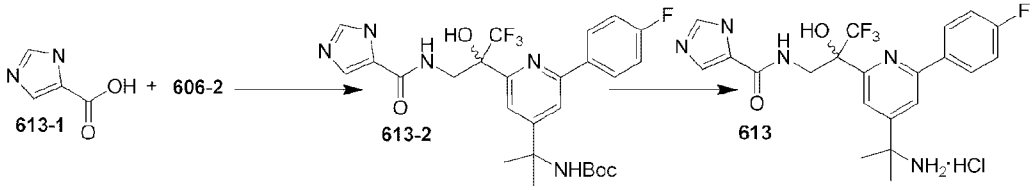
[1218] Compound **609** was prepared following the general procedure for preparing **606** using **609-1** and **606-2**. The crude product was purified by prep-HPLC to give **609** (13.5 mg, 34%) as a white solid. +ESI-MS: m/z 465.9 $[M+H]^+$.

EXAMPLE 330
Preparation of Compound 610



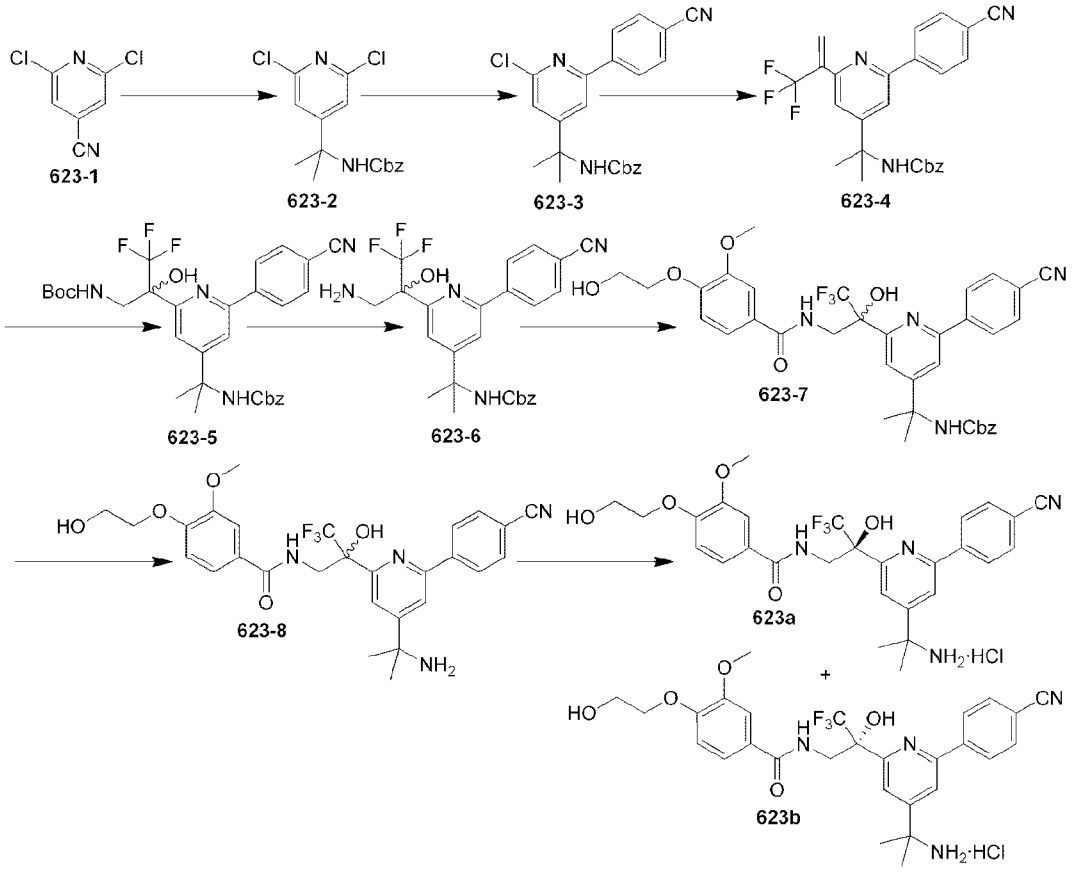
[1219] Compound **610** was prepared following the general procedure for preparing **606** using **610-1** and **606-2**. The crude product was purified by prep-HPLC to give **610** (34 mg, 57%) as a white solid. +ESI-MS: m/z 518.9 $[M+H]^+$.

EXAMPLE 331
Preparation of Compound 613



[1220] Compound **613** was prepared following the general procedure for preparing **606** using **613-1** and **606-2**. The crude product was purified by prep-HPLC to give **613** (29 mg, 50%) as a white solid. +ESI-MS: m/z 451.9 $[M+H]^+$.

EXAMPLE 332
Preparation of Compounds 623a and 623b



[1221] To a solution of **623-1** (20 g, 116 mmol) in anhydrous toluene (200 mL) was added MeMgBr (3 M, 115.61 mL) slowly at 0°C under N_2. After addition and stirring for 30 mins, $Ti(i\text{-}PrO)_4$ (36.1 g, 127.2 mmol) was added dropwise The mixture was heated at 100 °C for 30 mins. After cooling to r.t., copious quantities of diatomite was added to the mixture. The mixture was basified with aqueous NaOH solution (2 M) and filtered through a pad of diatomite. The cake was washed with EA, and the filtrate was separated and concentrated to provide crude 2-(2,6-dichloro-4-pyridyl)propan-2-amine (~25 g).

[1222] Crude 2-(2,6-dichloro-4-pyridyl)propan-2-amine was dissolved in anhydrous DCM (250 mL). The solution was treated with CbzCl (20.79 g, 121.90 mmol) and DIPEA (31.51 g, 243.80 mmol). The mixture was stirred at r.t. overnight. The mixture was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by column chromatography using 3~10%

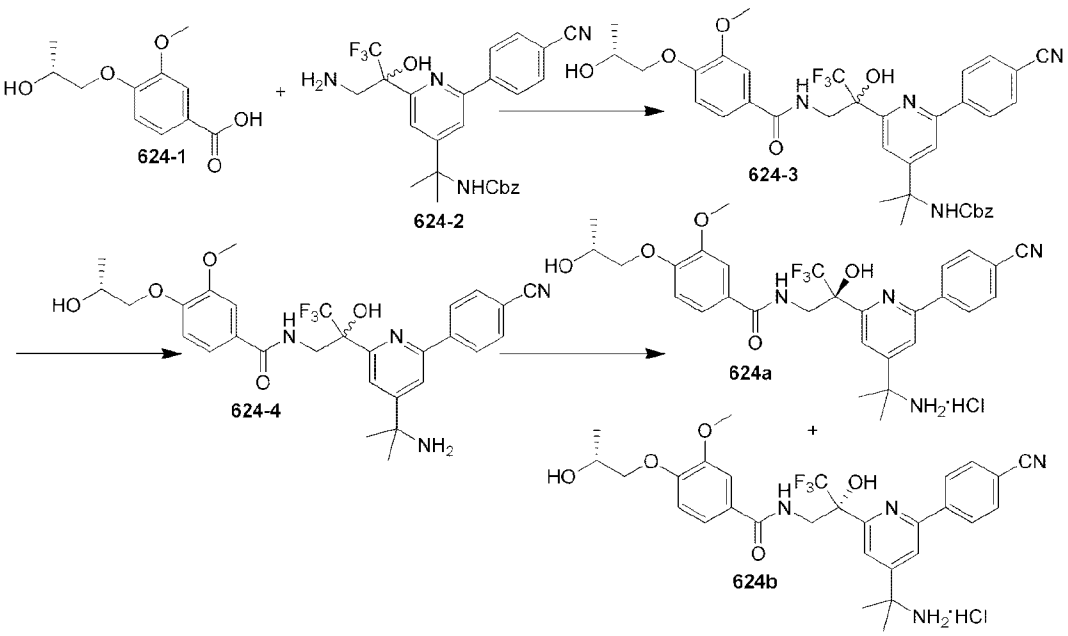
EA in PE as the eluent to give **623-2** (15 g, 36% yield over 3 steps) as a white solid. +ESI-MS: m/z 338.8 $[M+H]^+$.

[1223] To a stirring solution of **623-2** (5.0 g, 14.7 mmol) in dioxane (100 mL) and water (10 mL) were added (4-cyanophenyl)boronic acid (2.17 g, 14.7 mmol), Cs_2CO_3 (9.6 g, 29.5 mmol), and Pd(dppf)Cl2 (1.08 g, 1.47 mmol) under N_2. The mixture was stirred at 80 °C for 1 h under N_2. After cooling to r.t., the mixture was diluted with EA (100 mL) and water (100 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by column chromatography using 3~20% EA in PE as the eluent to give **623-3** (2.0 g, 33% yield) as a white solid.

[1224] Compound **623-8** was prepared following the general procedure for preparing **533** using **623-3**. Racemic **623-8** was separated by SFC and prep-HPLC to afford **623a** (62 mg) and **623b** (29 mg) as white solids. **623a:** +ESI-MS: m/z 559.4 $[M+H]^+$ and **623b:** +ESI-MS: m/z 559.0 $[M+H]^+$.

EXAMPLE 333

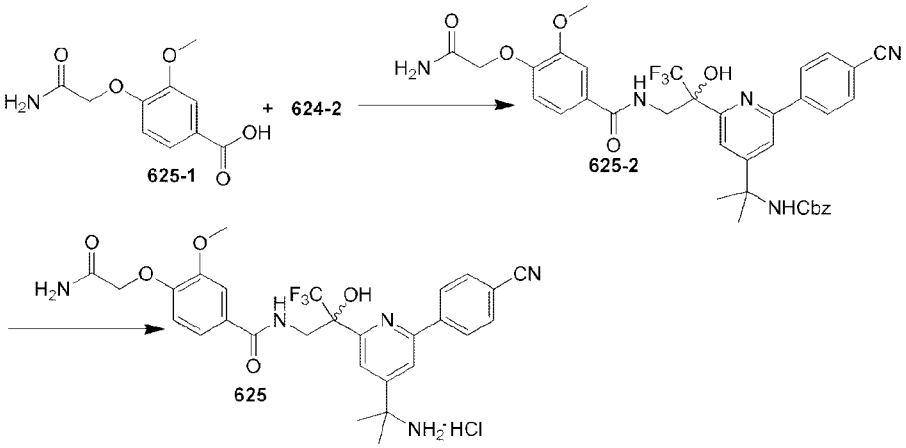
Preparation of Compounds 624a and 624b



[1225] Compounds **624a** (white solid, 62 mg) and **624b** (white solid, 62 mg) were prepared following the general procedure for preparing **623a** and **623b** using **624-1** and **624-2**. **624a:** +ESI-MS: m/z 573.1 $[M+H]^+$ and **624b:** +ESI-MS: m/z 573.1 $[M+H]^+$.

EXAMPLE 334

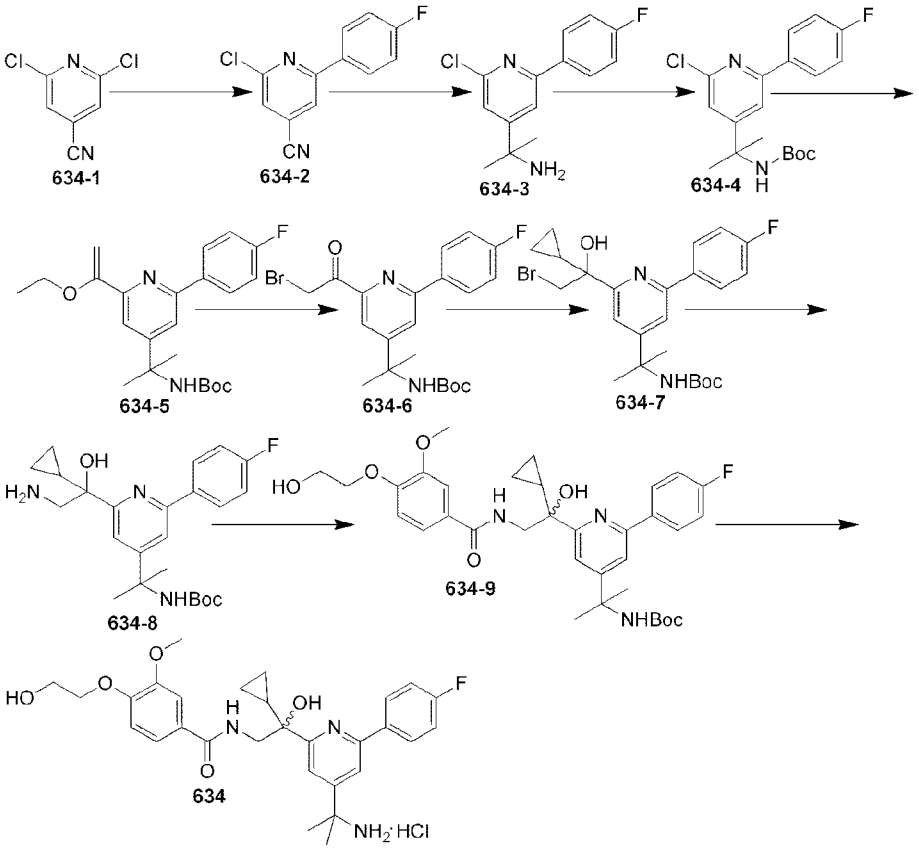
Preparation of Compound 625



[1226] Compound **625** (white solid, 32 mg) was prepared following the general procedure for preparing **623a** and **623b** using **625-1** and **624-2**. +ESI-MS: m/z 572.1 $[M+H]^+$.

EXAMPLE 335

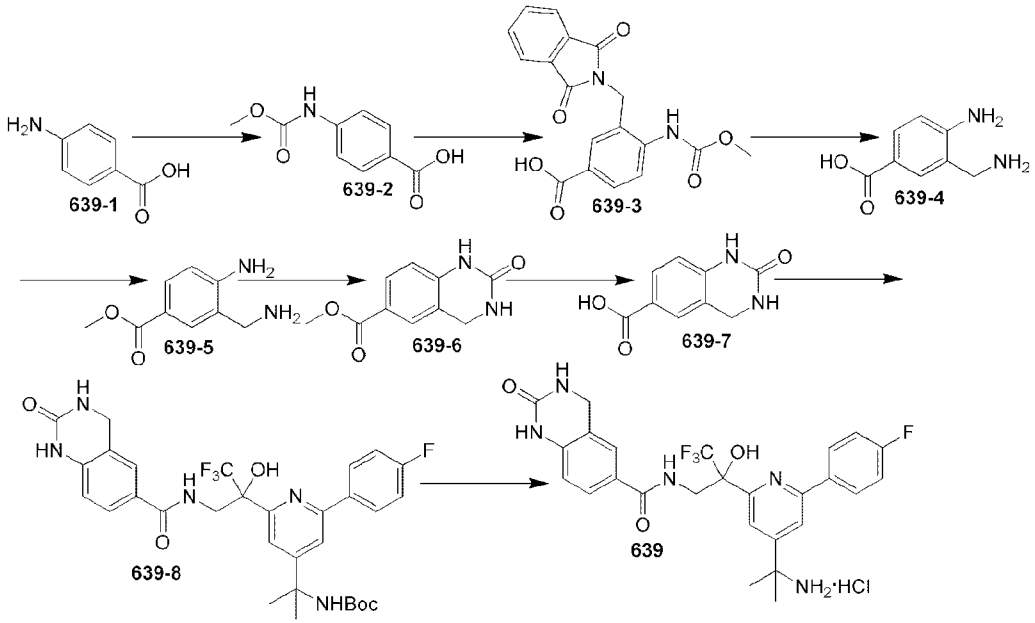
Preparation of Compound 634



[1227] Compound **634** (white solid, 10 mg) was prepared following the general procedure for preparing **406** using **634-1** and **634-2**. +ESI-MS: m/z 524.1 $[M+H]^+$.

EXAMPLE 336

Preparation of Compound 639

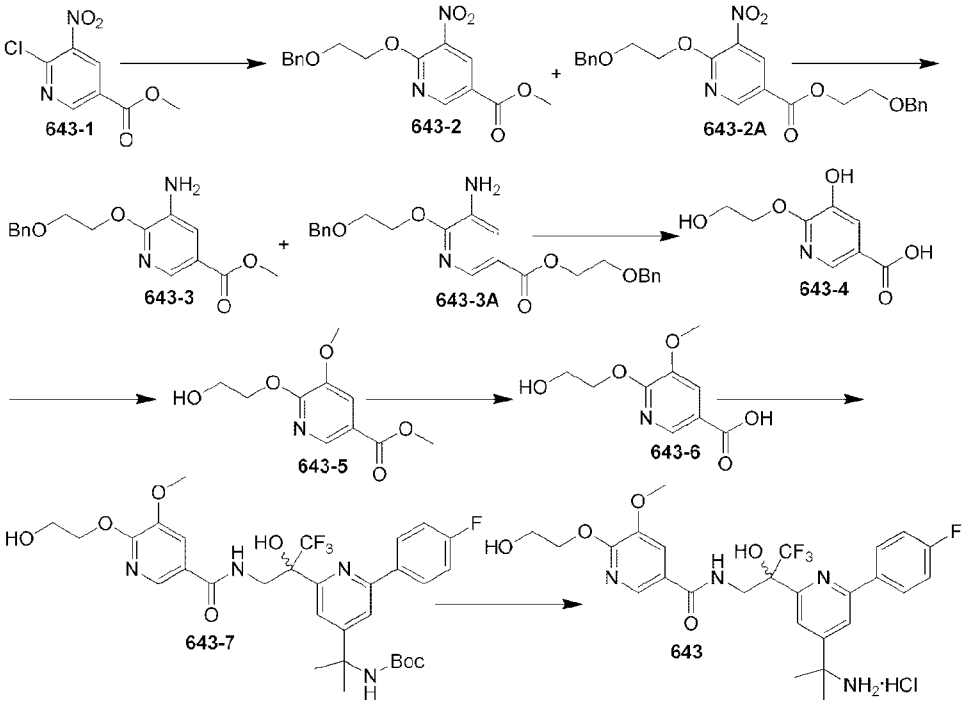


[1228] **639-6** was prepared as provided in Pascal, R., et al., *Eur. J. Org. Chem.* (2000) 2000(22):3755-3761.

[1229] To a solution of **639-6** (1.1 g, 5.3 mmol) in H_2O (10 mL) was added NaOH (426 mg, 10.7 mmol) in one portion. The mixture was stirred at 25 °C for 17 h. The solid was formed upon acidification to pH 1 with concentrated HCl (37%). The precipitate was collected by filtration, washed with water and dried in vacuum to give **639-7** (0.5 g, 49%) as a white solid, which was used for the next step without further purification. +ESI-MS: m/z 193.1 $[M+H]^+$.

[1230] Compound **639** (28 mg, 45%) was prepared following the general procedure for preparing **606** using **639-7**. +ESI-MS: m/z 532.0 $[M+H]^+$.

EXAMPLE 337
Preparation of Compound 643



[1231] To a solution of **643-1** (1.5 g, 6.9 mmol) in DMF (20 mL) was added 2-benzyloxyl ethanol (6.3 g, 41 mmol) at 25 °C. The solution was stirred for 6 h and then poured into H_2O (20 mL). The mixture was extracted with EA (2 x 40 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using 5~10% EA in PE as the eluent to give a mixture of **643-2** and **643-2A** (1.50 g).

[1232] To a solution of **643-2A** and **643-2A** (1.50 g, crude mixture) in EtOH/H_2O (20/10mL) were added Fe (1.5 g, 26.7 mmol) and NH_4Cl (1.5 g, 28 mmol) at 25 °C. The solution was heated to 80 °C and stirred for 2 h. The mixture was filtered, and the filtrate was concentrated to give a mixture of **643-3** and **643-3A** (1.20 g, crude). The products were used for the next step without further purification.

[1233] A mixture of **643-3** and **643-3A** (1.2 g, crude) in H_2SO_4/H_2O (1:1) (10mL) was cooled to -5 °C. $NaNO_2$ (376 mg, 5.45 mmol) was added in portions at -5 °C. The solution was stirred at -5 °C for 0.5 h. The solution was heated to 120 °C. After stirring 0.5 h at 120 °C, the solution was poured into ice water (20 mL) and extracted with

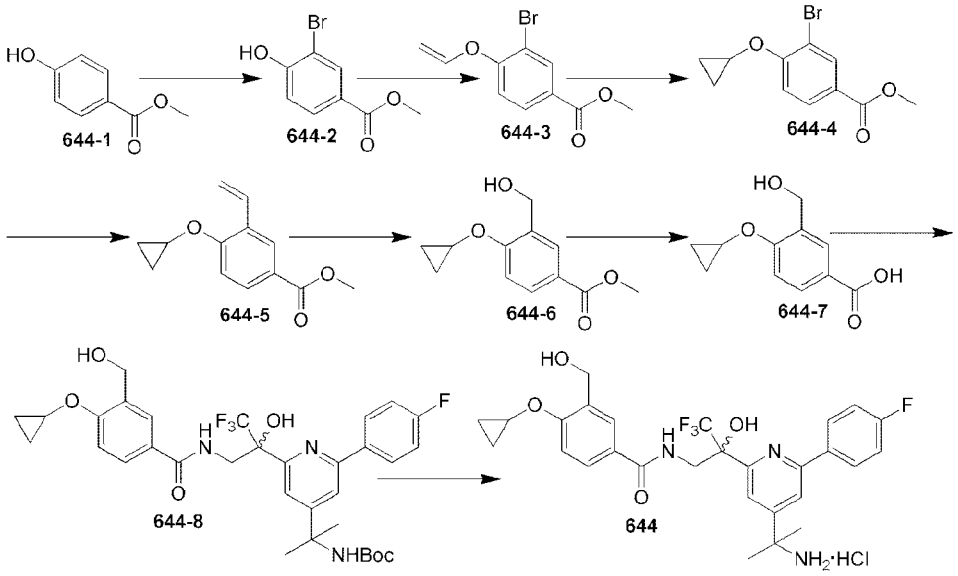
EA (2 x 20 mL). The organic phase was concentrated at low pressure. The residue was purified by chromatography to give **643-4** (0.3 g, crude).

[1234] To a solution of **643-4** (0.3 g, crude) in DMF (5 mL), K_2CO_3 (320 mg, 2.3 mmol) was added dropwise CH_3I (2.14 g, 15.1 mmol) at r.t. The solution was stirred for 3 h. The mixture was poured into H_2O (10 mL) and extracted with EA (2 x 20 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude **643-5** (210 mg), which was used in the next step directly.

[1235] To a mixture of **643-5** (210 mg, crude) in MeOH (2 mL) was added an aq. NaOH solution (2 mL, 2 M) in one portion at 25 °C. The mixture was heated to 60 °C and stirred for 2 h. The mixture was cooled to r.t. and acidified to pH=3~4 by the addition of 1 M aqueous HCl. The mixture was extracted with EA (3 x 10mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-TLC (EA) to afford **643-6** (110 mg, 56%).

[1236] Compound **643** (white solid, 14 mg, 24%) was prepared following the general procedure for preparing **606** using **643-6**. +ESI-MS: m/z 553.1 $[M+H]^+$.

EXAMPLE 338
Preparation of Compound 644



[1237] **644-2** was prepared as provided in PCT Publication No. WO 2013/007663, published January 17, 2013

[1238] **644-4** was prepared following the general procedure for preparing **272** using **644-2**.

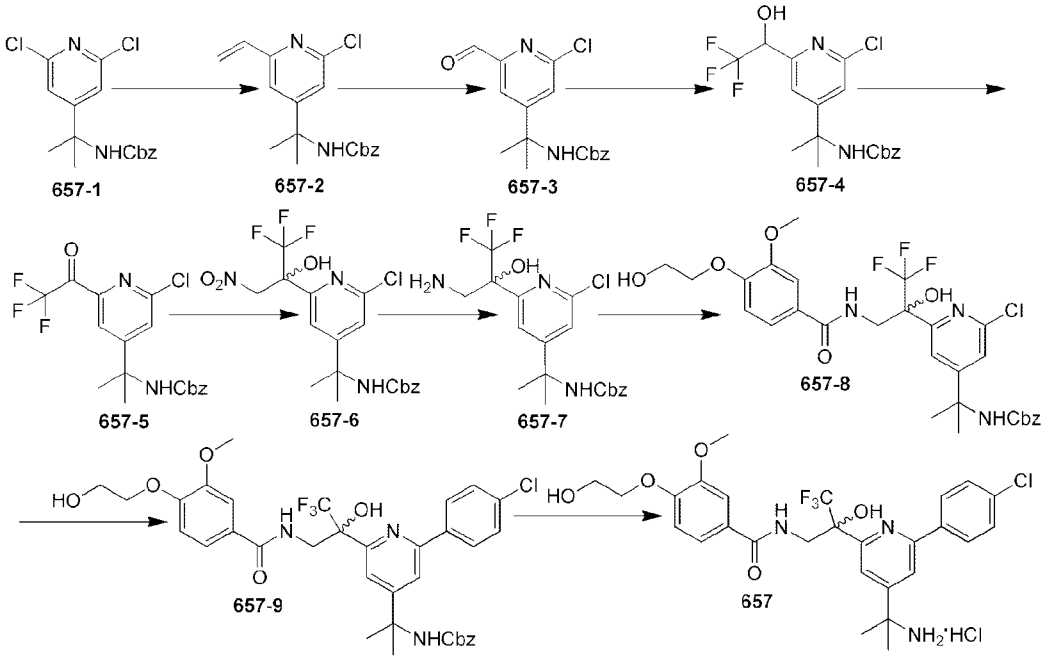
[1239] A mixture of **644-4** (1.5 g, 5.5 mmol), potassium vinyl trifluoroborate (1.6g, 11.1 mmol), Cs_2CO_3 (1.8 g, 5.5 mmol) and $Pd(dppf)Cl_2$ (0.4 g, 0.5 mmol) in i-PrOH (10 mL) was de-gassed. The mixture was heated to 80 °C for 15 h under N_2. After cooling to r.t, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography using 5~20% DCM in PE to give **644-5** (0.9 g, 74.5%).

[1240] Ozone was bubbled into a solution of **644-5** (0.87 g, 4 mmol) in anhydrous MeOH (10 mL) at -78 °C for 10 mins. After the excess ozone was purged by N_2, $NaBH_4$ (304 mg, 8 mmol) was added at 25 °C. The solution was stirred at 25 °C for 30 mins. The reaction was quenched with H_2O and extracted with EA (3 x 20 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography 10~25% DCM in PE to give **644-6** (0.7 g, 79%) as a solid.

[1241] To a solution of **644-6** (0.5 g, 2.3 mmol) in MeOH (3 mL) was added NaOH (0.5 g, 12.5 mmol) in H_2O (3 mL). After stirring at 60 °C for 1 h, the mixture was acidified to pH=3~4 by addition of 2 M HCl solution. The mixture was extracted with EA (3 x 10 mL). The combined organic solutions were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give **644-7** (0.4 g, 85.3%).

[1242] Compound **644** (while solid, 27 mg, 42%) was prepared following the general procedure for preparing **606** using **644-7**. +ESI-MS: m/z 548.0 $[M+H]^+$.

EXAMPLE 339
Preparation of Compound 657



[1243] **657-6** was prepared following the general procedure for preparing **606** using **657-1**.

[1244] To a stirring solution of **657-6** (2 g, 4.3 mmol) in EtOH (40 mL) were added $SnCl_2 \cdot 2H_2O$ (3.9 g, 17.3 mmol) and conc. HCl (5.4 mL, 12 M). After stirring at 60 °C for 12 h, the mixture was cooled to r.t., and EtOH was removed under reduced pressure. The residue was diluted with water (10 mL) and neutralized by sat. aq. Na_2CO_3 solution. The aqueous phase was extracted with EA (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using 50~100% EA in PE as the eluent to afford **657-7** (0.82 g, 44%) as a yellow oil. +ESI-MS: m/z 432.3 $[M+H]^+$.

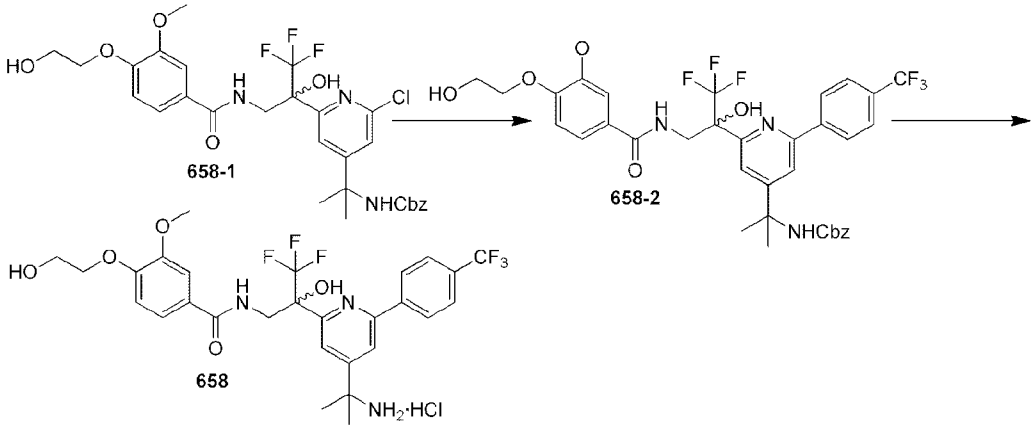
[1245] To a solution of 4-(2-hydroxyethoxy)-3-methoxybenzoic acid (1.5 g, 7.2 mmol) in anhydrous DMF (30 mL) were added HATU (2.7 g, 7.2 mmol) and DIEA (2.3 g, 18 mmol). After stirring at 25 °C for 30 mins, a solution of **657-7** (2.5 g, 6.0 mmol) in DMF (5 mL) was added dropwise. The mixture was stirred at 25 °C for 1~2 h. The solution was poured into water (50 mL), and extracted with EA (3 x 30 mL) . The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under

reduced pressure. The residue was purified by column chromatography using DCM:MeOH=200:1~80:1 as the eluent to afford **657-8** (2.2 g, 59 %) as yellow oil.

[1246] **657-8** (100 mg, 0.16 mmol), 4-Cl-phenyl boronic acid (50 mg, 0.32 mmol) and Cs_2CO_3 (156 mg, 0.48 mmol) were taken up into a microwave tube in co-solvent dioxane:H_2O (1.2 mL, v:v=5:1). The solution was degassed and $Pd(dppf)Cl_2$ (3.5 mg, 0.05 mmol) was added. The sealed tube was heated to 110 °C by microwave irradiation and stirred for 1 h. The solution was cooled to r.t. and poured into water (10 mL). The mixture was extracted with EA (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purification by prep-TLC to give **657-9** (49 mg, 44%)

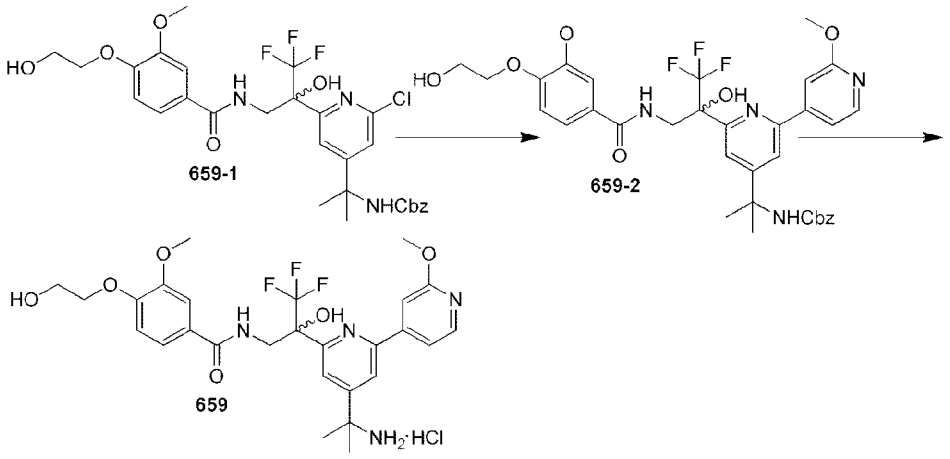
[1247] To a solution of **657-9** (49 mg) in CH_3CN (1 mL) was added one drop of TMSI at r.t., and the mixture stirred at r.t. for 10 mins. The mixture was poured into water, neutralized with sat. $NaHCO_3$ solution, and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **657** (15 mg) as a white solid. +ESI-MS: m/z 567.9 $[M+H]^+$.

EXAMPLE 340
Preparation of Compound 658



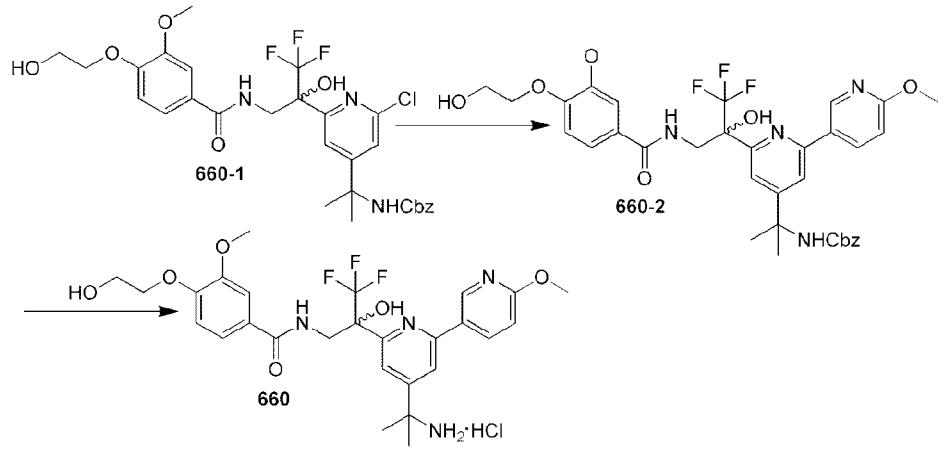
[1248] Compound **658** (white solid, 8 mg) was prepared following the general procedure for preparing **657** using **658-1** and 4-CF_3-phenyl boronic acid. The crude product was purified by prep-HPLC. +ESI-MS: m/z 602.1 $[M+H]^+$.

EXAMPLE 341
Preparation of Compound 659



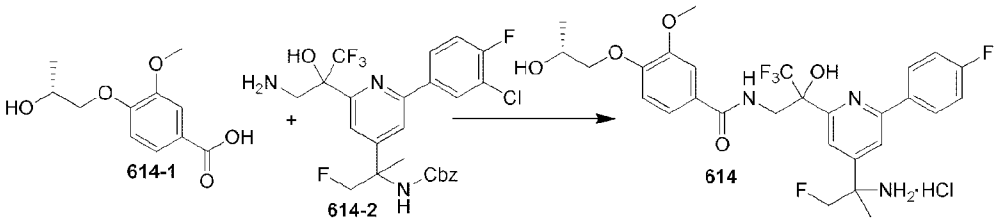
[1249] Compound **659** (white solid, 11 mg) was prepared following the general procedure for preparing **657** using **659-1** and 2-methoxy-4-pyridyl boronic acid. The crude product was purified by prep-HPLC. +ESI-MS: m/z 565.1 $[M+H]^+$.

EXAMPLE 342
Preparation of Compound 660



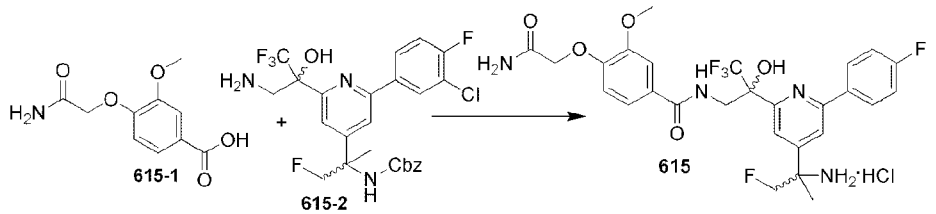
[1250] Compound **659** (white solid, 10 mg) was prepared following the general procedure for preparing **657** using **660-1** and 2-methoxy-4-pyridyl boronic acid. The crude product was purified by prep-HPLC. +ESI-MS: m/z 565.1 $[M+H]^+$.

EXAMPLE 343
Preparation of Compound 614



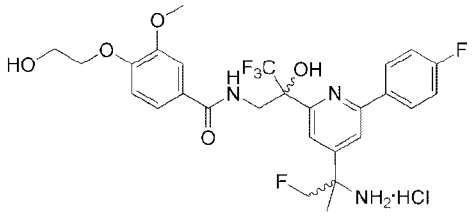
[1251] A mixture of **614-1** (23 mg, 0.1 mmol), **614-2** (50 mg, 0.1 mmol) and TEA (1 mmol) were dissolved in DCM (4 mL). HATU (38 mg, 0.1 mmol) was added, and the mixture was stirred for 30 mins. The mixture was diluted with brine (5mL), and the aqueous phase was extracted with DCM (2 x 5 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL) and hydrogenated over Pd/C (10 mg, 10%) at 15 psi for 17 h. The catalyst was removed by filtration, and the cake was washed with MeOH (5 mL). The combined filtrates was concentrated and purified by prep-HPLC to give **614** (28 mg, 45 %). +ESI-MS: m/z 584.0 $[M+H]^+$.

EXAMPLE 344
Preparation of Compound 615



[1252] Compound **615** (white solid, 43 mg) was prepared following the general procedure for preparing **614** using **615-1** and **615-2**. The crude product was purified by prep-HPLC. +ESI-MS: m/z 583.1 $[M+H]^+$.

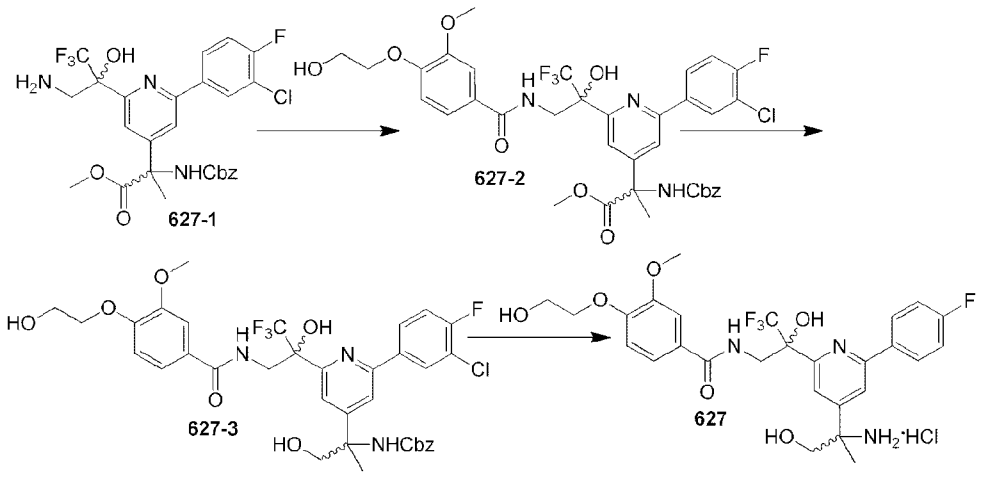
EXAMPLE 345
Preparation of Compound 626



[1253] To a solution of **540** (160 mg, 0.26 mmol) in MeOH (2 mL) was added Pd/C (150 mg) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred at 25 °C for 12 h. The mixture was filtered through a pad of Celite, and the pad was washed with MeOH. The combined filtrates were concentrated under reduced pressure. The residue was purified by prep-HPLC of acidity with HCl to give **626** (69 mg, 43%). +ESI-MS: m/z 570.0 $[M+H]^+$.

EXAMPLE 346

Preparation of Compound 627

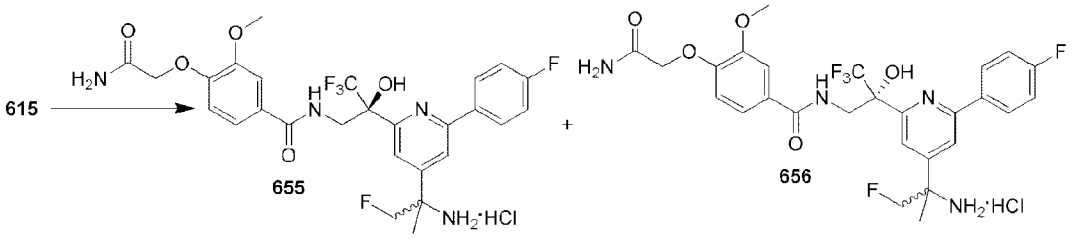


[1254] A mixture of **627-1** (66 mg, 0.3 mmol), **627-2** (150 mg, 0.3 mmol) and TEA (1 mmol) were dissolved in DCM (4 mL). HATU (120 mg, 0.2 mmol) was added, and the mixture was stirred for 30 mins. The reaction was diluted with brine (5mL), and the aqueous phase was extracted with DCM (2 x 5 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude **627-2**, which was used in next step without further purification. +ESI-MS: m/z 764.1 $[M+H]^+$.

[1255] To a solution of **627-2** (0.7 g, crude) in MeOH (20 mL) was added $LiBH_4$ (59 mg, 2.8 mmol) in one portion at r.t. The mixture was stirred for 1 h. The reaction was quenched with 2N HCl solution and extracted with EA (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=30:1~3:1 as the eluent to afford **627-3** (0.6, 89%) as an oil. +ESI-MS: m/z 736.0 $[M+H]^+$.

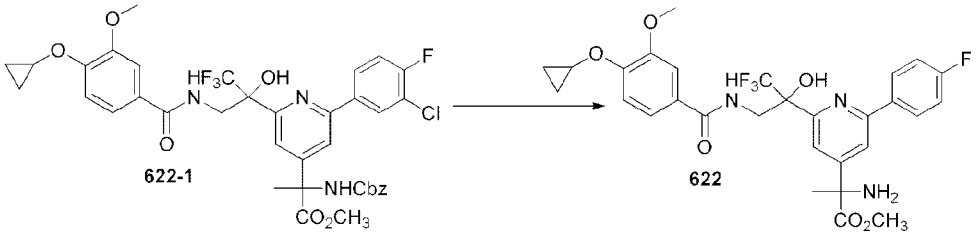
[1256] Compound **627** (white solid, 180 mg) was prepared following the general procedure for preparing **540** using **627-3**. +ESI-MS: m/z 568.1 $[M+H]^+$.

EXAMPLE 347
Preparation of Compounds 655 and 656



[1257] Compound **615** (30 mg) was separated by SFC to give solutions of peak 1 and peak 2. The two peaks were acidified by aq. HCl (2 M) and lyophilized to give **655** (9.2 mg) and **656** (8.9 mg) as a white solid. **655:** +ESI-MS: m/z 583.1 $[M+H]^+$ and **656:** +ESI-MS: m/z 583.1 $[M+H]^+$.

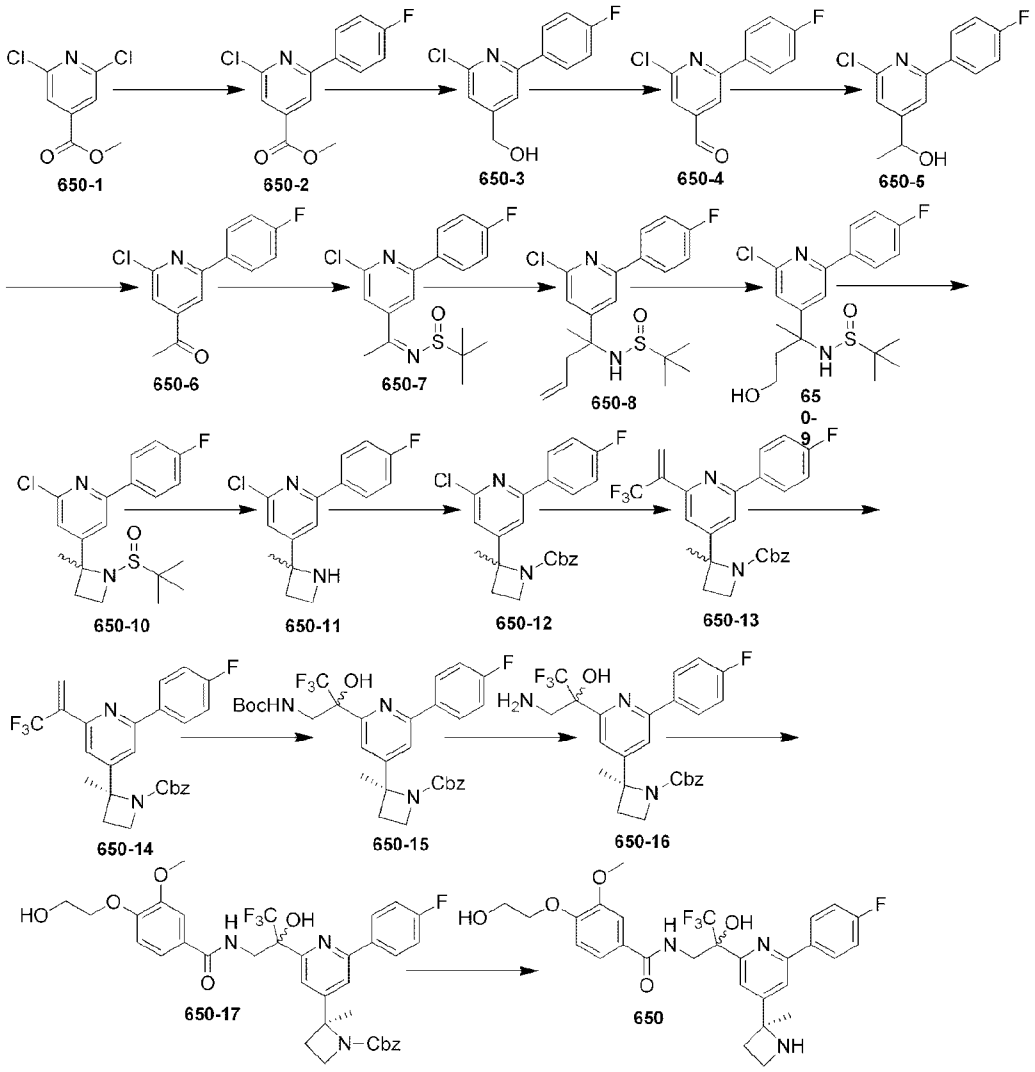
EXAMPLE 348
Preparation of Compound 622



[1258] **622-1** (white solid, 610 mg) was prepared following the general procedure for preparing **536**. +ESI-MS: m/z 760.1 $[M+H]^+$.

[1259] Compound **622** (12 mg,) was prepared following the general procedure for preparing **581** using **622-1**. LCMS: m/z 592.15 $[M+H]^+$.

EXAMPLE 349
Preparation of Compound 650

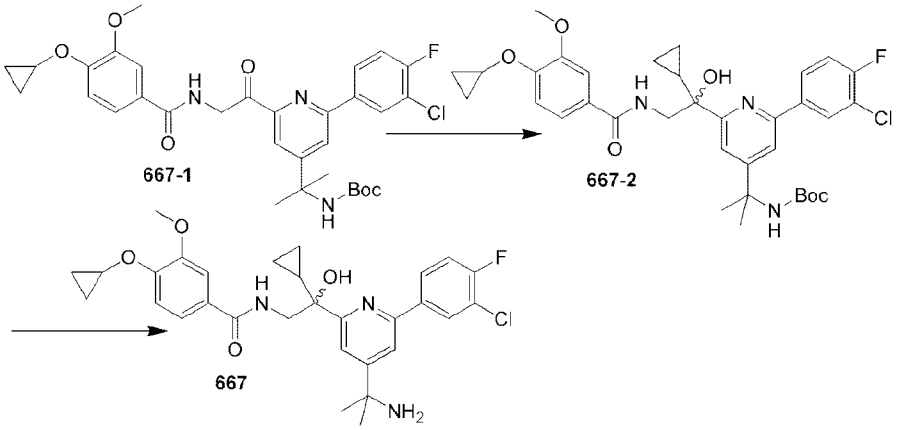


[1260] **650-17** (white solid, 210 mg) was prepared following the general procedure for preparing **563** using **650-1** and 4-F-phenyl boronic acid. +ESI-MS: m/z 698.1 $[M+H]^+$.

[1261] To a stirring mixture of **650-17** (200 mg, 0.28 mmol) in CH_3CN (2 mL) were added NaI (215 mg, 1.4 mmol) and TMSCl (152 mg, 1.4 mmol). The mixture was stirred at 65 °C for 20 mins. The mixture was cooled to r.t. and diluted with EtOAc. The reaction was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried

over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product mixture was purified via prep-HPLC to afford **650** (10 mg) as a white solid. LCMS 564.20 m/z $[M+H]^+$.

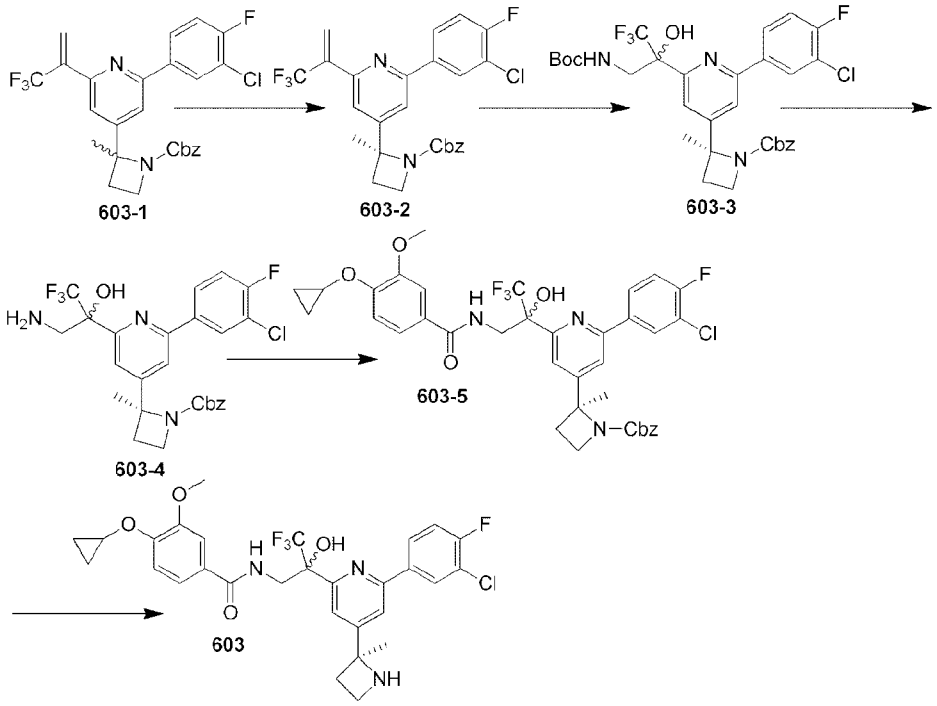
EXAMPLE 350
Preparation of Compound 667



[1262] To a solution of **667-1** (100 mg, 0.16 mmol) in THF (1 mL) was added cyclopropylmagnesium chloride (2 mL, 1 mmol) dropwise at r.t. The mixture was stirred for 2 h. The reaction was quenched with aq. NH_4Cl and extracted with EA (3 x 10 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EA=1:1) to give **667-2** (62 mg, 58.4%).

[1263] To a solution of **667-2** (62 mg, 0.1 mmol) in DCM (2 mL) was added TFA (2 mL) at r.t. The mixture was stirred for 30 mins. The mixture was neutralized by aq. $NaHCO_3$ solution and extracted by EA (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **667** (9 mg, 16.3%) as a white solid. +ESI-MS: m/z 554.0 $[M+H]^+$.

EXAMPLE 351
Preparation of Compound 603



[1264] Enantiomer **603-2** (270 mg) was obtained by SFC separation of racemic **603-1** (1.1 g).

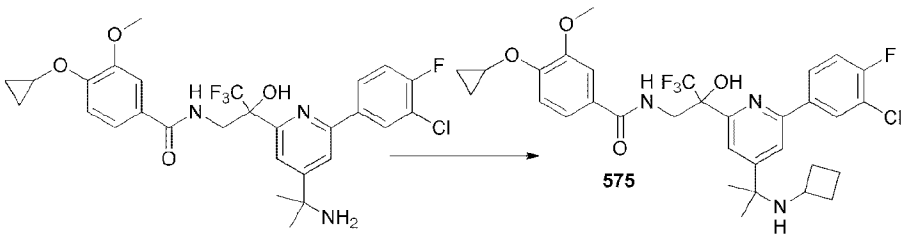
[1265] To a stirring mixture of **603-2** (270 mg 0.8 mmol) in 2-methylpropan-2-ol (6 mL):H_2O (2 mL) at 0 °C were added BocN-OTs (308 mg 1.07 mmol) and $K_2OsO_4 \cdot H_2O$ (60 mg, 0.16 mmol) at r.t. The mixture was stirred at r.t. for 30 h. The mixture was diluted with water and extracted with DCM (3 x 10 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA=1:1 as the eluent to afford **603-3** (~200 mg, ~60%). +ESI-MS: m/z 638.1 $[M+H]^+$.

[1266] To a mixture of **603-3** (200 mg, 0.32 mmol) in DCM (6 mL) was added TFA (3 mL) at r.t. The mixture was stirred for 30 mins, neutralized with aqueous $NaHCO_3$ and extracted with EA (3 x 10 mL). The combined organic layers were washed by brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude **603-4** (110 mg), which was used without further purification. +ESI-MS: m/z 538.1 $[M+H]^+$.

[1267] To a solution of 4-(cyclopropoxy)-3-methoxy-benzoic acid (37 mg, 0.17 mmol), HATU (100 mg 0.26 mmol) and DIPEA (57 mg, 0.44 mmol) in anhydrous DMF (3 mL) was added **603-4** (110 mg crude) at r.t. The solution was stirred for 5 h at r.t. with TLC monitoring. The mixture was diluted with 1.0 N aqueous $NaHCO_3$ solution and extracted with EA (3 x 10 mL). The combined organic layers were washed by brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using PE:EA = 1:1 as the eluent and prep-HPLC to give **603-5** (43 mg, 28.7%). +ESI-MS: m/z 728.1 $[M+H]^+$.

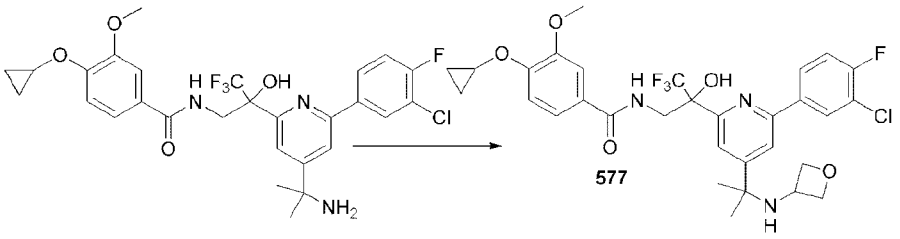
[1268] To a stirring mixture of **603-5** (15 mg, 0.041 mmol) in CH_3CN (1 mL) at r.t. were added NaI (32 mg, 0.2 mmol) and TMSCl (22 mg, 0.2 mmol). The mixture was stirred at 55 °C for 15 mins. The mixture was diluted with EtOAc and washed with a 10% aq. $Na_2S_2O_3$ solution. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The reaction was concentrated and the crude product was purified by prep-HPLC to provide **603**. +ESI-MS: m/z 594.20 $[M+H]^+$.

EXAMPLE 352
Preparation of Compound 575



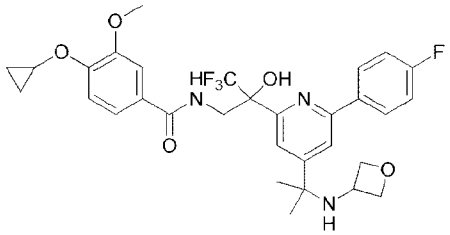
[1269] Cyclobutanone (17 μL, 0.22 mmol) and sodium cyanoborohydride (47 mg, 0.22 mmol) were added to a solution of **314** (43 mg, 0.074 mmol) every 30 mins for 6 h. The mixture was diluted with EtOAc, washed with 1N HCl and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by reverse phase HPLC to give **575** (14 mg, 23%). LCMS: m/z 637.20 $[M+H]^+$.

EXAMPLE 353
Preparation of Compound 577



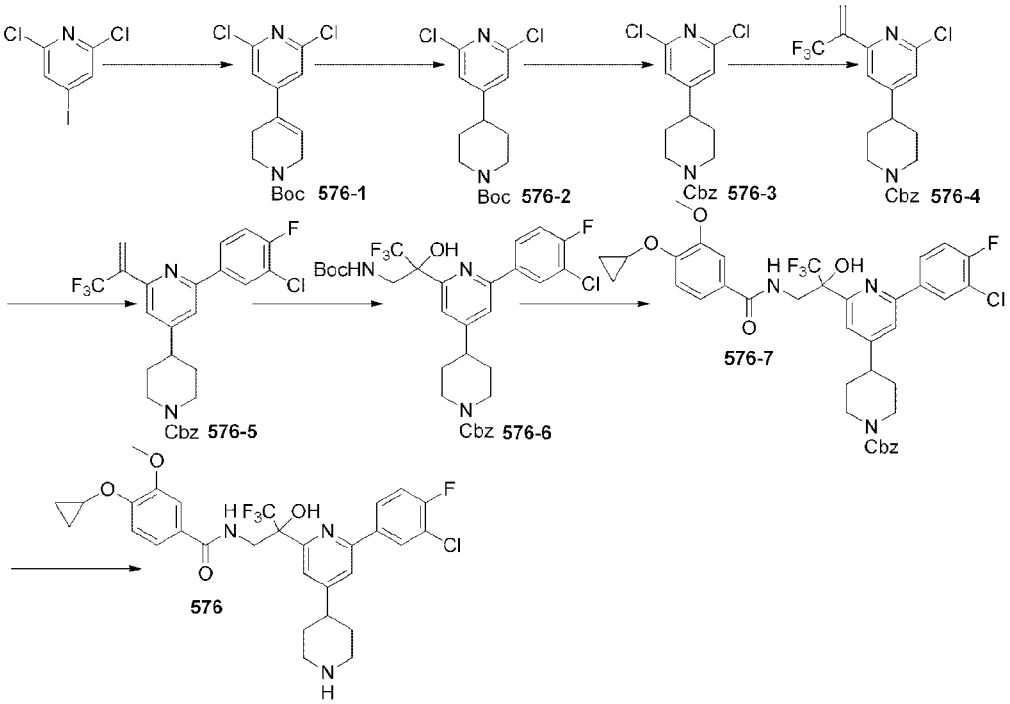
[1270] Compound **577** was prepared following the general procedure for preparing **575**. LCMS: m/z 639.10 $[M+H]^+$.

EXAMPLE 354
Preparation of Compound 581



[1271] **577** (12 mg, 0.019 mmol) was hydrogenated over 10% Pd/C (3 mg) in EtOH (2 mL) for 1 h. The catalyst was removed by filtration and the crude product was purified by reverse-phase HPLC to give **581** (8 mg, 66%). LCMS: m/z 604.20 $[M+H]^+$.

EXAMPLE 355
Preparation of Compound 576



[1272] $Pd(dppf)Cl_2$ (66 mg, 0.091 mmol) was added to a solution of 2,4-dichloro-4-iodopyridine (0.50 g, 1.8 mmol), (1-(tert-Butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)boronic acid (0.54 g, 1.8 mmol) and cesium carbonate (1.8 g, 5.5 mmol) in dimethoxyethane (10 mL) and water (1 mL). The mixture was heated under microwave irradiation at 110 °C for 1 h. The mixture was diluted with EA, washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **576-1** (0.47 g, 72%). LCMS: m/z 329.00 $[M+H]^+$.

[1273] A solution of **576-1** (0.83 g, 2.5 mmol) and platinum oxide (83 mg) in EtOH was stirred under H_2 atmosphere for 1 h. The mixture was filtered to remove catalyst and concentrated. The product (0.80 g, 96%) was used without further purification. LCMS: m/z 331.05 $[M+H]^+$.

[1274] HCl (4N in dioxane, 3 mL) was added to **576-2** (0.80 g, 2.4 mmol). The mixture was stirred at r.t. for 30 mins and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (10 mL), and DIEA (1.1 mL, 6.0 mmol) and benzyl chloroformate (0.41 mL, 2.9 mmol) were added. The reaction was stirred at r.t. for 1 h. The

mixture was diluted with EA, washed with 1N HCl and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **576-3** (0.49 g, 54%). LCMS: m/z 365.05 $[M+H]^+$.

[1275] $Pd(dppf)Cl_2$ (0.45 g, 0.61 mmol) was added to a solution of **576-3** (0.49 g, 1.3 mmol), 1-(trifluoromethyl)vinylboronic acid hexylene glycol ester (0.30 g, 1.3 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol) in DME (3 mL) and water (0.3 mL). The reaction vessel was heated under microwave irradiation for 20 mins at 110 °C. The mixture was diluted with EA. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **576-4** (0.23 g, 41%). LCMS: m/z 425.05 $[M+H]^+$.

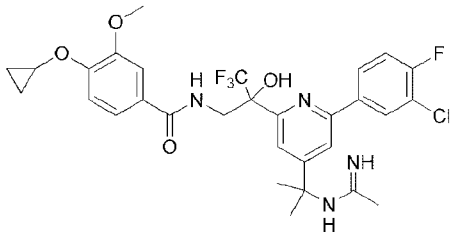
[1276] $Pd(dppf)Cl_2$ (20 mg, 0.027 mmol) was added to a solution of **576-4** (0.23 g, 0.54 mmol), 3-chloro-4-fluorophenyl boronic acid (95 mg, 0.54 mmol), Cs_2CO_3 (0.53 g, 1.6 mmol) in DME (2 mL) and water (0.2 mL). The reaction vessel was heated under microwave irradiation at 110 °C for 1 h. The mixture was diluted with EA. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **576-4** (0.11 g, 38%). LCMS: m/z 519.10 $[M+H]^+$.

[1277] Potassium osmate (11 mg, 0.029 mmol) was added to a solution of **576-5** (0.11 g, 0.21 mmol) and tert-butyl (tosyloxy)carbamate (91 mg, 0.33 mmol) in t-butanol (1 mL) and water (0.33 mL). The solution was stirred overnight at r.t. The crude mixture was purified by chromatography on silica gel (EA:hexane) to give **576-6** (0.12 g, 85%). LCMS: m/z 652.20 $[M+H]^+$.

[1278] HCl (2 mL, 4N in dioxane) was added to **576-6** (0.12 g, 0.18 mmol), and the mixture was stirred at r.t. for 2 h. The solvent was removed by evaporation and the amine salt was re-dissolved in DMF (1 mL). 4-cyclopropoxy-3-methoxybenzoic acid (57 mg, 0.28 mmol), HATU (0.14 g, 0.37 mmol) and DIEA (0.14 mL, 0.74 mmol) were added, and the mixture was stirred at r.t. for 2 h. The mixture was diluted with EA. The organic phase was washed with 1N HCl, water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **576-7** (35 mg, 26%). LCMS: m/z 742.20 $[M+H]^+$.

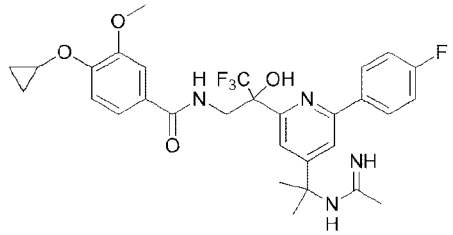
[1279] Chlorotrimethylsilane (23 μL, 0.24 mmol) was added dropwise to a solution of **576-7** (35 mg, 0.047 mmol) and NaI (28 mg, 0.24 mmol) in CH_3CN (1 mL), and the mixture was stirred for 30 mins. The mixture was diluted with EA, washed with $Na_2S_2O_3$ and brine, dried and concentrated. The crude product was purified by reverse-phase HPLC to provide **576** (13 mg, 37%). LCMS: m/z 609.15 $[M+H]^+$.

EXAMPLE 356
Preparation of Compound 579



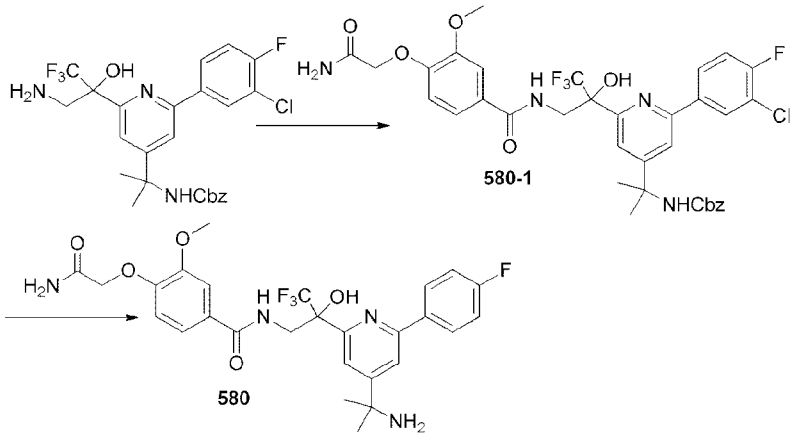
[1280] Ethyl acetimidate hydrochloride (150 mg, 1.2 mmol) was added to a solution of **314** (50 mg, 0.086 mmol) in EtOH (3 mL). The mixture heated at reflux for 24 h. The mixture was diluted with EA, washed with brine, dried and concentrated. The crude product was purified by reverse phase HPLC to give **579** (8 mg, 16%). LCMS: m/z 624.15 $[M+H]^+$.

EXAMPLE 357
Preparation of Compound 585



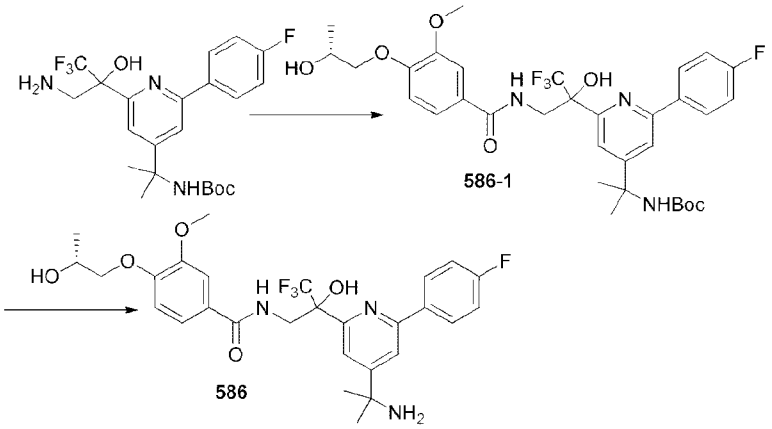
[1281] Compound **585** was prepared following the general procedure for preparing **579** using **318** and ethyl acetimidate. LCMS: m/z 590.20 $[M+H]^+$.

EXAMPLE 358
Preparation of Compound 580



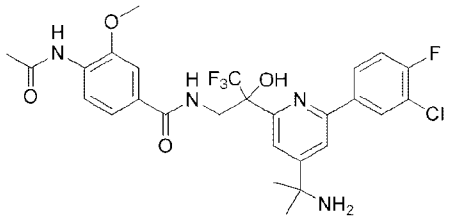
[1282] Benzyl(2-2(3-amino-1,1,1-trifluoro-2-hydroxypropan-2-yl)-6-(3-chloro-4-fluorophenyl)pyridine-4-yl)propan-2-yl)carbamate was coupled with 4-(2-amino-2-oxoethoxy)-3-methoxybenzoic acid following the general procedure for **576-7**. **580-1** was hydrogenated following the general procedure for preparing **581**. LCMS: m/z 565.15 $[M+H]^+$.

EXAMPLE 359
Preparation of Compound 586



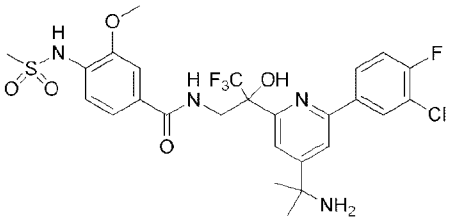
[1283] **586-1** was prepared following the general procedure for **576-7**. HCl in dioxane (3 mL) was added to **568-1** (92 mg, 0.18 mmol), and the mixture was stirred at r.t. for 3 h. The mixture was concentrated, and the crude product purified by reverse-phase HPLC to provide **586** (43 mg, 47%). LCMS: m/z 566.20 $[M+H]^+$.

EXAMPLE 360
Preparation of Compound 592



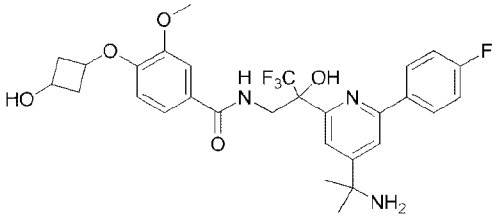
[1284] Compound **592** was prepared following the general procedure for **586** using 4-acetamido-3-methoxybenzoic acid. LCMS: m/z 583.15 $[M+H]^+$.

EXAMPLE 361
Preparation of Compound 593



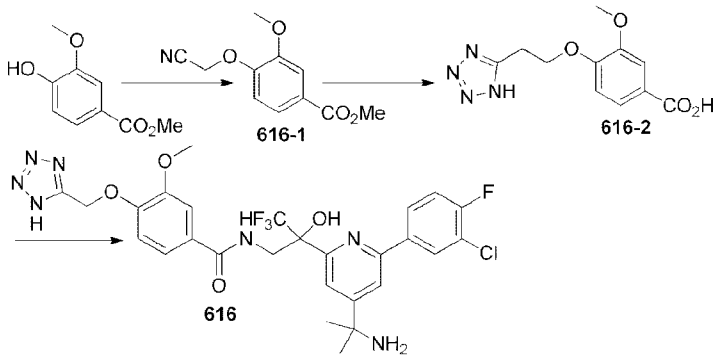
[1285] Compound **593** was prepared following the general procedure for **586**. LCMS: m/z 619.00 $[M+H]^+$.

EXAMPLE 362
Preparation of Compound 596



[1286] Compound **596** was prepared following the general procedure for **586** using 4-(3-hydroxycyclobutoxy)-3-methoxybenzoic acid. LCMS: m/z 578.20 $[M+H]^+$.

EXAMPLE 363
Preparation of Compound 616

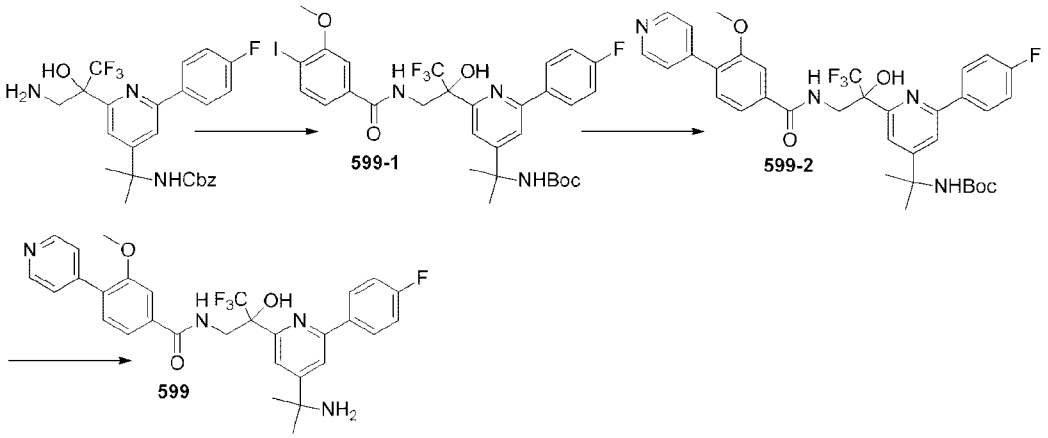


[1287] To a stirring mixture of methyl 4-hydroxy-3-methoxybenzoate (1 g, 5.49 mmol) in DMF (5 mL) at r.t. were added K_2CO_3 (1.14 g, 8.24 mmol) and 2-bromoacetonitrile. The mixture was stirred at r.t. for several hours and then diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product mixture was purified via a silica gel chromatography to afford **616-1** as a white solid.

[1288] To a stirring mixture of **616-1** (190 mg, 0.856 mmol) in DMF (2 mL) were added NaN_3 (71.5 mg, 1.1 mmol) and NH_4Cl (59 mg, 1.1 mmol). The mixture was carried out under microwave irradiation for 45 mins at 100 °C. The mixture was diluted with EtOAc and water, and the layers were separated. To the aqueous layer was added a 10% aqueous HCl solution until a white precipitation was formed. The tetrazole-product was filtered off, and then dissolved directly in aq. NaOH solution (1.5 mL, 2N). The mixture was heated at 80 °C for 30 mins. The mixture was cooled to r.t. and acidified with a 10% aq. HCl solution. The white solid was filtered off and dry under reduced pressure. Crude **616-2** was used without further purification. LCMS: m/z 265.05 $[M+H]^+$.

[1289] Compound **616** was prepared following the general procedure for **586** using **616-2**. LCMS: m/z 624.15 $[M+H]^+$.

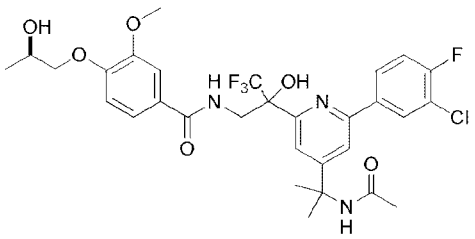
EXAMPLE 364
Preparation of Compound 599



[1290] **599-1** was prepared following the general procedure for **576-7**. $Pd(dppf)Cl_2$ (12 mg, 0.016 mmol) was added to a solution of **599-1** (0.23 g, 0.32 mmol), pyridine-4-boronic acid (65 mg, 0.016 mmol) and cesium carbonate (0.31 g, 0.96 mmol) in dimethoxyethane (2 mL) and water (0.2 mL). The mixture was heated under microwave irradiation at 110 °C for 20 mins. The mixture was diluted with EA, washed with brine, dried and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **599-2** (0.11 g, 50%).

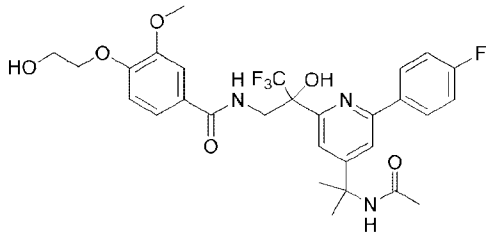
[1291] **599-2** was prepared following the general procedure for **586** to give **599**. LCMS: m/z 569.20 $[M+H]^+$.

EXAMPLE 365
Preparation of Compound 601



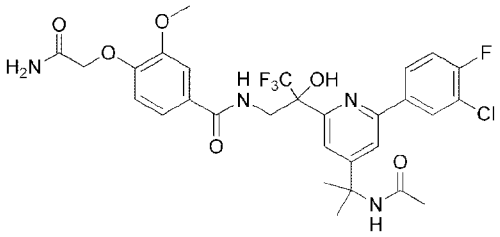
[1292] DIEA (87 μL, 0.50 mmol) was added to a solution of **317** (0.10 g, 0.16 mmol), acetic acid (20 mL, 0.33 mmol) and HATU (0.14 g, 0.35 mmol) in DMF. The mixture was stirred at r.t. for 1 h. The crude product was purified by reverse phase HPLC to provide **601** (17 mg, 17%). LCMS: m/z 642.15 $[M+H]^+$.

EXAMPLE 366
Preparation of Compound 611



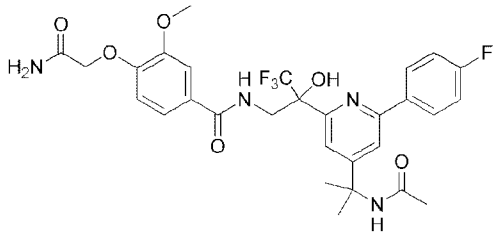
[1293] Compound **611** was prepared following the general procedure for **601** using **320**. LCMS: m/z 594.20 $[M+H]^+$.

EXAMPLE 367
Preparation of Compound 612



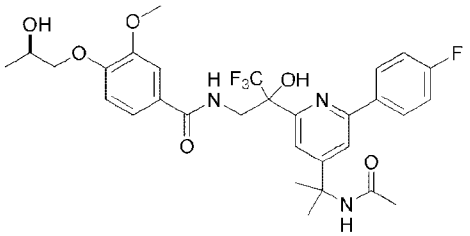
[1294] Compound **612** was prepared following the general procedure for **601** using **322**. LCMS: m/z 641.15 $[M+H]^+$.

EXAMPLE 368
Preparation of Compound 621



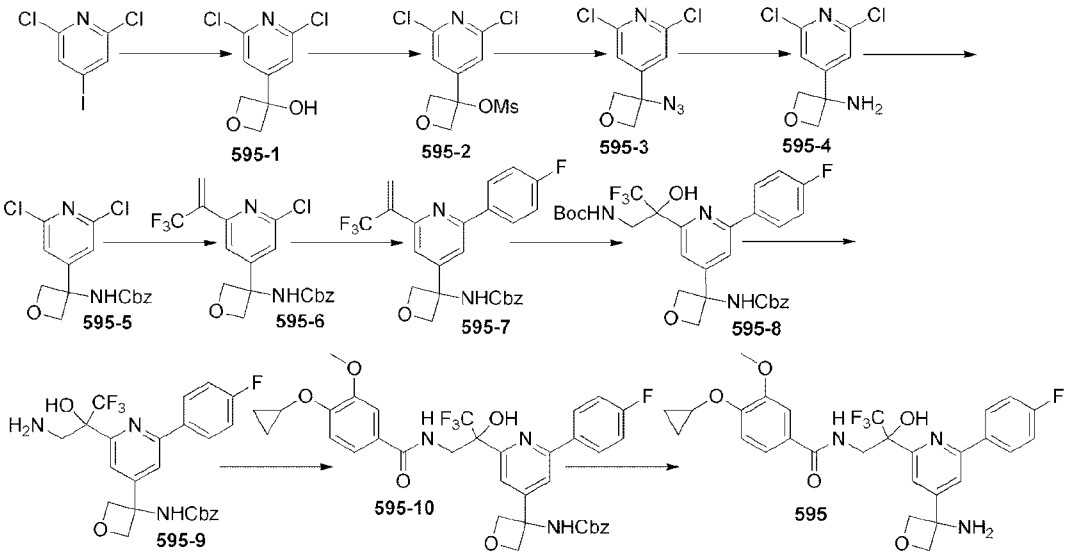
[1295] Compound **621** was prepared following the general procedure for **601** using **580**. LCMS: m/z 607.20 $[M+H]^+$.

EXAMPLE 369
Preparation of Compound 620



[1296] Compound **620** was prepared following the general procedure for **601** using **586**. LCMS: m/z 608.2 $[M+H]^+$.

EXAMPLE 370
Preparation of Compound 595



[1297] Isopropylmagnesium chloride (2M in THF, 2.0 mL, 4.0 mmol) was added dropwise to a solution of 2,6-dichloro-4-iodopyridine (1.0 g, 3.7 mmol) at -40 °C. The solution was stirred for 30 mins. 3-Oxetanone (0.28 mL, 4.4 mmol) was added dropwise. The mixture was stirred and warmed to r.t. for 2 h. The reaction was quenched with 1N HCl, extracted with EA, washed with brine, dried and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **595-1** (0.42 g, 51%).

[1298] Methanesulfonylchloride (1.1 mL, 15 mmol) was added dropwise to a solution of **595-1** (2.14 g, 9.7 mmol) and diisopropylethylamine (3.4 mL, 19 mmol) in CH_2Cl_2. The mixture was stirred at 0 °C for 1 h. The mixture was washed with 1N HCl and

brine, dried and concentrated. The residue was purified by chromatography on silica gel (EA:hexane) to give **595-2** (1.91 g, 66%).

[1299] Sodium azide (0.83 g, 1.3 mmol) was added to a soltuion of **595-2** (1.91 g, 0.64 mol) in DMSO (3 mL), and the mixture was stirred at 70 °C for 2 h. The mixture was diluted with EA, washed with water and brine, dried and concentrated. The product was purified by chromatography on silica gel (hexane:EA) to provide **595-3** (0. 67 g, 42%).

[1300] Trimethylphosphine (1M in THF, 2.2 mL, 2.2 mmol) was added to a solution of **595-3** (0.357 g, 1.5 mmol) in EA (5 mL). The mixture was stirred for 20 mins. Water (0.5 mL) was added, and the mixture was stirred at 70 °C for 1 h. The mixture was washed with brine, dried and concentrated to provide **595-4** (0.31 g, 93%) which was used without further purification.

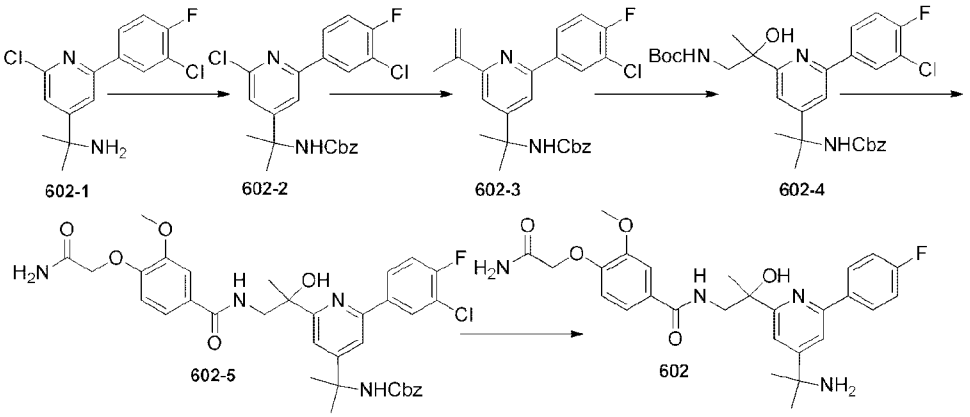
[1301] Benzyl chloroformate (0.98 mL, 6.9 mmol) was added to a solution of **595-4** (4.6 mmol) in THF (15 mL) and sat. sodium carbonate (15 mL). The mixture was stirred at r.t. overnight, and the aqueous layers were separated. The organic layer was washed with brine, dried and concentrated. The product was purified by chromatography on silica gel (hexane:EA) to provide **595-5** (1.4 g, 87%).

[1302] Compound **595-6** was prepared following the general procedure for **576-4**. LCMS: m/z 413.05 $[M+H]^+$. Compound **595-7** was prepared following the general procedure for **576-5**. LCMS: m/z 473.10 $[M+H]^+$. Compound **595-8** was prepared following the general procedure for **576-6**. LCMS: m/z 606.15 $[M+H]^+$.

[1303] **595-8** (75 mg, 0.12 mmol) was dissolved in hexafluoroisopropanol (1.5 mL). The solution was heated under microwave irradiation at 150 °C for 65 mins. The mixture was concentrated, and crude **595-9** was used without further purification. LCMS: m/z 505.46 $[M+H]^+$.

[1304] **595-10** was prepared following the general procedure for **576-7**. LCMS: m/z 696.20 $[M+H]^+$. Compound **595** was prepared following the general procedure for **580** using **595-10**. LCMS: m/z 562.15 $[M+H]^+$.

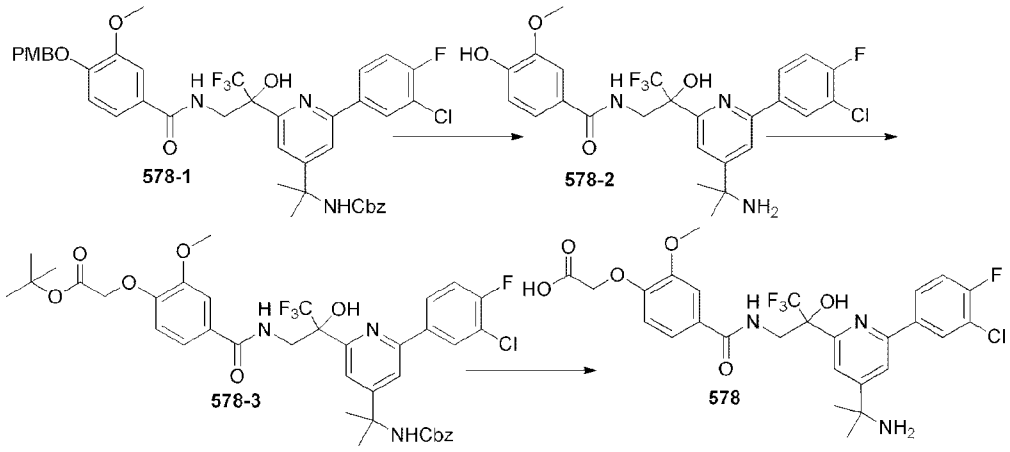
EXAMPLE 371
Preparation of Compound 602



[1305] Benzyl chloroformate (0.61 mL, 4.3 mmol) was added dropwise to a solution of **602-1** (0.86 g, 2.9 mmol) and diisopropylethylamine (1.0 mL, 5.7 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at r.t. overnight. The mixture was washed with 1N HCl and brine, dried and concentrated. Crude **602-2** (0.73 g, 58%) was purified by chromatography (hexane:EA). LCMS: m/z 433.05 $[M+H]^+$.

[1306] **602-3** was prepared following the general procedure for **576-4**. LCMS: m/z 439.10 $[M+H]^+$. **602-4** was prepared following the general procedure for **576-6**. LCMS: m/z 572.15$[M+H]^+$. **602-5** was prepared following the general procedure for **576-7**. LCMS: m/z 679.20 $[M+H]^+$. Compound **602** was prepared following the general procedure for **580** using **602-5**. LCMS: m/z 511.15 $[M+H]^+$.

EXAMPLE 372
Preparation of Compound 578

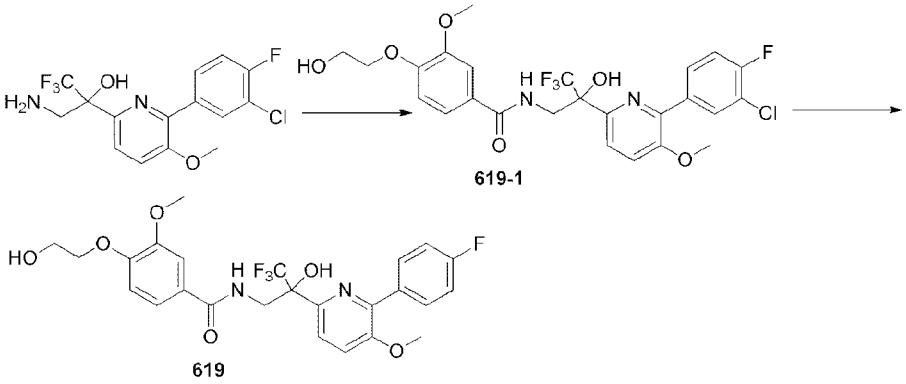


[1307] Trifluoroacetic acid (0.3 mL) was added to **578-1** (55 mg, 0.069 mmol) in CH_2Cl_2, and the mixture was stirred at r.t. for 4 mins. The reaction was quenched with cold sodium bicarbonate and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, concentrated and used without further purification.

[1308] Potassium carbonate (50 mg, 0.35 mmol) was added to a solution of **578-2** (0.069 mmol) and tert-butyl bromoacetate (30 μL, 0.21 mmol) in DMF (1 mL). The mixture was heated at 55 °C for 1 h. The mixture was diluted with EA, and washed with water and brine. The crude product was purified by column chromatography (hexane:EA) to provide **578-3**. LCMS: m/z 790.20 $[M+H]^+$.

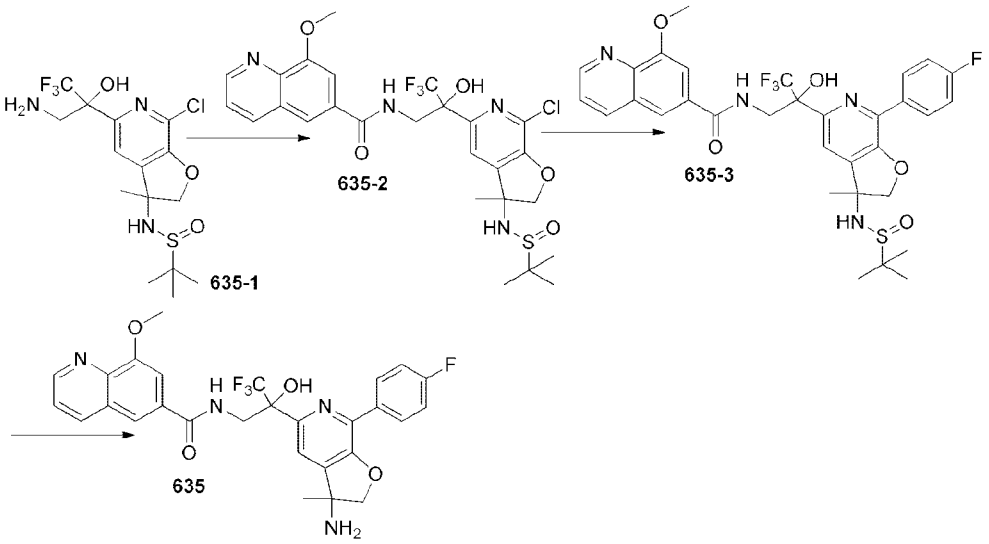
[1309] Compound **578** was prepared following the general procedure for **576** using **578-3**. LCMS: m/z 600.15 $[M+H]^+$.

EXAMPLE 373
Preparation of Compound 619



[1310] **619-1** was prepared following the general procedure for **576**. Compound **619** was prepared following the general procedure for **580**. LCMS: m/z 525.15 $[M+H]^+$.

EXAMPLE 374
Preparation of Compound 635

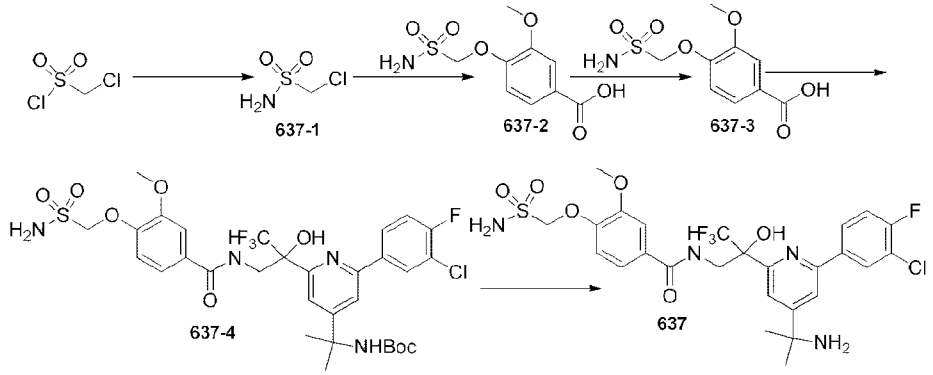


[1311] DIEA (90 μL, 0.52 mmol) was added to a solution of **635-1** (72 mg, 0.17 mmol), 8-methoxyquinoline-6-carboxylic acid (45 mg, 0.21 mmol) and HATU (98 mg, 0.26 mmol). The mixture was stirred at r.t. for 2 h. The mixture was purified by reverse-phase HPLC to provide **635**-2 (50 mg, 48%). LCMS: m/z 601.10 $[M+H]^+$.

[1312] $Pd(dppf)Cl_2$ (3 mg, 0.0041 mmol) was added to a solution of **635-2** (50 mg, 0.083 mmol), 4-fluorophenyl boronic acid (17 mg, 0.12 mmol), K_3PO_4 (0.11 mg, 0.22 mmol), KH_2PO_4 (45 mg, 0.22 mmol) in DME (1 mL), EtOH (0.6 mL) and water (0.2 mL). The solution was heated under microwave irradiation at 110 °C for 4 h. The mixture was diluted with EA, washed with brine, dried and concentrated. Crude **635-3** was purified by silica gel chromatography (MeOH:EtOAc). LCMS: m/z 661.20 $[M+H]^+$.

[1313] **635-3** (27 mg) was dissolved in MeOH (1 mL). To this stirring mixture was added a solution of HCl in dioxane (0.2 mL). The mixture was stirred at r.t. for 5 mins. The mixture was concentrated, and **635** (5 mg, 25%) was purified by reverse-phase HPLC. LCMS: m/z 557.15 $[M+H]^+$.

EXAMPLE 375
Preparation of Compound 637



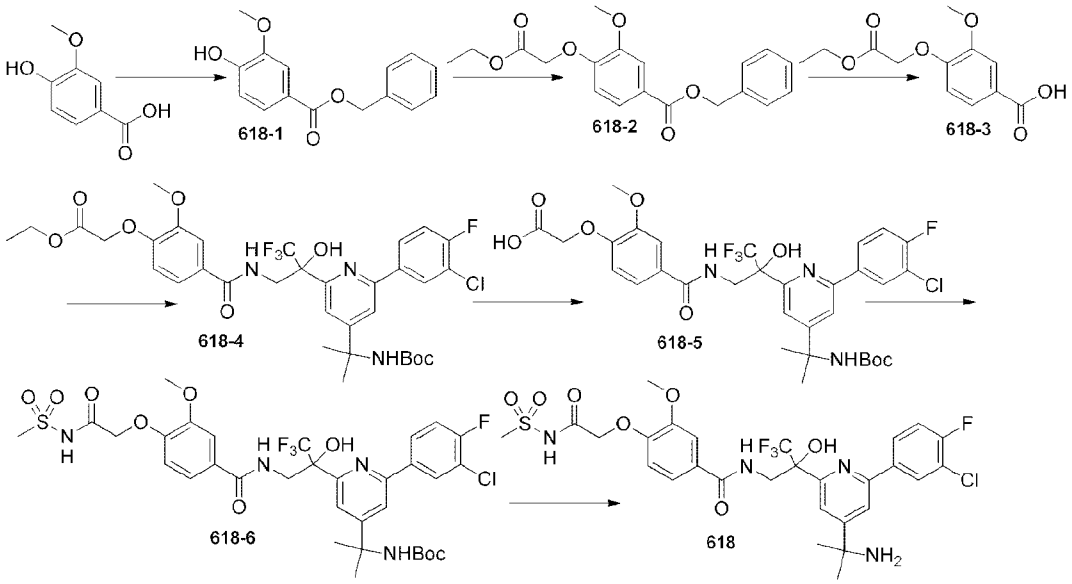
[1314] Chloromethanesulfonyl chloride (0.4 mL, 4.4 mmol) was added dropwise to a solution of ammonia (0.5 M in dioxane, 8.8 mL, 4.4 mmol) and DIEA (0.92 mL, 5.3 mmol) at 0 °C. The solution was stirred for 1 h. The reaction was washed with 1N HCl and brine, dried and concentrated. The crude product was used without further purification.

[1315] Potassium carbonate (1.2 g, 8.8 mmol) was added to a solution of methyl vanillate (0.40 g, 2.2 mmol) and **637-1** (4.4 mmol) in DMF (2.0 mL). The mixture was stirred at 65 °C overnight. The reaction was diluted with EA, washed with water and brine, dried and concentrated. The crude product was purified by silica gel chromatography (hexane:EA) to provide **637-2** (50 mg, 8%).

[1316] NaOH (2N, 1 mL) was added to a solution of **637-2** (50 mg, 0.18 mmol) in MeOH (3 mL). The mixture was stirred at r.t. overnight. The mixture was acidified by the addition of 2N HCl and extracted with EA. The organic extracts were washed with brine, dried and concentrated. Crude **637-3** was used without further purification.

[1317] **637-4** was prepared following the general procedure for **576-7**. Compound **637** was prepared following the general procedure for **586**. LCMS: m/z 635.15 $[M+H]^+$.

EXAMPLE 376
Preparation of Compound 618



[1318] Cesium carbonate (1.0 g, 5.9 mmol) as added to vanillic acid (2.0 g, 12 mmol) suspended in 90% aq. MeOH (20 mL). The mixture was stirred at r.t. for 30 mins. The solvents were removed and the crude product was dried by co-evaporating (2x) with toluene. The cesium salt was re-dissolved in DMF (15 mL). Benzyl bromide was added, and the mixture was stirred at r.t. overnight. The mixture was diluted with EA, washed with water and brine, dried and concentrated. The product was purified by silica gel chromatography (hexane:EA) to yield **618-1** (0.4 g, 12%).

[1319] Ethyl bromoacetate (0.34 mL, 3.1 mmol) was added to a solution of **618-1** (0.4 g, 1.5 mmol) and potassium carbonate (0.64 g, 4.6 mmol) in DMF (3 mL). The mixture was stirred at r.t. for 3 h. The mixture was washed with water and brine, dried and concentrated. The crude product was purified by column chromatography (hexane:EA) to yield **618-2** (0.177 g, 34%).

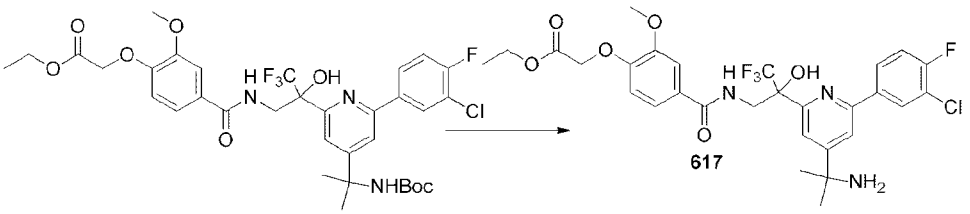
[1320] **618-2** (0.177 g 0.51 mmol) was hydrogenated over 10% Pd/C (35 mg) in EtOH for 45 mins. The catalyst was removed by filtration, and the mixture was concentrated to yield **618-3** (0.13 g, 100%), which was used without further purification.

[1321] **618-4** was prepared following the general procedure for **576-7**. LCMS: m/z 728.20 $[M+H]^+$. NaOH (2N, 2 mL) was added to a solution of **618-4** (0.302 g, 0.43

mmol) in MeOH (10 mL). The mixture was stirred overnight at r.t. The mixture was acidified with 1N HCl and extracted with EA. The organic extracts were washed with brine, dried and concentrated to yield **618-5** (0.29 g, 92%). LCMS: m/z 700.20 $[M+H]^+$.

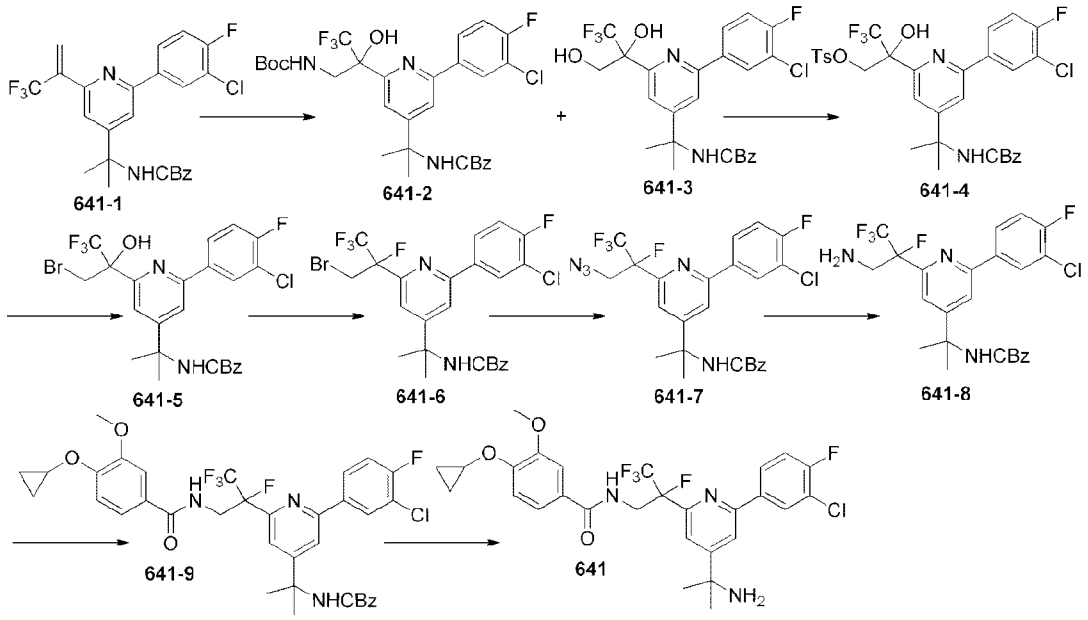
[1322] DMAP was added to a solution of **618-5** (50 mg, 0.071 mmol), methyl sulfonamide (10 mg, 0.11 mmol) and EDCI (16 mg, 0.086 mmol) in DMF (1 mL). The mixture was stirred at r.t. overnight. The product was purified by reverse-phase HPLC to yield **618-6** (27 mg). LCMS: m/z 777.05 $[M+H]^+$. Compound **618** was prepared following the general procedure for **586**. LCMS: m/z 677.05 $[M+H]^+$.

EXAMPLE 377
Preparation of Compound 617



[1323] Compound **617** was prepared following the general procedure for **586**. LCMS: m/z 628.15 $[M+H]^+$.

EXAMPLE 378
Preparation of Compound 641



[1324] To a stirring mixture of **641-1** (950 mg, 1.9 mmol) in t-BuOH:water (3:1, 3 mL total volume) at r.t. were added potassium osmate dihydrate (105 mg, 0.3 mmol) and tert-butyl tosyloxycarbamate (1 g, 3.8 mmol). The mixture was stirred at r.t. overnight. The mixture was diluted with water and DCM. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel chromatography to afford **641-3** as a minor product (200 mg, 10%); LCMS: m/z 527.2 $[M+H]^+$.

[1325] tert-butyl tosyloxycarbamate was prepared as follows. To a stirring mixture of tert-butyl hydroxycarbamate (2 g, 15 mmol) in THF (10 mL) at 0 °C was added TsCl (2.8 g, 15 mmol) and TEA (2.2 mL, 15.8 mmol). The mixture was stirred at 0 °C for 20 mins and then quickly warmed to r.t. for 5 mins. The mixture was diluted with DCM and washed with water. An aqueous workup with DCM gave the crude product, which was purified via a silica gel to afford tert-butyl tosyloxycarbamate as a white solid.

[1326] To a stirring mixture of **641-3** (200 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) at r.t. were added TsCl (376 mg, 1.96 mmol) and TEA (320 μL, 2.34 mmol). The mixture was stirred at r.t. for 30 mins. The reaction was quenched with sat. $NaHCO_3$ solution. The layers were separated. The aqueous layer was extracted with EtOAc (2 x 25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the crude product afforded **641-4** (128 mg) as a colorless oil. LCMS: m/z 681.10 $[M+H]^+$.

[1327] To a stirring mixture of **641-4** (128 mg, 0.188 mmol) in acetone (2 mL) at r.t. was added LiBr. The mixture was heated at reflux for 1 h and then cooled to r.t. The mixture was concentrated under reduced pressure. Chromatography of residue afforded **641-5** as a colorless oil (80 mg, 72% yield). LCMS: m/z 589 $[M+H]^+$.

[1328] To a stirring mixture of **641-5** (80 mg, 0.135 mmol) in DCM (1.5 mL) at 0 °C was added DAST (58 μL, 0.41 mmol). The mixture was stirred at 0 °C for 30 mins and then quickly warmed to r.t. for 5 mins. The reaction was quenched with a cold aq. $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product mixture was purified via a silica gel column to afford **641-6** (56 mg, 74% yield). LCMS: m/z 591.0 $[M+H]^+$.

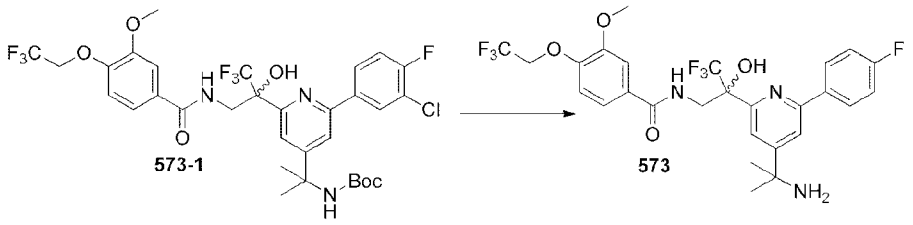
[1329] To a stirring mixture of **641-6** (50 mg, 0.084 mmol) in DMF (1 mL) were added tetrabutylammonium azide (240 mg, 0.84 mmol) and tetrabutylammonium iodide (12 mg). The mixture was stirred at 100 °C for several hours. The mixture was directly loaded onto a silica gel column, eluting with hexane:EtOAc to afford **641-7** (30 mg, 64%) as a colorless oil. LCMS: m/z 554.10 $[M+H]^+$.

[1330] To a stirring mixture of **641-7** (30 mg, 0.054 mmol) in THF:water (10:1, 1.1 mL) was added triphenylphosphine, polymer-bound (142 mg, 0.54 mmol). The mixture was stirred at 70 °C for 30 mins and then cooled to r.t. The mixture was filtered through a plug of celite. The plug was washed several times with EtOAc. The crude mixture was concentrated under reduced pressure, and the crude product was used in the next step without further purification.

[1331] To a stirring mixture of 4-cyclopropoxy-3-methoxybenzoic acid in DMF (1 mL) were added HATU (21 mg, 0.054 mmol) and DIPEA (15 μL, 0.11 mmol). The mixture was stirred at r.t. for 5 mins. A solution of **641-8** in DMF (0.5 mL) was added. The mixture was stirred at r.t. for 10 mins. The reaction was quenched with a 10% aq. solution of $NaHCO_3$ (10 mL). The mixture was diluted with DCM, and an aqueous work up with DCM was followed. The crude product was purified via prep-HPLC to afford **641-9** (20 mg, 52%, 2 steps) as a white solid. LCMS: m/z 718.2 $[M+H]^+$.

[1332] To a stirring mixture of **641-9** (20 mg, 0.0286 mmol) in AcCN (1 mL) at r.t. were added NaI (22 mg, 0.143 mmol) and TMSCl (19 mg, 0.143 mmol). The mixture was warmed to 60 °C until the starting materials were consumed. The mixture was cooled to r.t. and diluted with CH_2Cl_2. The mixture was washed with a 10% aq. solution of $Na_2S_2O_3$. The aqueous layer was extracted with DCM (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was further purified via prep-HPLC to afford **641**. LCMS: m/z 584.15 $[M+H]^+$.

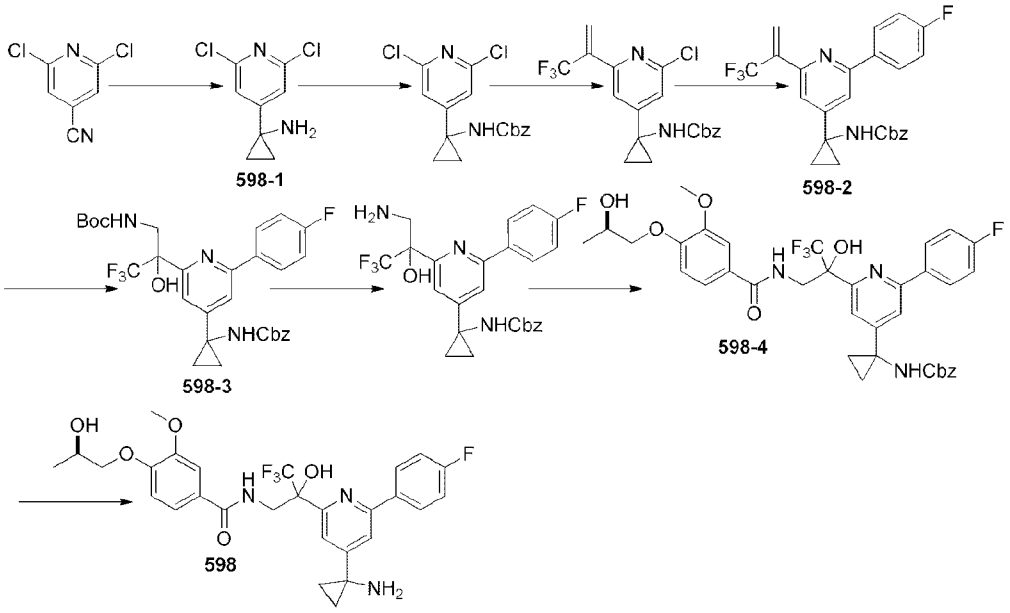
EXAMPLE 379
Preparation of Compound 573



[1333] To a stirring solution of **573-1** (30 mg, 0.41 mmol) in EtOAc:EtOH (5 mL:5mL) was added Pd/C (20 mg). The mixture was placed under a H_2 balloon. The mixture was stirred for several hours until the starting material was consumed. The crude mixture was filtered through a plug of celite, and the plug was washed with EtOAc (2 x 20 mL). The mixture was concentrated under reduced pressure, which was used without further purification.

[1334] The N-Boc protected amine was dissolved in a 4N HCl in dioxane. The mixture was stirred overnight at r.t. The crude product mixture was concentrated under reduced pressure. The crude product mixture was purified via a prep-HPLC to afford **573** as a white solid. LCMS: m/z 590.15 $[M+H]^+$.

EXAMPLE 380
Preparation of Compound 598



[1335] To a stirring mixture of 2,6-dichloroisonicotinonitrile (1 g, 5.78 mmol) in Et_20 at r.t. under Ar was added $Ti(OiPr)_4$ (1.97 mL, 6.65 mmol). The mixture was stirred for 10 mins and then cooled to 0 °C. A solution of EtMgBr (3.54 mL, 12.14 mmol) in 2-methyltetrafuran was added over 10 mins. The mixture was stirred at r.t. for 1 h, and then cooled to 0 °C. BF_3.OEt (1.3 mL, 10.58 mmol) was added. The mixture was warmed to r.t. and stir for 30 mins. The reaction was quenched with 1N HCl (5 mL) and then 2N NaOH (10 mL). The mixture was diluted with DCM. The aqueous layer was extracted with DCM, dried over MgSO4, filtered and concentrated under reduced pressure. Chromatography of the residue afford **598-1** (100 mg, 8.5%) as a colorless oil. LCMS: m/z 203.1 $[M+H]^+$.

[1336] To a stirring mixture of **598-1** (100 mg, 0.49 mmol) in DCM (1 mL) at 0 °C were added CBzCl (84.2 mg, 0.49 mmol) and DIPEA (86 μL, 0.49 mmol). The mixture was warmed to r.t. for 20 mins. The reaction was quenched with a cold sat. $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filltered and concentrated under reduced pressure. Chromatography of the residue afford N-CBz protected amine (100 mg, 60%). LCMS: m/z 337.0 $[M+H]^+$.

[1337] To a stirring mixture of benzyl (1-(2,6-dichloropyridin-4-yl)cyclopropyl)carbamate (100 mg, 0.297 mmol) in DME (2 mL, deoxygenated prior to using) were added 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (132 mg, 0.59 mmol), a solution of Cs_2CO_3 (290 mg, 0.89 mmol in 0.3 mL of water) and $PdCl_2$(dppf) (45 mg, 0.062 mmol). The mixture was heated under microwave irradiation for 1 h at 110 °C. The crude product mixture was diluted with EtOAc and water. An aqueous workup with EtOAc was followed. The crude product was purified via a silica gel chromatography to afford desired product. The mixtures was used in the next step without further purification (70 mg). LCMS: m/z 397.10 $[M+H]^+$.

[1338] To a stirring mixture of products from the previous step (70 mg, 0.176 mmol) in DME (1.5 mL, deoxygenated prior to using) were added 4-fluorophenylboronic acid (36 mg, 0.259 mmol), a solution of Cs_2CO_3 (171 mg, 0.52 mmol in 0.3 mL of water), and $PdCl_2$(dppf) (26 mg, 0.035 mmol). The mixture was carried out under microwave irradiation at 110 °C for 1 h. The crude product was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated under

reduced pressure. The crude product was purified via a silica gel chromatography to yield benzyl (1-(2-(4-fluorophenyl)-6-(3,3,3-trifluoroprop-1-en-2-yl)pyridin-4-yl)cyclopropyl)carbamate as the desired product. LCMS: m/z 457. $[M+H]^+$.

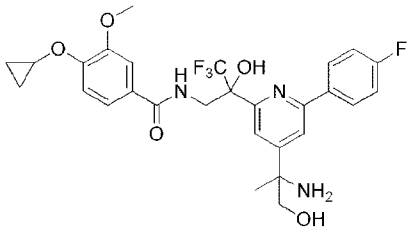
[1339] To a stirring mixture of **598-2** (50 mg, 0.085 mmol) in t-BuOH:water (3:1, 1.3 mL) at r.t. were added potassium osmate dihydrate (8 mg, 0.0215 mmol) and tert-butyl tosyloxycarbamate (62 mg, 0.215 mmol). The mixture was stirred at r.t. overnight, and then diluted with water and DCM. The aqueous layer was extracted with DCM, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel chromatography to afford **598-3** (24 mg, 37%). LCMS: m/z 590.20 $[M+H]^+$.

[1340] The N-Boc protected amine was dissolved in a solution of HCl in dioxane (2 mL, 4N) at r.t. The mixture was stirred at r.t. until the starting material was consumed. The mixture was concentrated under reduced pressure to afford the crude amino alcohol, which was used without further purification. LCMS: m/z 490.10 $[M+H]^+$.

[1341] To a stirring mixture of (R)-4-(2-hydroxypropoxy)-3-methoxybenzoic acid (9 mg, 0.04 mmol) in DMF (0.5 mL) were added HATU (15.2 mg, 0.04 mmol) and DIPEA (17 μL, 0.1 mmol). The mixture was stirred at r.t. for 10 mins. A solution of the crude amino alcohol in DMF (0.2 mL) was added. The mixture was stirred at r.t. for 10 mins. The reaction was quenched with a 10% aq. $NaHCO_3$ solution (1 mL). The mixture was diluted with DCM, and an aqueous work up with DCM was followed. The crude product was purified via prep-HPLC to afford benzyl (1-(2-(4-fluorophenyl)-6-(1,1,1-trifluoro-2-hydroxy-3-(4-((R)-2-hydroxypropoxy)-3-methoxybenzamido)propan-2-yl)pyridin-4-yl)cyclopropyl)carbamate (7 mg, 24% 2 steps) as a white solid. LCMS: m/z 698.2 $[M+H]^+$.

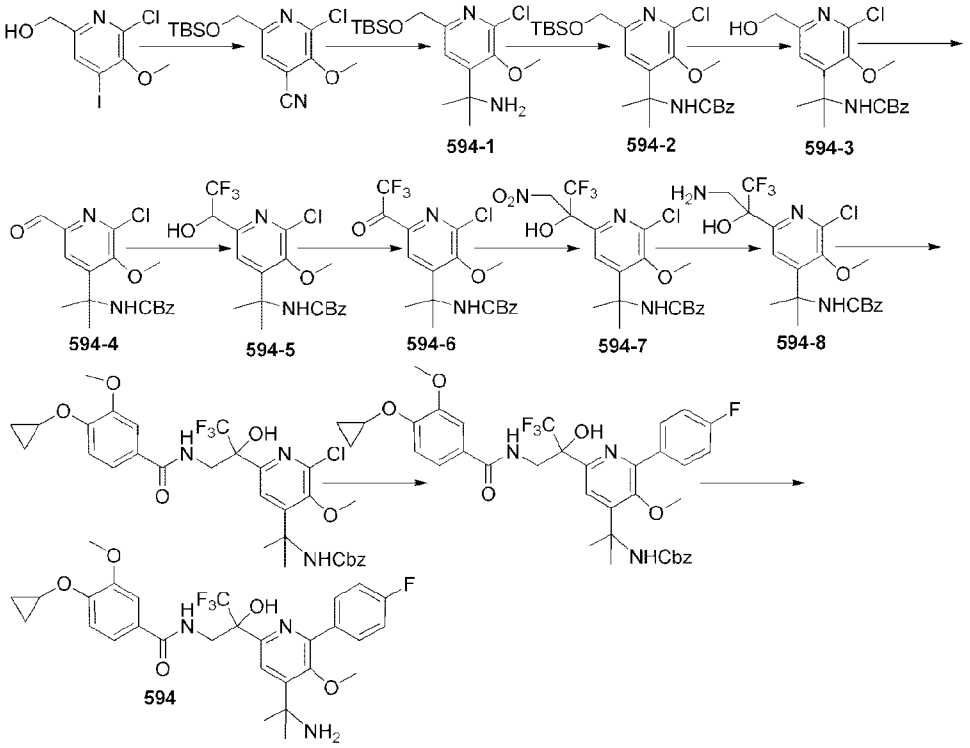
[1342] To a stirring mixture of **598-4** (7 mg, 0.01 mmol) in AcCN (0.5 mL) at r.t. were added NaI (7.5 mg, 0.05 mmol) and TMSCl (5.4 mg, 0.05 mmol). The mixture was warmed to 60 °C until the starting material was consumed. The mixture was cooled to r.t. and diluted with CH_2Cl_2. The mixture was washed with a 10% aq. $Na_2S_2O_3$ solution. The aqueous layer was extracted with DCM (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was further purified via prep-HPLC to afford **598**. LCMS: m/z 564.20 $[M+H]^+$.

EXAMPLE 381
Preparation of Compound 600



[1343] To a stirring solution of **533** (10 mg, 0.016 mmol) in EtOAc:EtOH (5 mL:1 mL) was added Pd/C (15 mg). The mixture was placed under a H_2 balloon. The mixture was stirred for several hours until the starting material was consumed. The crude mixture was filtered through a plug of celite, and the plug was washed several times with EtOAc (2 x 20 mL). The mixture was concentrated under reduced pressure and purified via prep-HPLC to afford **600** as a white solid (3 mg, 32%). LCMS: m/z 564.2 $[M+H]^+$.

EXAMPLE 382
Preparation of Compound 594



[1344] Iodomethane (0.66 mL, 11 mmol) was added dropwise to a solution of 2-chloro-3-hydroxy-6-(hydroxymethyl)-4-iodopyridine (2.03 g, 7.1 mmol) and potassium

carbonate (2.0 g, 14 mmol) in DMF (8 mL). The mixture was stirred at r.t. for 1 h. The mixture was diluted with EA, washed with water and brine, dried and concentrated. The product (1.77 g, 64%) crystallized upon standing.

[1345] DIPEA (2.0 mL, 12 mmol) was added dropwise to a solution of (6-chloro-4-iodo-5-methoxypyridin-2-yl)methanol (1.77 g, 5.91 mmol), tert-butylchlorodimethylsilane (1.3 g, 8.9 mmol) and a catalytic amount of imidazole in CH_2Cl_2 (10 mL). The mixture was stirred at r.t. overnight. The mixture was diluted with CH_2Cl_2, washed with 1N HCl and brine, dried and concentrated. The crude product was purified by column chromatography (hexane:EA) to yield the product (2.18 g, 75%) as a white solid.

[1346] Copper cyanide (1.0 g, 12 mmol) was added to a solution of 6-(((tert-butyldimethylsilyl)oxy)methyl)-2-chloro-4-iodo-3-methoxypyridine (1.0 g, 2.4 mmol) in dimethyl acetamide (3 mL). The mixture was heated at 140 °C for 2 h, and then diluted with DCM. A 10% aq. solution of NH_4OH was added. The mixture was stirred at r.t. for 20 mins, and the layers were separated. An aqueous work up with EtOAc was followed. Chromatography of residue afforded 6-(((tert-butyldimethylsilyl)oxy)methyl)-2-chloro-3-methoxyisonicotinonitrile (520 mg,70%) as a colorless oil.

[1347] To a stirring mixture of 6-(((tert-butyldimethylsilyl)oxy)methyl)-2-chloro-3-methoxyisonicotinonitrile (520 mg, 1.66 mmol) in Et_2O (3.9 mL) at 0 °C was added a solution of MeMgBr in 2-methyltetrafuran (1.47 mL, 4.71 mmol). After 1 h of stirring at r.t., $Ti(OiPr)_4$ was added. The mixture was heated at reflux for 2 h and then diluted with CH_2Cl_2. The mixture was cooled to r.t., and copious quantities of Celite were added. The crude mixture was basified with a solution of NaOH (2 mL, 2N) and filtered through a plug of Celite. The plug was washed several times with DCM. The filtrate was washed with a 10% aq. HCl solution. The layers were separated, and the organic layer was washed with sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of residue afforded **594-1** (147 mg, 26%) as a colorless oil. LCMS: m/z 345.15 $[M+H]^+$.

[1348] To a stirring mixture of **594-1** (147 mg, 0.45 mmol) in DCM (1.5 mL) at 0 °C were added CBzCl (114 mg, 0.67 mmol) and DIPEA (233 μL, 0.49 mmol). The mixture

was warmed to r.t. for 10 mins. The reaction was quenched with a cold sat. $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filltered and concentrated under reduced pressure. Chromatography of the residue afford **594-2** (110 mg, 57%) as a white solid.

[1349] To a stirring mixture of **594-2** (110 mg, 0.25 mmol) in THF (762 μL) at rt was added dropwise a solution of TBAF (0.85 mL) in THF. The mixture was stirred at r.t. until the starting material was consumed. Silica gel was added, and the mixture was stirred at r.t. for 10 mins. resulting mixture was concentrated under reduced pressure. Chromatography of the residue **594-3**, which was used without further purification. LCMS: m/z 365.05 $[M+H]^+$.

[1350] To a stirring mixture of **594-3** (110 mg, ~0.3 mmol) in CH_2Cl_2 (1.3 mL) at r.t. was added and Dess–Martin periodinane (383 mg, 0.9 mmol). The mixture was stirred at r.t. until the alcohol was consumed. The reaction was quenched with a 5% $NaHSO_3$ solution and a sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product mixture was purified via a silica gel column to afford **594-4** (90 mg, 55% 2 steps). LCMS: m/z 363.05 $[M+H]^+$.

[1351] To a stirring mixture of **594-4** (90 mg, 0.248 mmol) in DMF (0.5 mL) were added $TMSCF_3$ (53 mg, 0.37 mmol) and a TBAF solution in THF (37 μL). The mixture was stirred at r.t. for 1 h. Silica gel was added, and the mixture was stirred for 10 mins. The crude mixture was concentrated under reduced pressure. Chromatography of the residue afford **594-5** (86 mg, 80%). LCMS: m/z 433.05 $[M+H]^+$.

[1352] To a stirring mixture of **594-5** (86 mg, 0.198 mmol) in CH_2Cl_2 (1.0 mL) at r.t. was added the Dess–Martin periodinane reagent (421 mg, 0.99 mmol). The mixture was stirred at r.t. until the alcohol was consumed. The reaction was quenched with a 5% aqueous solution of $NaHSO_3$ and a sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product mixture was purified via a silica gel column to afford **594-6** (80 mg, 90%). LCMS: m/z 449.05 $[M+H_2O+H]^+$.

[1353] To a stirring mixture of **594-6** (30 mg, 0.074 mmol) in $MeNO_2$ (0.5 mL) was added TEA (20 μL, 0.147 mmol). The mixture was stirred at r.t. for 30 mins, and then diluted with DCM and washed with water. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filltered and concentrated under reduced pressure. Chromatography of the residue afford **594-7** (30 mg, 82%) as a white solid. LCMS: m/z 492.05 $[M+H]^+$.

[1354] To a stirring mixture of **594-7** (30 mg, 0.061 mmol) in EtOAc (0.3 mL) at r.t. was added $SnCl_2.2H_20$ (166 mg, 0.74 mmol). The mixture was heated at reflux for 1 h and then cooled to r.t. The mixture was concentrated under reduced pressure. The crude product mixture was direclty loaded into a silica gel column to afford **594-8**. LCMS: m/z 462.05 $[M+H]^+$.

[1355] To a stirring mixture of 4-cyclopropoxy-3-methoxybenzoic acid (12.6 mg, 0.06 mmol) in DMF (0.5 mL) were added HATU (23 mg, 0.06 mmol) and DIPEA (16 μL, 0.09 mmol). The mixture was stirred at r.t. for 10 mins. A solution of **594-8** in DMF (0.2 mL) was added, and the mixture was stirred at r.t. for 10 mins. The reaction was quenched with a 10% aq. $NaHCO_3$ solution(10 mL). The mixture was diluted with DCM and an aqueous work up with DCM was followed. The crude product was purified via prep-HPLC to afford benzyl (2-(2-chloro-6-(3-(4-cyclopropoxy-3-methoxybenzamido)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-3-methoxypyridin-4-yl)propan-2-yl)carbamate (30 mg, quantitative) as a white solid. LCMS: m/z 652.15 $[M+H]^+$.

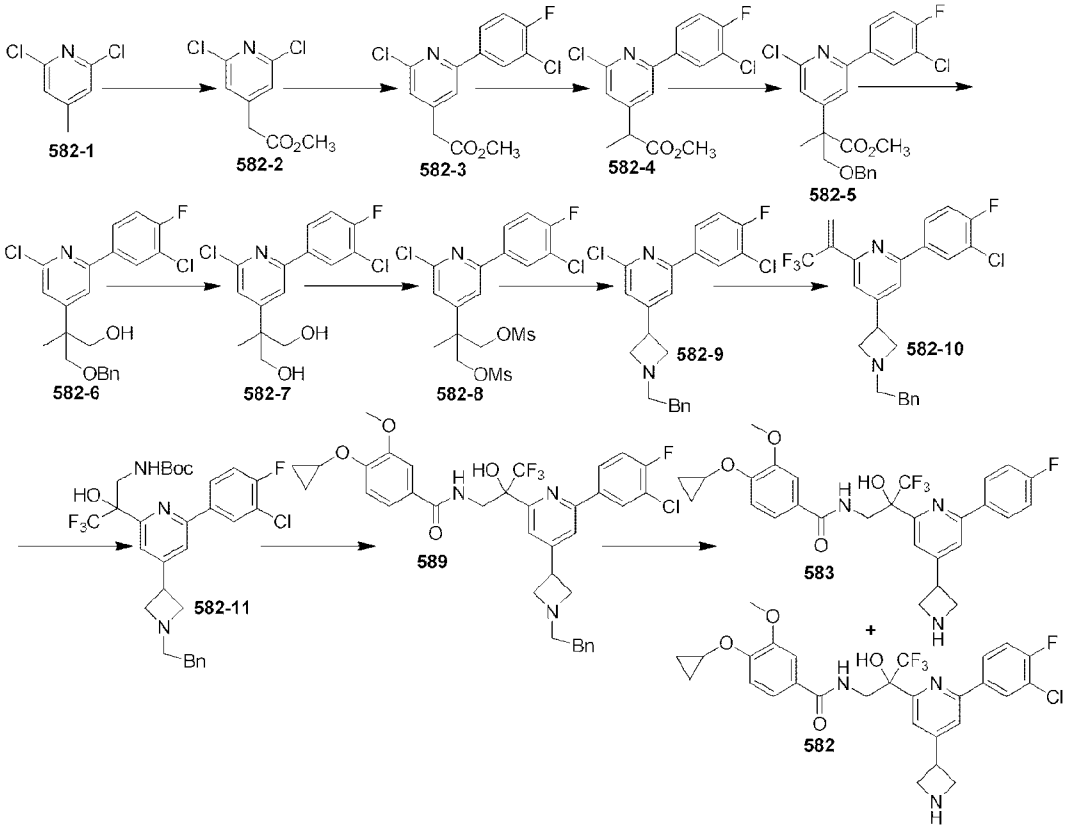
[1356] To a stirring mixture of benzyl (2-(2-chloro-6-(3-(4-cyclopropoxy-3-methoxybenzamido)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-3-methoxypyridin-4-yl)propan-2-yl)carbamate (30 mg, 0.046 mmol) in DME (2 mL, deoxygenated prior to using) were added 4-fluorophenyl boronic acid (8 mg, 0.055 mmol), a solution of Cs_2CO_3 (45 mg, 0.14 mmol in 0.3 mL of water) and $PdCl_2$(dppf) (5 mg, 0.007 mmol). The mixture was stirred at 110 °C under microwave reaction conditions for 1 h. The crude product mixture was diluted with EtOAc and water. An aqueous workup with EtOAc was followed. The crude product mixture was purified via a silica gel chromatography to afford the product and unreacted starting material (25 mg). LCMS: m/z 712.20 $[M+H]^+$.

[1357] To a stirring solution of N-Cbz protected amine and unreacted starting material from the previous step (25 mg) in EtOAc:i-PrOH:HOAc (5 mL:1 mL:1 mL) was

added Pd/C (20 mg). The mixture was placed under a H_2 balloon. The mixture was stirred for several hours until the starting material was consumed. The crude mixture was filtered through a plug of celite, and the plug was washed with EtOAc (2 x 20 mL). The mixture was concentrated under reduced pressure. The crude product mixture was purified via HPLC to afford **594** as a white solid. LCMS: m/z 578.15 $[M+H]^+$.

EXAMPLE 383

Preparation of Compounds 582, 583 and 589



[1358] To a stirred solution of **582-1** (50 g, 310 mmol) in anhydrous THF (1.2 L) was added LDA (310 mL, 620 mmol) at -78 °C under N_2. The mixture was stirred at -78 °C for 0.5 h. A solution of dimethyl carbonate (67.1 g, 750 mmol) in dry THF (150 mL) was added dropwise. The solution was warmed to 0 °C and stirred for 1 h below 0 °C. The reaction was quenched with aq. NH_4Cl (500 mL), extracted with EA (3 x 1 L). The combined organic phase was washed with a. sodium bicarbonate (1 L) and brine, and dried over sodium sulfate. The organic layer was concentrated to dryness, and the residue was

purified by column chromatography (PE:EA = 20:1) to give **582-2** (50 g, 73.5 %) as a colorless oil.

[1359] To a solution of crude **582-2** (50 g, 230 mmol) in dioxane:H_2O (6:1) (1 L) was added 4-fluoro-3-chloro-phenyl boronic acid (40 g, 230 mmol), Cs_2CO_3 (223.3 g, 680 mmol) and $Pd(dppf)Cl_2$ (16.8 g, 23 mmol) under N_2. The mixture was degassed (3x) and refilled with N_2. The mixture was stirred at 80 °C in a pre-heated oil bath for 4 h. After cooling to r.t., the mixture was diluted with water (1.5 L) and extracted with EA (3 x 1 L). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuum to dryness. The residue was purified by column chromatography (PE:EA=20:1~15:1) to yield **582-3** (42 g, 58.7%) as a light yellow solid.

[1360] To a solution of **582-3** (10 g, 31.9 mmol) in anhydrous THF (100 mL) was added LiHMDS (63.9 mL, 63.9 mmol) dropwise at -78 °C. The mixture was stirred at -78 °C for 30 mins. A solution of MeI (9.07 g, 63.9 mmol) in dry THF (50 mL) was added dropwise. The mixture was warmed to 0 °C and stirred at 0 °C for 1 h. The reaction was quenched with water (100 mL) and extracted with EA (3 x 150 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuum to dryness. The residue was purified by column chromatography (PE:EA=10:1) to yield **582-4** (3.5 g, 32%) as a light yellow solid.

[1361] To a solution of **582-4** (3.2 g, 10.22 mmol) in anhydrous THF (20 mL) was added NaHMDS (20.44 mL, 20.44 mmol) dropwise at -78 °C. The mixture was stirred at -78 °C for 30 mins. A solution of $BnOCH_2Cl$ (3.19 g, 20.44 mmol) in dry THF (10 mL) was added dropwise. The mixture was warmed to 0 °C and stirred for 1 h. The reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuum to dryness. The residue was purified by column chromatography (PE:EA=10:1) to yield **582-5** (2.7 g, 59%) as a yellow oil.

[1362] To a stirred solution of **582-5** (16.22 g, 36.29 mmol) in anhydrous THF (150 mL) was added $LiAlH_4$ (1.38 g, 36.29 mmol) powder in portions under N_2 at 0 °C for a period of 10~15 mins. The mixture was stirred at 0 °C for 0.5 h. The reaction was quenched with water (100 mL) and filtered via a plug of celite. The filtrate was extracted with EA (3 x

100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuum to dryness. The residue was purified by column chromatography (PE:EA=3:1) to give **582-6** (13.5 g, 89 %) as a yellow oil.

[1363] To a stirred solution of **582-6** (5 g, 11.93 mmol) in anhydrous DCM (50 mL) was added $FeCl_3$ (19.4 g, 119.3 mmol) powder in one portion at r.t. The mixture was stirred at r.t. for 1 h. The mixture was diluted with water (100 mL) and filtered via a bed of celite bed. The filtrate was extracted with EA (2 x 150 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuum to dryness. The residue was purified by column chromatography (PE:EA=1:1) to give **582-7** (3.6 g, 92 %) as a brown oil.

[1364] To a stirred solution of **582-7** (3.5 g, 10.6 mmol) in anhydrous DCM (20 mL) was added TEA (5.4 g, 53 mmol) at r.t. MsCl (4.8 g, 42.4 mmol) was added dropwise, and the mixture was stirred at r.t. for 1 h. The solution was washed with water (20 mL) and brine (20 mL), and then concentrated to dryness. The residue was purified by column chromatography (PE:EA=5:1) to give **582-8** (3.6 g, 69%) as a yellow oil.

[1365] **582-8** (480 mg, 0.987 mmol) was dissolved in benzyl amine (3 mL). The mixture was heated under microwave irradiation at 135 ^{o}C for 5 h. The crude mixture was cooled to r.t. and directly loaded into a silica gel column to afford a mixture of products. This mixture was further purified via prep-HPLC to afford **582-9** (100 mg, 25% yield) as a colorless oil: LCMS: m/z 401.05 $[M+H]^+$.

[1366] To a stirring mixture of **582-9** (100 mg, 0.249 mmol) in DME (2 mL, deoxygenated prior to using) were added 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (111 mg, 0.498 mmol), a solution of Cs_2CO_3 (243 mg, 0.75 mmol in 0.5 mL of water) and $PdCl_2$(dppf) (36 mg, 0.005 mmol). The mixture was stirred at 110 ^{o}C for 2 h under microwave reaction conditions. The crude product mixture was diluted with EtOAc and water. An aqueous workup with EtOAc was followed. The crude product mixture was purified via a silica gel chromatography to afford **582-10** (114 mg, quantitative yield). LCMS: m/z 461.05 $[M+H]^+$.

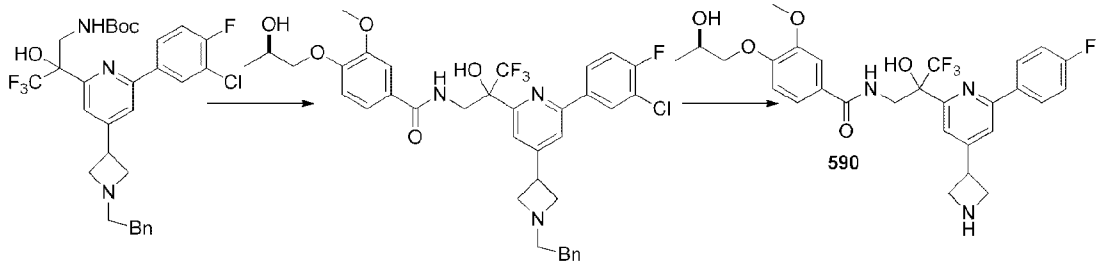
[1367] To a stirring mixture of **582-10** (26 mg, 0.056 mmol) in t-BuOH:water (3:1, 1.3 mL total volume) at r.t. were added potassium osmate dihydrate (3 mg, 0.008 mmol)

and tert-butyl tosyloxycarbamate (32 mg, 0.112 mmol). The mixture was stirred at r.t. overnight. The mixture was diluted with water and diluted with DCM. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product mixture was purified via a silica gel chromatography to afford **582-11** (15 mg, 45%). LCMS: m/z 594.2 $[M+H]^+$.

[1368] The N-Boc protected amine was dissolved in HCl in dioxane (3 mL, 4N). The mixture was stirred at r.t. for several hours until the starting material was consumed. The crude product was concentrated under reduced pressure and directly used in the next step without further purification. Coupling of the crude amine with 4-cyclopropoxy-3-methoxybenzoic acid following the general procedure for **598** afforded **589** as a white solid. LCMS: m/z 684.20 $[M+H]^+$.

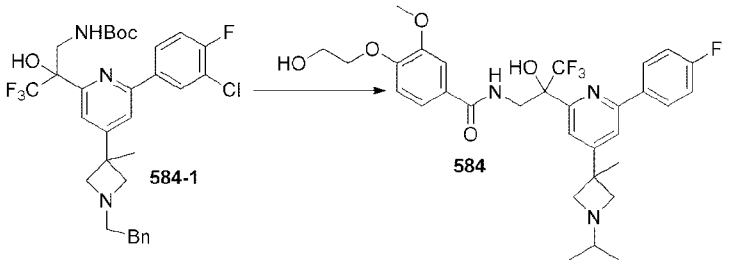
[1369] To a stirring solution of **589** (38 mg, 0.064 mmol) in EtOAc:iPrOH:HOAc (5 mL:1 mL:1mL) was added a 10% Pd/C (40 mg). The mixture was placed under a H_2 balloon. The mixture was stirred for several hours until the starting material was consumed. The crude mixture was filtered through a plug of celite, and the plug was washed with EtOAc (2 x 20 mL). The mixture was concentrated under reduced pressure and purified via prep-HPLC to afford **583** and **582**. **583**: LCMS: m/z 560.15 $[M+H]^+$ and **582**: LCMS: m/z 594.15 $[M+H]^+$.

EXAMPLE 384
Preparation of Compound 590



[1370] Compound **590** was prepared following the general procedure for **583** using (R)-4-(2-hydroxypropoxy)-3-methoxybenzoic acid and HATU. LCMS: m/z 578.15 $[M+H]^+$.

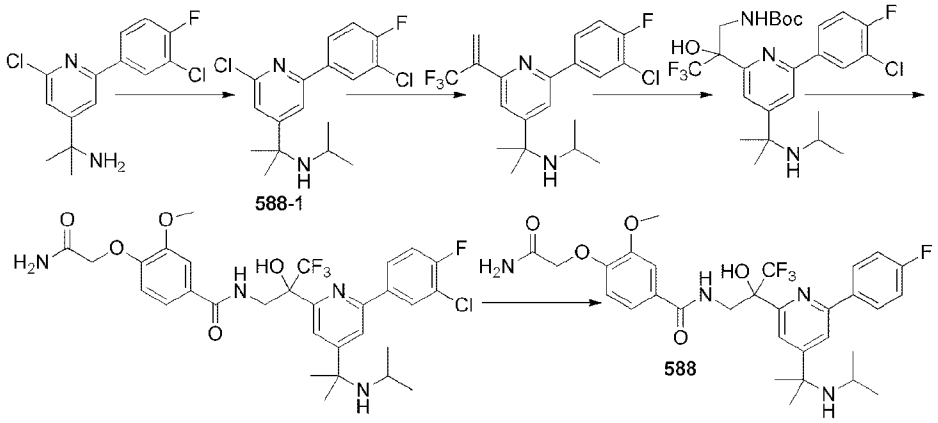
EXAMPLE 385
Preparation of Compound 584



[1371] **584-1** was prepared following the general procedure for **583** using 3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzoic acid and HATU.

[1372] To a stirring mixture of **584-1** in DCM (1 mL) was added TFA (0.2 mL). The mixture was stirred at r.t. for 5 mins, and then diluted with DCM. The reaction quenched with a cold $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product mixture was purified via prep-HPLC to afford **584** as a white solid. LCMS: m/z 606.25 $[M+H]^+$.

EXAMPLE 386
Preparation of Compound 588

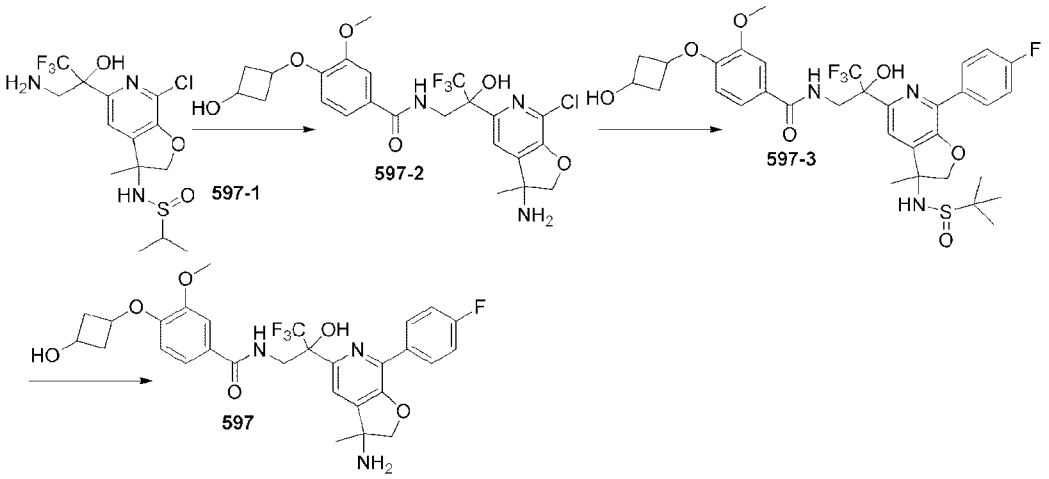


[1373] To a stirring mixture of 2-(2-chloro-6-(3-chloro-4-fluorophenyl)pyridin-4-yl)propan-2-amine (200 mg, 0.67 mmol) in DCE (1 mL) at r.t. were added acetone (78 mg, 1.33 mmol), HOAc (10 mg) and $Na(OAc)_3BH$ (280 mg). The mixture was stirred at r.t. overnight. The mixture was diluted with DCM, and the reaction quenched with a cold $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried with Na_2SO_4, filtered

and concentrated under reduced pressure. The crude product mixture was purified via a silica gel column to afford **588-1** (180 mg, 79%) as a colorless oil. LCMS: m/z 341.0 $[M+H]^+$.

[1374] Compound **588** was prepared following the general procedure for **582** and **583**. LCMS: m/z 607.2 $[M+H]^+$.

EXAMPLE 387
Preparation of Compound 597

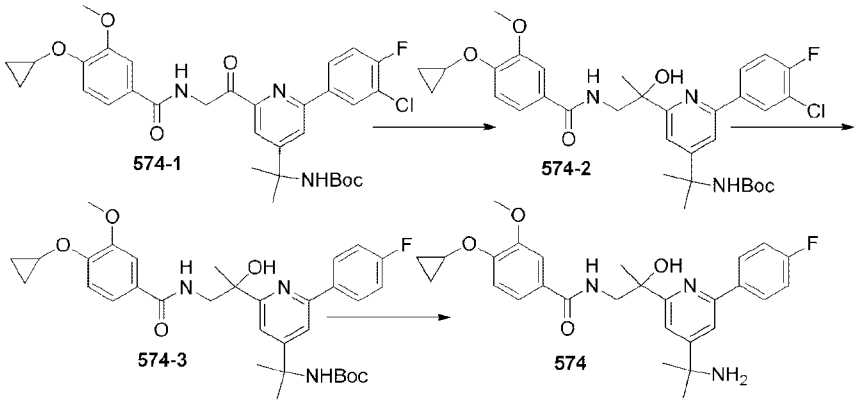


[1375] To a stirring mixture of 4-(3-hydroxycyclobutoxy)-3-methoxybenzoic acid (70 mg, 0.168 mmol) in DMF (1 mL) were added HATU (64 mg, 0.168 mmol) and DIPEA (60 μL, 0.336 mmol). The mixture was stirred at r.t. for 5 mins. A solution of **597-1** in DMF (0.5 mL) was added, and the mixture was stirred at r.t. for 10 mins. The reaction was quenched with a 10% aq. solution of $NaHCO_3$ (1 mL). The mixture was diluted with DCM, and an aqueous work up with DCM was followed. The crude product was purified via prep-HPLC to afford **597-2** (80 mg, 75%) as a white solid. LCMS: m/z 636.15 $[M+H]^+$.

[1376] To a stirring mixture of **597-2** (40 mg, 0.063 mmol) in DME:EtOH:H_2O (1.5 mL:0.5 mL:0.2 mL, deoxygenated prior to using) were added 4-fluorophenylboronic acid (9 mg, 0.063 mmol), K_3PO_4. $7H_2O$ (64 mg, 0.19 mmol), KH_2PO_4 (25 mg, 0.16 mmol) and $PdCl_2$(dppf) (7.5 mg, 0.01 mmol). The mixture was carried out under microwave irradiation at 110 °C for 5 h. The crude product mixture was diluted with EtOAc and water. An aqueous workup with EtOAc was followed. The crude product mixture was purified via a silica gel chromatography to afford **597-3**. LCMS: m/z 696.20 $[M+H]^+$.

[1377] To a stirring mixture of **597-3** in MeOH (5 mL) at r.t. was added a solution of HCl in dioxane (4N, 1 mL). The mixture was stirred for 10 mins, and then concentrated under reduced pressure. The crude product was purified via HPLC to afford **597** (30 mg, 70%) as a white solid. LCMS: m/z 592.1 $[M+H]^+$.

EXAMPLE 388
Preparation of Compound 574

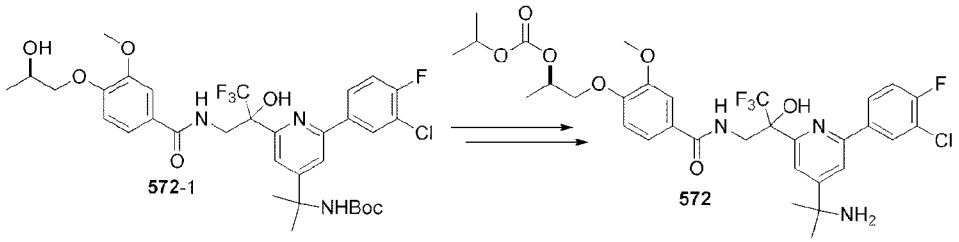


[1378] To a stirring mixture of **574-1** (130 mg, 0.21 mmol) in THF (2 mL) at r.t. was added dropwise a solution of MeMgBr in toluene (0.91 mL, 1.27 mmol). The mixture was stirred at r.t. for 2 h, and then diluted with EtOAc. The reaction quenched with a sat. NH_4Cl solution. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel chromatography to afford a mixture that included **574-2**. LCMS: m/z 628.20 $[M+H]^+$.

[1379] **574-2** (40 mg) was hydrogenated over 10% Pd/C (35 mg) in EtOAc:EtOH (5 mL each) for 2 h. The catalyst was removed by filtration, and the crude product was used in the next step without further purification. LCMS: m/z 594.25 $[M+H]^+$.

[1380] To HCl in dioxane (5 mL, 4N) was added **574-3** (20 mg), and the mixture was stirred at r.t. for 3 h. The mixture was concentrated, and the crude product was purified by prep-HPLC to provide **574**. LCMS: m/z 494.20 $[M+H]^+$.

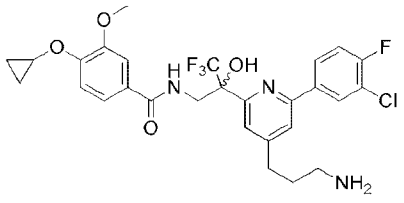
EXAMPLE 389
Preparation of Compound 572



[1381] To a stirring mixture of **572-1** (25 mg, 0.0357 mmol) in pyridine (1 mL) was added a solution of isopropylchloroformate (110 μL, 0.101 mmol) in toluene. The mixture was stirred at r.t. for 2 h. The mixture was diluted with DCM, and the reaction quenched with a sat. $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel chromatography to afford **572-2** as a colorless oil. LCMS: m/z 786.25 $[M+H]^+$.

[1382] To a stirring mixture of **572-2** (22 mg, 0.032 mmol) in AcCN (1 mL) at 0 °C were added NaI (24 mg, 0.15 mmol) and TMSCl (25 μL, 0.15 mmol). The mixture was stirred for an 10 mins, and then warmed to r.t. The mixture was diluted with EtOAc and washed with a 10% aq. $Na_2S_2O_3$ solution. The organic layer were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The mixture was concentrated, and the crude product purified by prep-HPLC to provide **572**. LCMS: m/z 686.2 $[M+H]^+$.

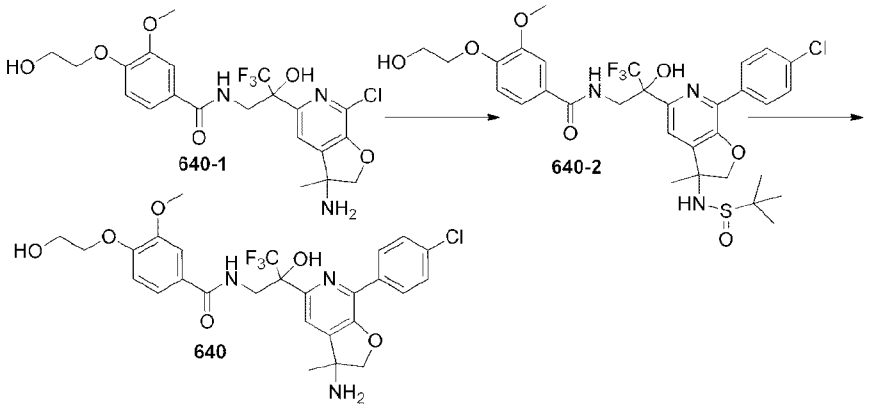
EXAMPLE 390
Preparation of Compound 591



[1383] To a stirring mixture of **544** (50 mg, 0.075 mmol) in HOAc:EtOAc (6 mL, 5:1) was added Pd/C (30 mg). The mixture was placed under a H_2 balloon for several hours. The mixture was filtered through a plug of Celite, and the plug was washed several times

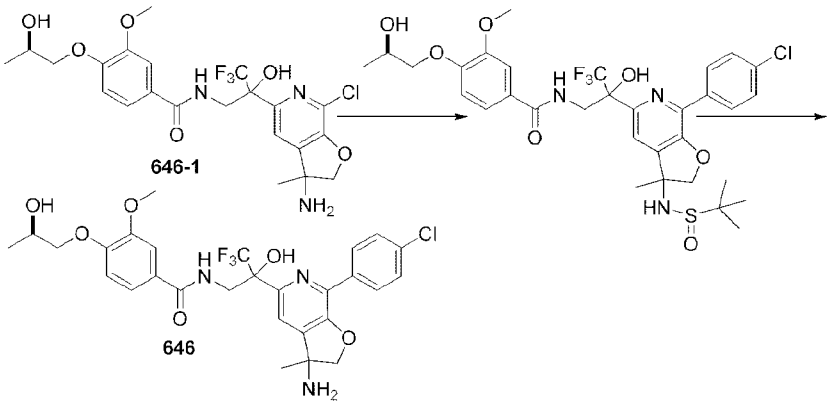
with EtOAc. The fitrate was concentrated under reduced pressure and purified via prep-HPLC to afford **544**. LCMS: m/z 582.10 $[M+H]^+$.

EXAMPLE 391
Preparation of Compound 640



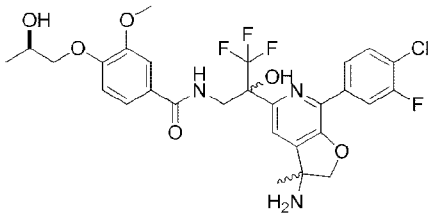
[1384] Suzuki coupling of **640-1** (50 mg) with 4-chlorophenylboronic acid followed by sulfinamide hydrolysis afforded **640** (20 mg) as a white solid. LCMS: m/z 582.15 $[M+H]^+$.

EXAMPLE 392
Preparation of Compound 646



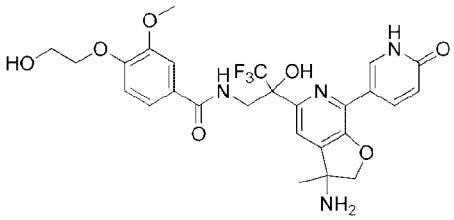
[1385] Compound **646** (white solid, 11.6 mg) was prepared following the general procedure for **640** using **646-1** (25 mg). LCMS: m/z 596.10 $[M+H]^+$.

EXAMPLE 393
Preparation of Compound 666



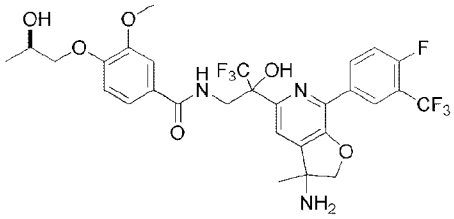
[1386] Compound **666** (white solid, 6.7 mg) was prepared following the general procedure for **640** using **646-1** (20 mg) and 4-chloro-3-fluorophenyl boronic acid. LCMS: m/z 614.15 $[M+H]^+$.

EXAMPLE 394
Preparation of Compound 649



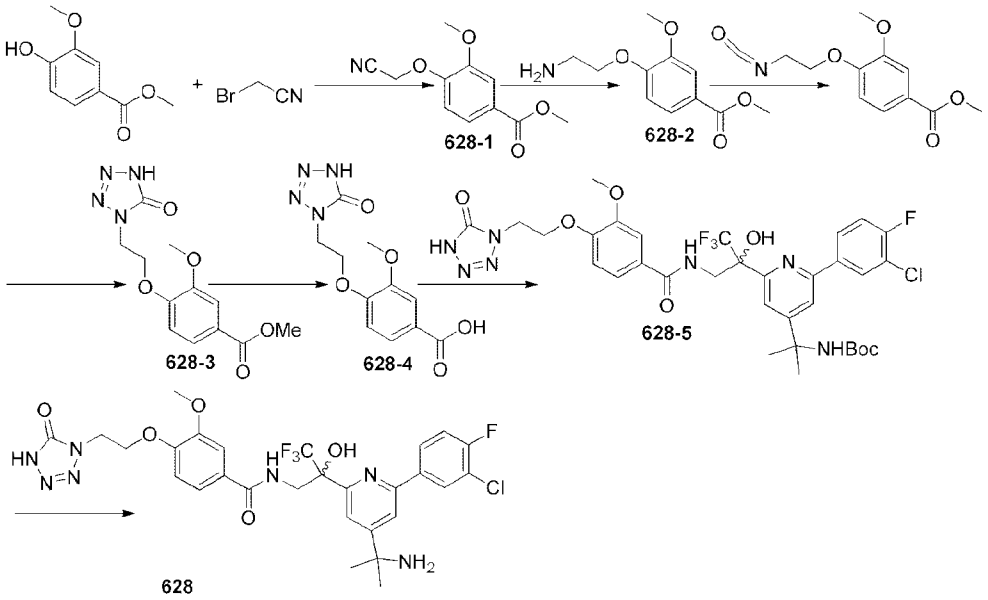
[1387] Compound **649** (white solid, 19.6 mg) was prepared following the general procedure for **640** using **640-1** (40 mg) and (6-oxo-1,6-dihydropyridin-3-yl)boronic acid. LCMS: m/z 565.15 $[M+H]^+$.

EXAMPLE 395
Preparation of Compound 665



[1388] Compound **649** (white solid, 9.2 mg) was prepared following the general procedure for **640** using **646-1** (35 mg) and (4-fluoro-3-(trifluoromethyl)phenyl)boronic acid. LCMS: m/z 648.15 $[M+H]^+$.

EXAMPLE 396
Preparation of Compound 628



[1389] To a stirring mixture of methyl-4-methoxybenzoate (1 g, 5.49 mmol) in DMF (5 mL) at r.t. was added K_2CO_3 (1.14 g, 8.24 mmol) and 2-bromoacetonitrile (653 mg, 5.49 mmol). The mixture was stirred at r.t. for 3 h, and then diluted with EtOAc and water. The aqueous layer was extracted with EtOAc. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel chromatography to afford **628-1** as a white solid.

[1390] To a stirring mixture of **628-1** (600 mg, 2.72 mmol) in THF (6 mL) was added dropwise a solution of borane and DMS complex in THF (0.26 mL, 2.72 mmol) at r.t. The mixture was slowly warmed to 60 °C for 1 h. The mixture was cooled to r.t. and diluted with EtOAc. The reaction was quenched with an aq. solution of HCl (1N). The mixture was stirred at r.t. for 10 mins and then neutralized with a sat. $NaHCO_3$ solution. The layers were separated, and the aquoues layer was extracted with EtOAc. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel chromatography to afford **628-2** as a white solid. LCMS: m/z 226.1 $[M+H]^+$.

[1391] To a stirring mixture of **628-2** (40 mg, 0.177 mmol) in DCM (0.6 mL) at 0 °C were added diphosgene (32 mg, 0.177 mmol) and DIPEA (42 μL, 0.27 mmol). The

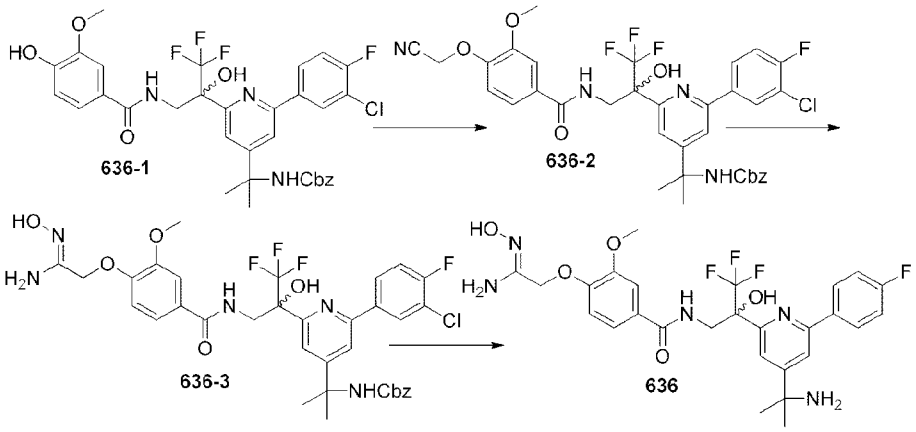
mixture was warmed to r.t. for 20 mins and then concentrated under reduced pressure. The crude product was dissolved in toluene (0.5 mL), and azidotrimethylsilane (0.14 mL) and 1 drop of BF_3. OEt_2 were added. The mixture was heated at reflux for 1 h. The crude mixture was cooled to r.t. and diluted with DCM. The reaction was quenched with water, and extracted with DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel chromatography to afford **628-3** as a white solid (18 mg, 36% in 2 steps).

[1392] **628-3** was dissolved in a solution of HCl in dioxane (1 mL). An aqueous solution of HCl (6N, 1 mL) was added, and the mixture was heated at 80 °C overnight. The mixture was cooled to r.t. and diluted with EtOAc. The aqueous layer was extracted with EtOAc. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via prep-HPLC to afford **628-4** as a white solid. LCMS: m/z 302.85 $[M+Na]^+$.

[1393] To a stirring mixture of tert-butyl (2-(2-(3-amino-1,1,1-trifluoro-2-hydroxypropan-2-yl)-6-(3-chloro-4-fluorophenyl)pyridin-4-yl)propan-2-yl)carbamate (8 mg, 0.0163 mmol) and **628-4** (from the previous step) in DCM (0.3 mL) were added EDCI (6.2 mg, 0.032 mmol), HOAt (4.5 mg, 0.033 mmol) and TEA (20 μL). The mixture was stirred for 5 mins, and the reaction was quenched with 2 drops of a solution of HCl (1N). The organic layer was transferred to a different flask and concentrated under reduced pressure. The crude product was purified via prep-HPLC to afford the desired product as a white solid; LCMS: m/z 754.20 $[M+H]^+$.

[1394] **628-5** was dissolved in a solution of HCl in dioxane (5 mL, 4N). The mixture was stirred at r.t. until the starting material was consumed. The crude mixture was concentrated under reduced pressure and purified via prep-HPLC to afford **628** as a white solid (8.5 mg). LCMS: m/z 654.1 $[M+H]^+$.

EXAMPLE 397
Preparation of Compound 636

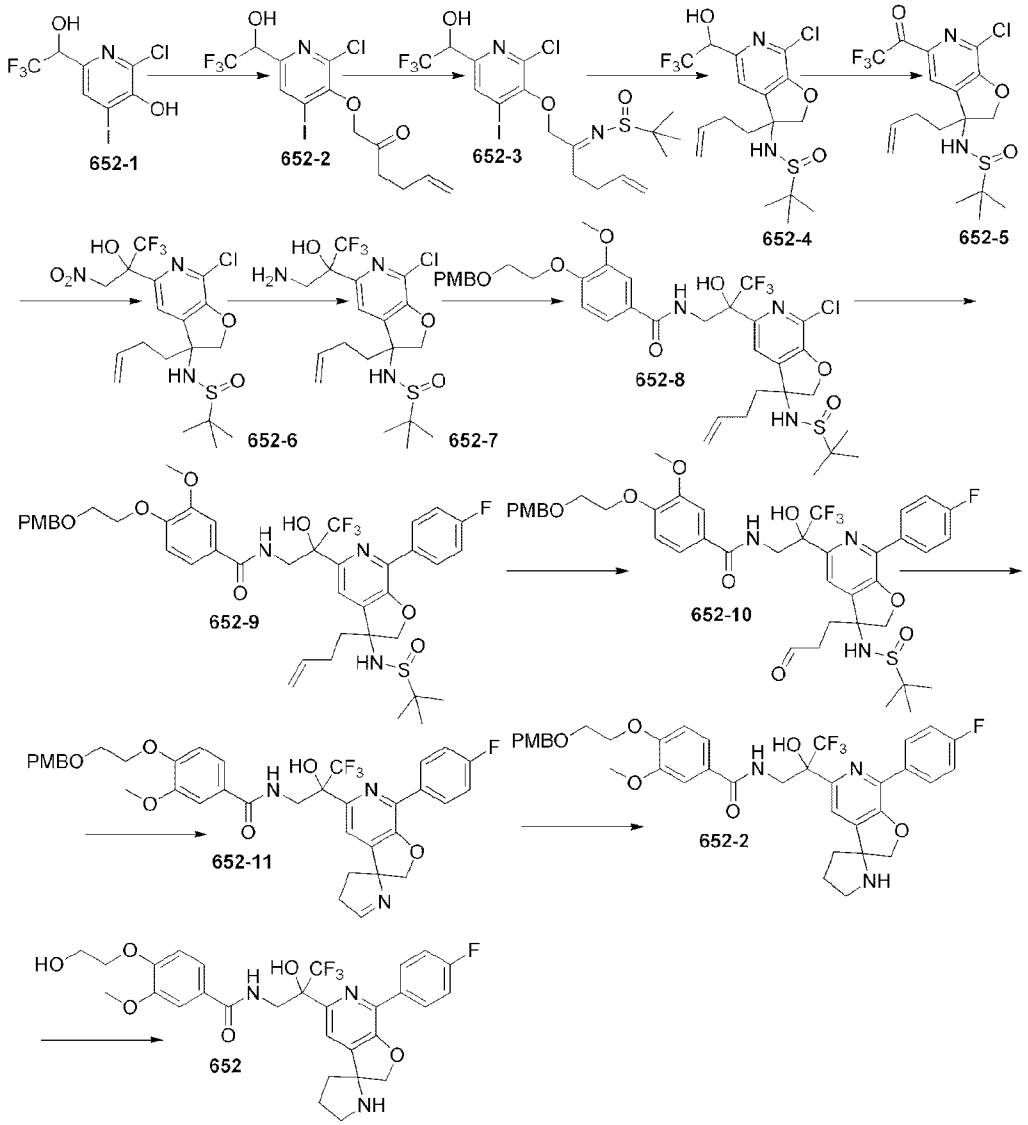


[1395] To a stirring mixture of **636-1** (130 mg, 0.192 mmol) in DMF (1 mL) were added added K_2CO_3 (80 mg, 0.576 mmol) and 2-bromoacetonitrile (46 mg, 0.38 mmol). The mixture was stirred at r.t. until the starting material was consumed. The mixture was diluted with EtOAc and washed with brine. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel column to afford **636-2** as a colorless oil (40 mg). LCMS: m/z 715.15 $[M+H]^+$.

[1396] To a stirring mixture of **636-2** (20 mg, 0.028 mmol) in pyridine (0.3 mL) was added NH_2OH•HCl (10 mg). The mixture was stirred at reflux for several hours. The mixture was cooled to r.t., diluted with toluene and concentrated under reduced pressure. This process was repeated twice. The crude product was purified via a silica gel column to afford **636-3** as a colorless oil (10 mg).

[1397] To a stirring mixture of **636-3** (10 mg, 0.013 mmol) in EtOAc:HOAc:EtOH (5:1:1, 7 mL) was added Pd/C (20 mg). The mixture was placed under a H_2 balloon for several hours. The mixture was filtered through a plug of Celite, and the plug was washed several times with EtOAc. The fitrate was concentrated under reduced pressure and purified via prep-HPLC to afford **636** (4.0 mg) as a white solid. LCMS: m/z 580.15 $[M+H]^+$.

EXAMPLE 398
Preparation of Compound 652



[1398] To a stirring mixture of **652-1** (750 mg, 2.12 mmol) were added 1-chlorohex-5-en-2-one (390 mg, 2.33 mmol) and potassium carbonate (410 mg, 2.97 mmol) in acetone (4.0 mL). The mixture was stirred at 50 °C for 2 h. The volatiles were removed under reduced pressure, and the residue was partitioned between water and EtOAc. The layers were separated, and the organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel column to afford **652-2** as a white solid (480 mg, 50%). LCMS: m/z 449.90 $[M+H]^+$.

[1399] A mixture of **652-2** (420 mg, 1.18 mmol), 2-methylpropane-2-sulfinamide (157 mg, 1.31 mmol) and titanium(IV) ethoxide (770 μL, 2.6 mmol) in THF (7 mL) was heated to 70 °C (sealed vial, degassed and purged with N_2). The mixture was stirred 70 °C for 3 h. The mixture was diluted with EtOAc and water was added. The mixture was stirred for 5 mins and then filtered through a pad of celite. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. Crude **652-3** was used in the next step without further purification. LCMS: m/z 552.95 $[M+H]^+$.

[1400] *n*-Buthyllithium (2.5 M solution in hexane, 0.64 mL, 1.6 mmol) was added to a solution of ethylmagnesium bromide (3.42 M in 2-Me THF, 0.24 mL, 0.8 mmol) in THF (2.5 mL), which had been pre-cooled to 0°C. After 10 mins, the mixture was cooled to -78 °C. A solution of **652-3** (460 mg, 0.83 mmol) in THF (1 mL) was added dropwise, and the mixture was stirred at -78 °C for 15 mins. The reaction was quenched with MeOH and diluted with EtOAc. The organic layer was washed with brine, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography of the residue afforded **652-4** as a brownish oil. LCMS: m/z 427.05 $[M+H]^+$.

[1401] To a stirring mixture of **652-4** (180 mg, 0.42 mmol) in DCM (2 mL) was added Dess-Martin reagent (537 mg, 1.26 mmol). The mixture was stirred at r.t. until the starting material was consumed. The mixture was diluted with EtOAc. The reaction quenched with 5% of $NaHSO_3$ and a sat. $NaHCO_3$ solution. The layers were seperated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel column to afford **652-5** as a white solid. LCMS: m/z 443.1 $[M+H+H_2O]^+$.

[1402] To a stirring mixture of **652-5** (135 mg, 0.305 mmol) in nitromethane (0.5 mL) at r.t. was added TEA (63 μL, 0.46 mmol). The mixture was stirred at r.t. for 30 mins and then diluted with DCM. The reaction was quenched with a sat. $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The crude product was purified via a silica gel column to afford **652-6** as a white solid (140 mg, 94%). LCMS: m/z 486.05 $[M+H]^+$.

[1403] To a stirring mixture of **652-6** (50 mg, 0.1 mmol) in EtOH:water (10:1, 1.1 mL) was added Fe (28 mg, 0.5 mmol) and NH_4Cl (27 mg, 0.5 mmol). The mixture was heated at 80 °C for 30 mins and thens cooled to r.t. The mixture was diluted with DCM (5 mL), and the reaction was quenched with a solution of NaOH (2N, 1 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel column to afford **652-7** as a white solid. LCMS: m/z 456.1 $[M+H]^+$.

[1404] To a stirring mixture of 3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzoic acid (14.5 mg, 0.044 mmol) in DMF (0.2 mL) were added HATU (17 mg, 0.044 mmol) and DIPEA (17 μL, 0.088 mmol). The mixture was stirred at r.t. for 5 mins. A solution of **652-7** (20 mg, 0.044 mmol) in DMF (0.1 mL) was added, and the mixture was stirred at for 10 mins. The reaction was quenched with a 10% aq. solution of $NaHCO_3$ (1 mL). The mixture was diluted with DCM, and an aqueous work up with DCM was followed. The crude product was purified via prep-HPLC to afford **652-8** (6.5 mg, 19%) as a white solid. LCMS: m/z 770.25 $[M+H]^+$.

[1405] To a stirring mixture of **652-8** (6.5 mg, 0.008 mmol) in DME:EtOH:H_2O (1.0 mL:0.3 mL:0.1 mL, deoxygenated prior to using) were added 4-fluorophenylboronic acid (9 mg, 0.063 mmol), $K_3PO_4 \cdot 7H_2O$ (14.3 mg, 0.04 mmol), KH_2PO_4 (5.5 mg, 0.04 mmol) and $PdCl_2$(dppf) (6.0 mg, 0.008 mmol). The mixture was carried out under microwave irradiation at 110 °C for 5 h. The crude product was concentrated under reduced pressure and purified via a silica gel chromatography to afford **652-9**. LCMS: m/z 830.2 $[M+H]^+$.

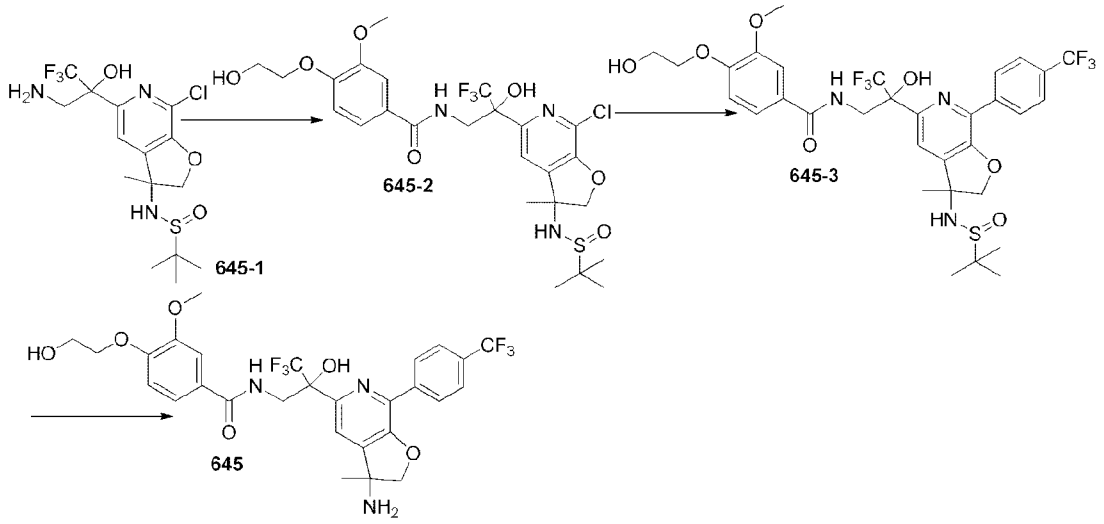
[1406] To a stirring mixture of **652-9** in t-BuOH:H_2O (3:1, 0.4 mL) were added $K_2OsO_4 \cdot 2H_20$ (1 mg). The mixture was stirred for 2 h and $NaIO_4$ (5 mg) was added. The mixture was stirred at r.t. overnight. The mixture was loaded directly into a silica gel column to afford **652-10**. LCMS: m/z 832.3 $[M+H]^+$.

[1407] To a stirring mixtue of **652-10** in MeOH (1.0 mL) was added a solution of HCl in dioxane (0.2 mL). The mixture was stirred for 10 mins at r.t. and concentrated under reduced pressure. Crude **652-11** was used in the next step without further purification.

[1408] **652-11** was dissolved in MeOH (0.5 mL) was added $NaBH_4$ (1.6 mg). The mixture was stirred at r.t. for 10 mins and then diluted with EtOAc. The reaction was quenched with a sat. $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude **652-12** was used in the next step without further purification.

[1409] To a stirring mixture of **652-12** in DCM (1.0 mL) was added TFA (0.1 mL). The mixture was stirred at r.t. until the starting material was consumed. The mixture was diluted with DCM, and the reaction was quenched with a cold sat. $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with EtOAc. The The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via prep-HPLC to afford **652** as a white solid (1.0 mg). LCMS: m/z 592.20 $[M+H]^+$.

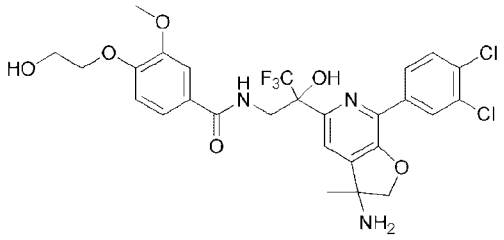
EXAMPLE 399
Preparation of Compound 645



[1410] **645-2** was prepared following the general procedure for **635-2**. LCMS: m/z 610.10 $[M+H]^+$. **645-3** was prepared following the general procedure for **635-3**. LCMS:

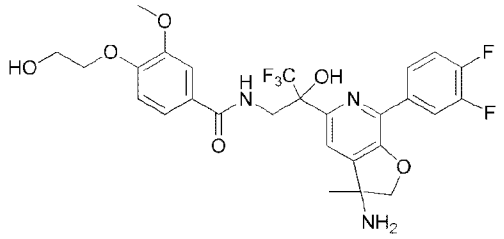
m/z 720.20 $[M+H]^+$. Compound **645** (15.7 mg) was prepared following the general procedure for **635** using **645-3** (45 mg, 0.063 mmol). LCMS: m/z 616.15 $[M+H]^+$.

EXAMPLE 400
Preparation of Compound 662



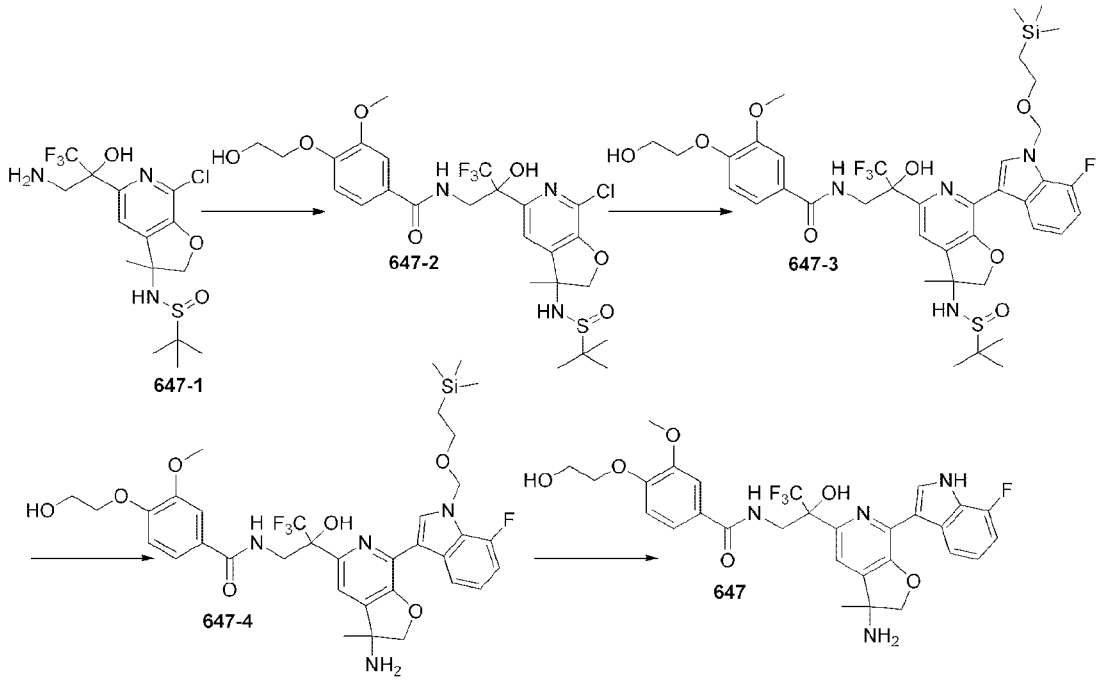
[1411] Compound **662** (5.7 mg) was prepared following the general procedure for **645**. LCMS: m/z 616.10 $[M+H]^+$.

EXAMPLE 401
Preparation of Compound 663



[1412] Compound **663** (11.4 mg) was prepared following the general procedure for **645**. LCMS: m/z 584.15 $[M+H]^+$.

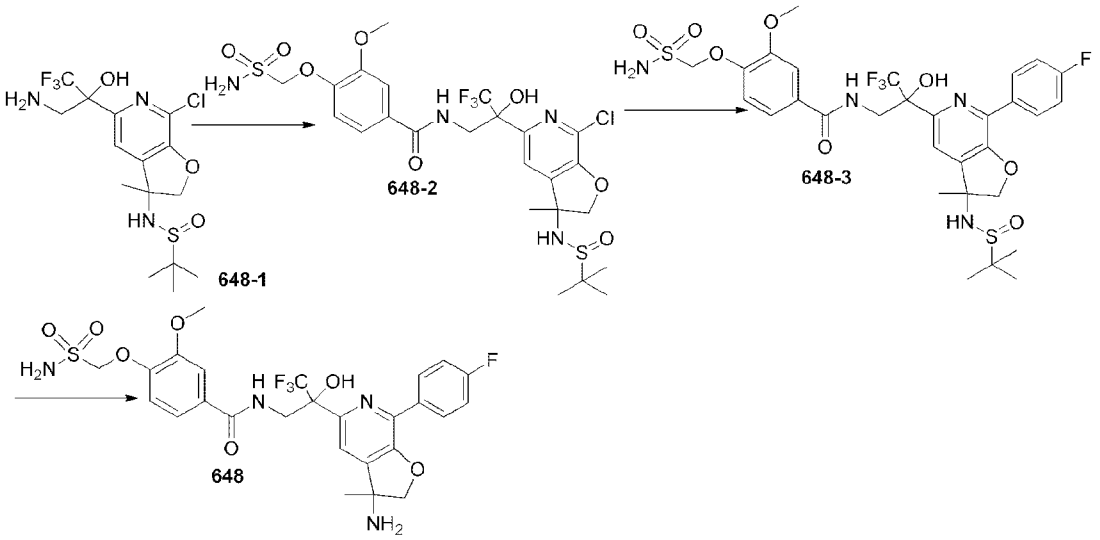
EXAMPLE 402
Preparation of Compound 647



[1413] **647-3** was prepared following the general procedure for **635-3**. LCMS: m/z 839.25 $[M+H]^+$. **647-4** was prepared following the general procedure for **635**. **647-4** (51 mg, 0.084 mmol) was treated with TBAF (1M in THF, 0.1 mL, 0.1 mol) in THF (2 mL) at 70 °C for 2 h. The mixture was concentrated, and the crude product purified by silica gel chromatography (CH_2Cl_2:MeOH:NH_3) to provide **647** (10 mg, 19%). LCMS: m/z 605.15 $[M+H]^+$.

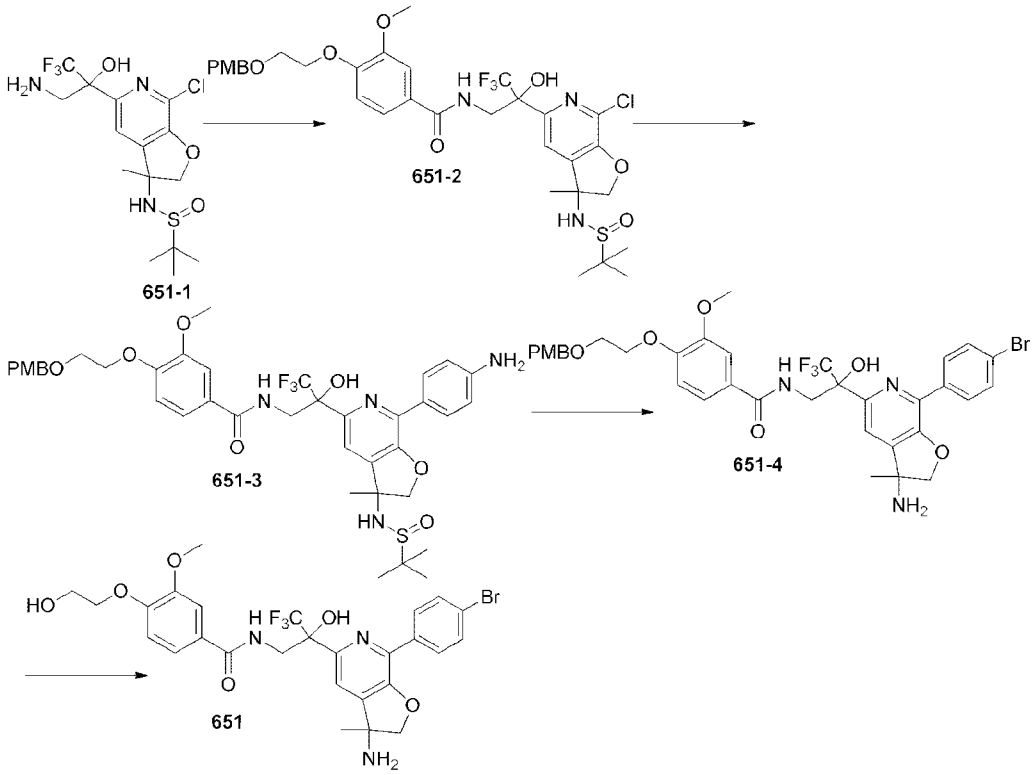
EXAMPLE 403

Preparation of Compound 648



[1414] **648-2** was prepared following the general procedure for **637-4**. LCMS: m/z 629.05 $[M+H]^+$. **648-3** was prepared following the general procedure for **635-3**. LCMS: m/z 719.15 $[M+H]^+$. Compound **648** (13.5 mg) was prepared following the general procedure for **635** using **648-3** (27 mg, 0.038 mmol). LCMS: m/z 615.15 $[M+H]^+$.

EXAMPLE 404
Preparation of Compound 651

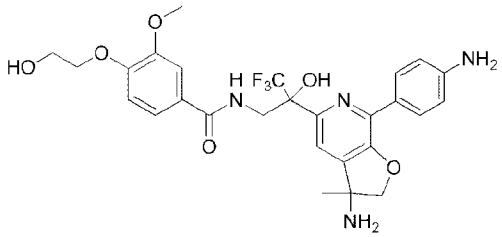


[1415] **651-2** was prepared following the general procedure for **637-2**. LCMS: m/z 730.20 $[M+H]^+$. **651-3** was prepared following the general procedure for **637-3**. LCMS: m/z 787.30 $[M+H]^+$.

[1416] A solution of **651-3** (15 mg, 0.019 mmol) in CH_3CN (0.5 mL) was added dropwise to a solution of isopentyl nitrite (4 uL, 0.029 mmol) and copper bromide (3 mg, 0.023 mmol) in CH_3CN (1 mL) at 65 °C. The mixture was stirred at 65 °C for 1 h and then cooled to 0 °C. The reaction was quenched with the addition of 1N HCl. The aqueous layer was basified with sodium bicarbonate and extracted with EA. The product was used without further purification to provide **651-4**. LCMS: m/z 748.15 $[M+H]^+$.

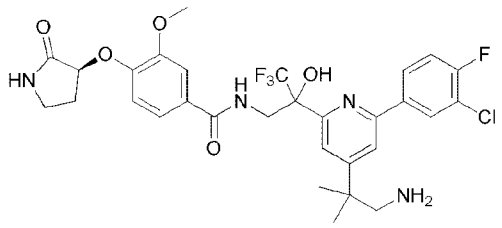
[1417] Trifluoroacetic acid (0.1 mL) was added to a solution of **651-4** in CH_2Cl_2 (0.9 mL), and the reaction was stirred at r.t. for 5 mins. The mixture was cooled to 0 °C. The reaction was quenched with bicarbonate and extracted with EA. The product was purified by reverse-phase HPLC to yield **651** (4.0 mg). LCMS: m/z 628.05 $[M+H]^+$.

EXAMPLE 405
Preparation of Compound 661



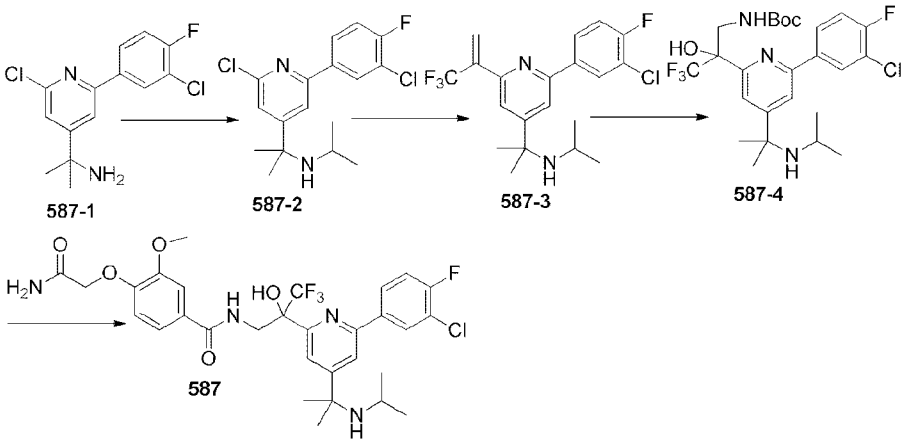
[1418] Compound **661** was prepared following the general procedure for **651**. LCMS: m/z 563.15 $[M+H]^+$.

EXAMPLE 406
Preparation of Compound 493



[1419] Compound **493** was prepared following the general procedure for **397** using (S)-3-methoxy-4-((2-oxopyrrolidin-3-yl)oxy)benzoic acid. LCMS: m/z 640.15 $[M+H]^+$.

EXAMPLE 407
Preparation of Compound 587

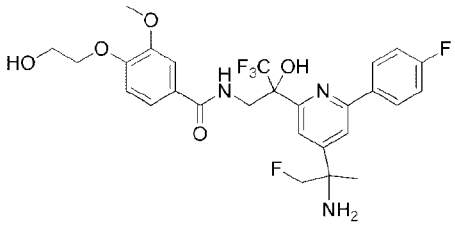


[1420] To a stirring mixture of **587-1** (200 mg, 0.67 mmol) in DCE (1 mL) at r.t. were added acetone (78 mg, 1.33 mmol), HOAc (10 mg), and $Na(OAc)_3BH$ (280 mg). The

mixture was stirred at r.t. overnight. The mixture was diluted with DCM, and the reaction was quenched with a cold $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel column to afford **587-1** (180 mg, 79%) as a colorless oil. LCMS: m/z 341.0 $[M+H]^+$.

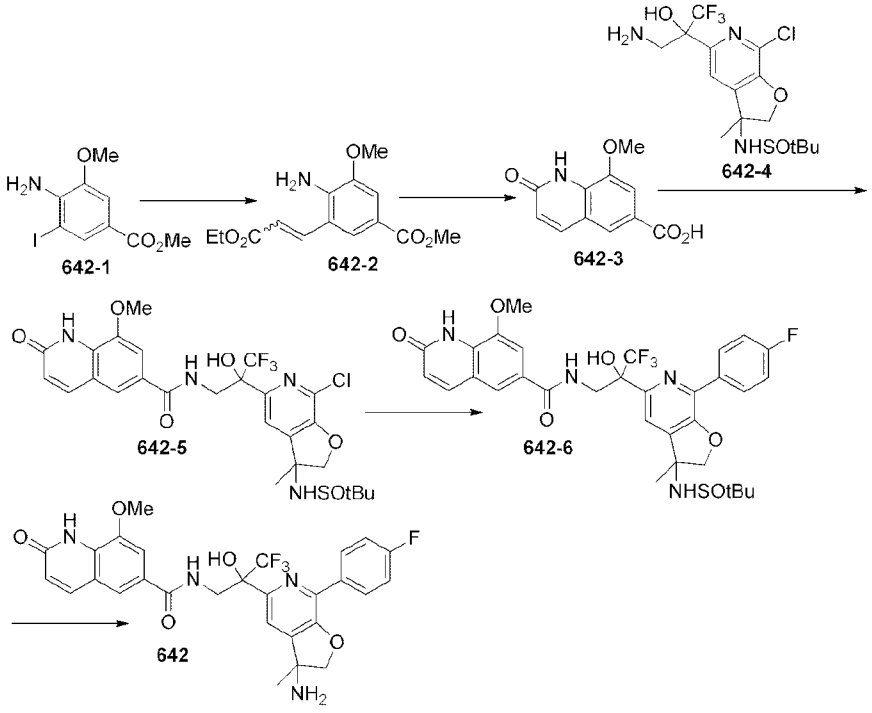
[1421] Compound **587** (35 mg) was prepared in 4 steps from **587-2** (180 mg). LCMS: m/z 641.15 $[M+H]^+$.

EXAMPLE 408
Preparation of Compound 664



[1422] Compound **664** is a single diastereomer of **626** and was obtained by chiral separation of **626** via SFC system. +ESI-MS: m/z 570.15 $[M+H]^+$.

EXAMPLE 409
Preparation of Compound 642



[1423] To a stirring mixture of **642-1** (540 mg, 1.76 mmol) in DMF (5 mL, deoxygenated prior to use) were added $Pd(OAc)_2$ (119 mg, 0.17 mmol), PPh_3 (102 mg, 0.387 mmol), TEA (0.3 mL, 2.11 mmol) and ethyl acrylate (0.42 mL, 3.87 mmol). The mixture was stirred at 85 °C overnight. The mixture was diluted with EtOAc and washed with brine. The layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via a silica gel chromatography to afford **642-2** as a yellow solid (410 mg, 83%). LCMS: m/z 280.05 $[M+H]^+$.

[1424] To a stirring mixture of **642-2** in a solution of HCl in dioxane (3 mL) was added concentrated HCl (1 mL). The mixture was stirred at 90 °C overnight. The crude product was cooled to r.t. and concentrated under reduced pressure to afford **642-3** as a brown solid. The solid was dissolved in toluene and concentrated under reduced pressure (2X). Crude **642-3** was used in the next step without further purification. LCMS: m/z 220.0 $[M+H]^+$.

[1425] To a stirring mixture of **642-3** (63 mg, 0.144 mmol) in DMF (0.5 mL) were added EDCI (33 mg, 0.173 mmol), HOAt (23 mg, 0.173 mmol) and TEA (41 μL, 0.088 mmol). The mixture was stirred at r.t. for 5 mins. A solution of **642-4** (60 mg, 0.144 mmol) in DMF (0.5 mL) was added. The mixture was stirred r.t. for 10 mins. The reaction was quenched with a 10% aq. solution of $NaHCO_3$ (1 mL). The mixture was diluted with DCM, and an aqueous work up with DCM was followed. The crude product was purified via prep-HPLC to afford **642-5** (20 mg) as a white solid. LCMS: m/z 617.1 $[M+H]^+$.

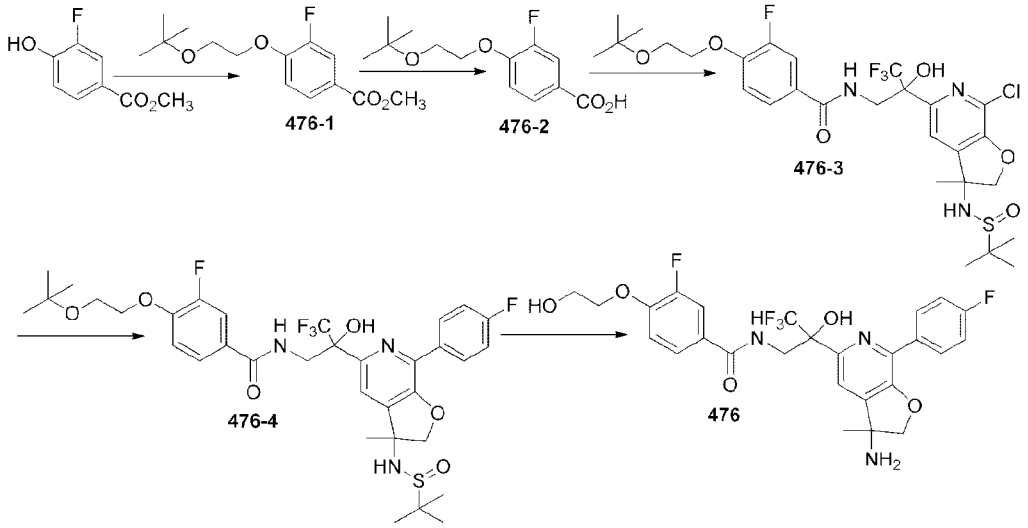
[1426] To a stirring mixture of **642-5** (20 mg, 0.032 mmol) in DME:EtOH:H_2O (1.0 mL:0.3 mL:0.1 mL, deoxygenated prior to using) were added 4-fluorophenylboronic acid (9 mg, 0.063 mmol), K_3PO_4. $7H_2O$ (43 mg, 0.128 mmol), KH_2PO_4 (17.4 mg, 0.128 mmol) and $PdCl_2(dppf)$ (20 mg). The mixture was carried out under microwave irradiation at 110 °C for 5 h. The crude product was concentrated under reduced pressure, and then purified via a silica gel chromatography to afford **642-6** as a brownish oil. LCMS: m/z 677.15 $[M+H]^+$.

[1427] To a stirring mixture of **642-6** in MeOH (1 mL) at r.t. was added a solution of HCl in dioxane (0.2 mL, 4N). The mixture was stirred at r.t. for 5 mins and then

concentrated under reduced pressure. The crude product was purified via prep-HPLC to afford **642** (8.5 mg) as a white solid. LCMS: m/z 573.1 $[M+H]^+$.

EXAMPLE 410

Preparation of Compound 476



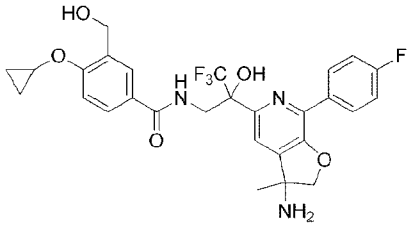
[1428] Diisopropylazadicarboxylate (0.29 mL, 1.5 mmol) was added to a solution of methyl 3-fluoro-4-hydroxybenzoate (0.21 g, 1.2 mmol, ethyl glycol mono-*tert*-butyl ether (0.32 mL, 2.5 mmol) and polymer bound triphenylphosphine (1.1 g, 1.9 mmol) in THF (5 mL). The mixture was stirred at r.t. for 1 h. The resin was removed by filtration, and the mixture was concentrated. The product was purified by column chromatography (hexane:EA) to **476-1** (0.34 g, 98%).

[1429] NaOH (2N, 3 mL) was added to a solution of **476-1** (0.34 g, 1.2 mmol) in MeOH (10 mL), and the mixture was heated at reflux for 1.5 h. The mixture was acidified with 1N HCl and extracted with EA. The organic extracts were washed with brine, dried and concentrated to obtain **476-2** (0.29 g, 91%).

[1430] **476-3** was prepared following the general procedure for **635-2** using **476-2**. **476-4** was prepared following the general procedure for **635-3** using **476-3**.

[1431] HCl (4N in dioxane, 1 mL) was added to a solution of **476-4** (32 mg, 0.049 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred at r.t. for 5 h. The mixture was concentrated and the crude product purified by HPLC to yield **476**. LCMS: m/z 555.05 $[M+H]^+$.

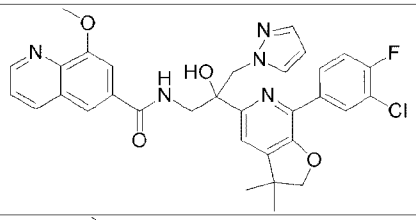
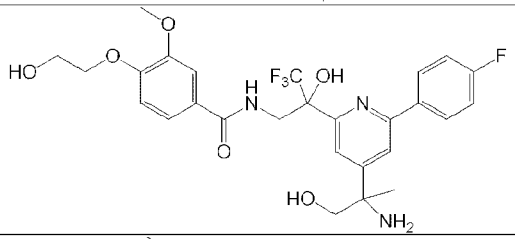
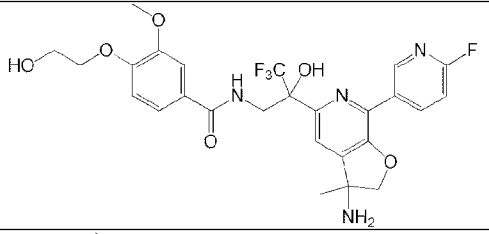
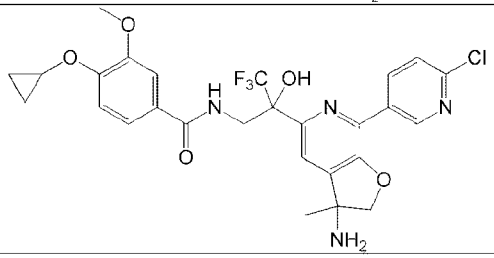
EXAMPLE 411
Preparation of Compound 481

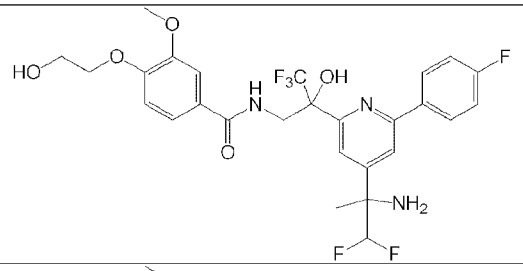
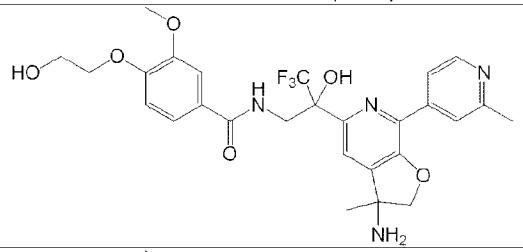
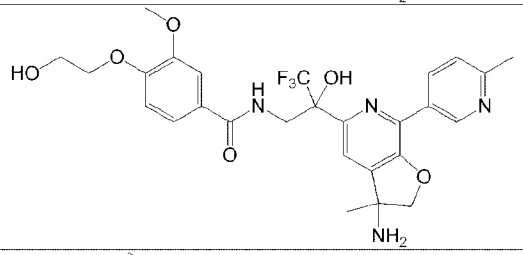
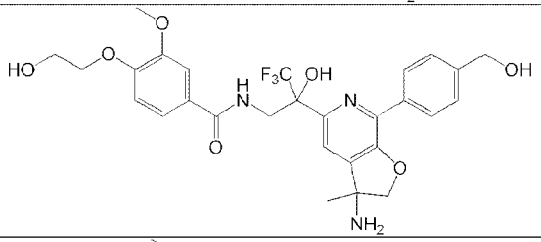
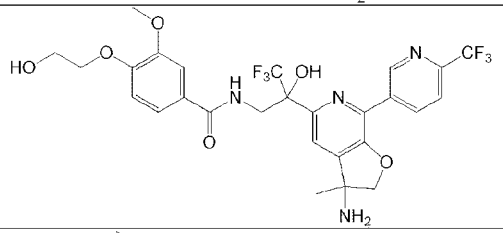
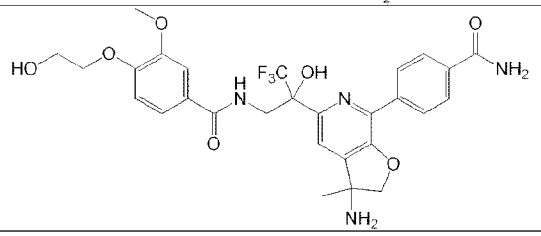


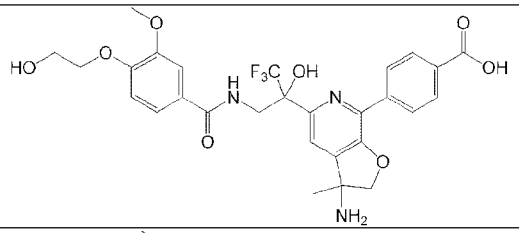
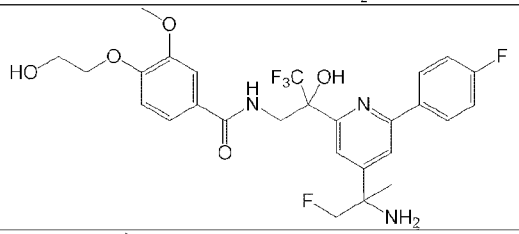
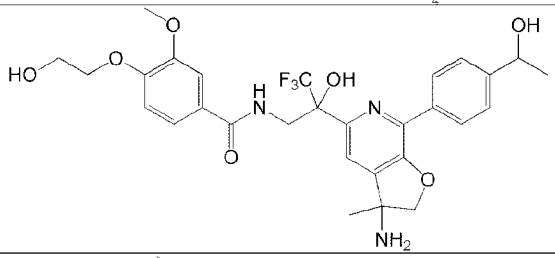
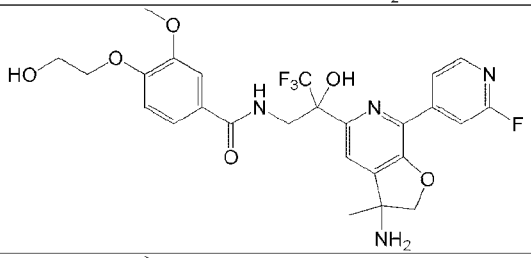
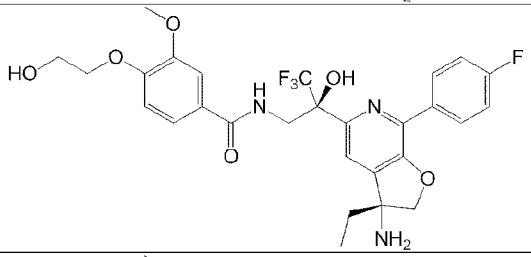
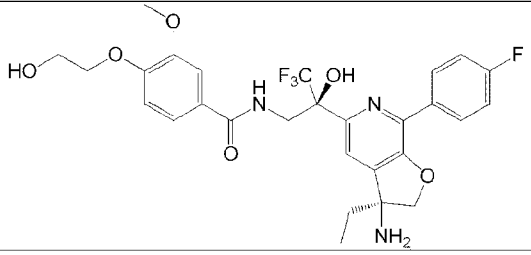
[1432] Compound **481** (8.7 mg) was prepared following the general procedure for **645**. LCMS: m/z 562.15 $[M+H]^+$.

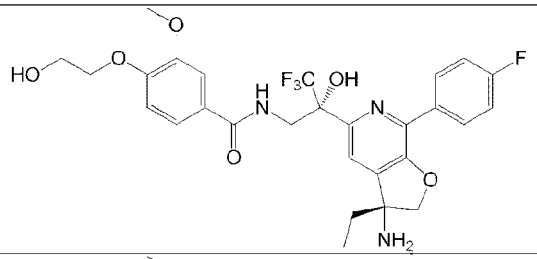
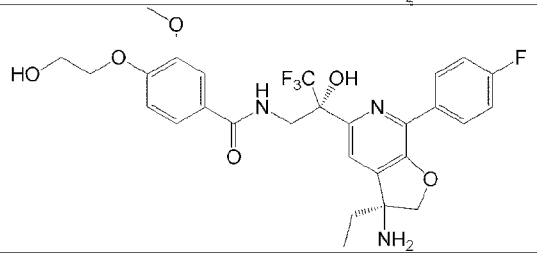
EXAMPLE 412

[1433] The following compounds were prepared following one or more of the methods provided herein.

No.	Structure	MS
472		nd
484		568.0 $[M+H]^+$
492		567.0 $[M+H]^+$
668		579.2 $[M+H]^+$

No.	Structure	MS
669		610.1 $[M+Na]^+$
670		563 $[M+H]^+$
671		563.0 $[M+H]^+$
672		578.0 $[M+H]^+$
673		617.1 $[M+H]^+$
674		591.1 $[M+H]^+$

No.	Structure	MS
675		614.0 $[M+Na]^+$
676		570.1 $[M+H]^+$
677		nd
678		nd
679		nd
680		nd

No.	Structure	MS
681		nd
682		nd

EXAMPLE A
RSV Antiviral Assay

[1434] 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 µl/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 µM or 1 µM 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 $TCID_{50}$/30 µL with medium and 30 µl 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% CO_2 for 5 days.

[1435] 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 µl 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.

[1436] 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 μM. Table B includes compounds with an EC_{50} value that is equal to or higher than 1 μM and less than 50 μM. Other tested compounds disclosed herein had an EC_{50} value of 50 μM or greater.

Table A

Compound	Compound	Compound	Compound	Compound	Compound
101	176	218	255	298	334
115	181	219	256	299	335
116	182	220	257	303	336
116b	184	221	258	304	338
117	185	222	259	305	339
117b	189	223	260	308	340
118	191	224	261	309	342
118b	192	226	262	310	343
119	193	227	263	312	344
120	194	228	267	314	345
120b	195	232	270	315	346
122	198	234	272	317	347
122a	199	235	273	318	348
123	200	237	274	320	349
124	202	238	281	321	353
125	204	239	282	322	356
126	205	240	283	323	357
127	208	241	284	324	358
130	209	243	285	325	359
135	210	244	287	326	360
140	211	245	289	327	361
142	212	246	292	328	362
143	213	248	294	330	364
166	214	249	296	331	365
167	217	250	297	333	366

Compound	Compound	Compound	Compound	Compound	Compound
368	431	482	525	562	615
369	433	483	526	563	619
370	434	485	527	565	620
371	435	486	528	568	621
372	436	487	529	569	623b
373	442	488	530	570	624b
383	443	489	531	571	626
384	444	490	532	574	627
385	445	491	533	575	628
387	447	494	534	577	629
388	448	495	535	579	630
391	449	496	536	580	631
392	451	497	537	583	632
394	452	498	538	586	633b
396	453	498d	539	587	634
400	454	499	540	590	635
403	455	500	541	591	638
405	456	501	542	592	640
406	459	502	543	593	642
409	460	503	545	594	643
411	461	504	546	595	644
413	462	505	547	596	645
414	464	507	548	597	646
415	465	508	550	598	650
418	466	510	551	599	653
419	467	514	552	604d	654
421	469	515	553	605a	656
423	470	516	554	605b	662
424	473	517	556	605d	663
425	474	518	557	610	664
426	475	519	558	611	665
428	476	520	559	612	666
429	479	521	560	614	667

Table B

Compound	Compound	Compound	Compound	Compound	Compound
100	109	117a	131	148	175
102	111	118a	132	149	177
104	112	120a	133	150	178
106	113	121	134	161	179
107	114	122b	137	165	196
108	116a	129	145	174	206

Compound	Compound	Compound	Compound	Compound	Compound
207	266	278	410	478	623a
215	275	279	416	484	624a
216	283	280	417	492	633a
229	186	286	432	549	637
233	187	290	437	561	639
251	190	302	438	604b	655
252	197	313	440	604a	673
253	236	337	450	605c	
254	268	368	463	607	
264	276	404	471	608	
265	277	407	477	609	

EXAMPLE B
Cytotoxicity Determination

[1437] 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 μM 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 μL CCK-8 into each well and incubate in a CO_2 incubator at 37°C for 3-4 hours. Read the plates to obtain the optical densities which are used to calculate 50% cytotoxicity concentration (CC_{50}).

[1438] 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 μM. Table D includes compounds with a CC_{50} value that is equal to or less than 100 μM and greater than 10 μM. Other tested compounds disclosed herein had a CC_{50} value of less than 10 μM.

Table C

Compound	Compound	Compound	Compound	Compound	Compound
108	150	183	199	234	294
109	175	187	205	236	302
116a	176	189	206	244	303
117b	177	190	209	245	304
120	178	191	213	247	331
120b	179	192	220	248	335
121	180	194	228	287	345
123	181	195	229	291	353
135	182	196	233	292	358

Compound	Compound	Compound	Compound	Compound	Compound
370	420	474	611	624a	670
373	421	484	612	624b	671
387	427	492	613	625	672
403	439	561	615	627	673
404	441	562	616	628	674
405	446	580	620	634	675
406	447	604a	621	643	
408	451	604b	623a	653	
419	470	608	623b	655	

Table D

Compound	Compound	Compound	Compound	Compound
100	131	214	257	308
101	132	215	258	309
102	133	216	259	310
104	134	217	260	312
106	137	218	261	313
107	140	219	262	315
110	142	221	263	317
111	143	222	264	318
112	145	223	265	320
113	148	224	266	321
114	149	226	267	322
115	161	227	268	326
116	163	232	269	327
116b	165	235	270	328
117	166	237	277	330
117a	167	238	278	333
118	174	239	279	334
118a	184	240	283	336
118b	185	241	285	337
119	186	242	286	338
120a	193	243	288	339
122	197	246	289	340
122a	200	249	290	342
122b	202	250	293	343
124	204	251	295	344
125	207	252	296	346
126	208	253	297	347
127	210	254	298	348
129	211	255	299	349
130	212	256	305	356

Compound	Compound	Compound	Compound	Compound
357	431	482	540	598
359	432	483	541	599
360	433	485	542	604c
361	434	486	543	605a
362	435	487	545	605b
364	436	488	546	605c
365	437	489	547	605d
366	438	490	548	606
368	440	491	549	607
369	442	495	550	609
371	443	496	551	610
372	444	498	552	614
383	445	498d	553	617
384	448	500	554	619
385	449	501	556	626
386	450	502	557	629
388	452	503	558	630
391	453	504	559	631
392	454	507	560	632
396	455	510	563	633a
400	456	514	565	633b
407	457	515	568	635
409	458	516	569	637
410	459	517	570	638
411	460	518	571	639
412	461	525	574	640
413	462	526	575	642
414	463	527	577	644
415	464	528	578	645
416	465	529	579	646
417	466	530	583	650
418	467	531	586	654
422	468	532	587	656
423	469	533	590	662
424	471	534	592	663
425	473	535	593	664
426	475	536	594	665
428	476	537	595	666
429	477	538	596	
430	479	539	597	

EXAMPLE C
RSV Polymerase Inhibition Assay

[1439] 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 $MgCl_2$, 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% (IC_{50}) was calculated by fitting the data to a non-linear regression (sigmoidal). The IC_{50} values were derived from the mean of several independent experiments and are shown in Tables E and F.

[1440] Table E includes compounds with an IC_{50} of < 1 μM. Table F includes compounds with an IC_{50} < 10 μM. Table G includes compounds with an IC_{50} value of < 100 μM.

Table E

Compound	Compound	Compound	Compound	Compound
101	128	190	210	228
115	130	191	211	232
116	140	192	212	233
116b	141	193	213	234
117	142	194	214	235
117b	143	195	215	236
118	147	196	217	237
118b	166	197	218	238
119	167	198	219	239
120	176	199	221	240
120b	179	200	220	241
122	181	202	222	243
122a	182	204	223	244
123	183	205	224	245
125	184	207	225	246
126	185	208	226	248
127	189	209	227	249

Compound	Compound	Compound	Compound	Compound
250	307	354	405	470
251	308	355	406	473
252	309	356	409	474
254	310	357	411	475
255	311	358	413	476
256	312	359	415	479
257	314	360	418	481
258	315	361	419	482
259	316	362	421	483
260	317	364	423	485
261	318	365	424	486
262	319	366	425	487
263	320	367	428	488
264	321	369	431	489
266	322	370	432	491
267	323	371	434	493
270	324	372	435	494
271	325	373	436	495
272	326	375	437	496
273	327	376	440	497
274	328	378	442	498
275	329	379	443	498c
276	330	380	444	498d
278	331	383	445	499
279	332	384	447	500
280	333	385	448	501
281	334	386	449	501
282	335	387	451	502
283	336	388	452	503
284	337	389	453	504
285	338	390	454	505
287	339	391	455	506
289	340	392	456	507
292	341	393	459	508
297	342	394	460	509
298	343	395	461	510
299	344	396	462	511
301	345	397	463	514
302	346	398	464	515
303	347	399	465	516
304	348	400	466	517
305	349	402	467	518
306	353	403	469	519

Compound	Compound	Compound	Compound	Compound
520	549	581	615	643
521	550	582	617	644
522	551	583	618	645
523	552	584	619	646
524	553	585	620	647
525	554	586	621	648
526	555	588	622	650
527	556	589	623b	651
528	557	590	624b	652
529	558	591	625	653
530	559	593	626	654
531	560	594	627	655
532	562	595	628	656
533	563	596	629	657
534	565	598	630	658
535	567	599	631	662
536	568	600	632	663
537	569	601	633a	664
538	570	602	633b	665
539	571	603	634	666
540	573	604d	635	667
541	574	605a	636	668
452	575	605c	637	669
543	576	605d	638	676
545	577	610	639	
546	578	611	640	
547	579	612	641	
548	580	614	642	

Table F

Compound	Compound	Compound	Compound	Compound
109	153	247	350	477
114	154	253	352	478
120a	165	265	363	480
122b	168	268	377	484
124	174	277	404	490
145	175	286	416	492
146	177	290	417	498b
148	187	294	426	512
149	188	296	438	513
150	203	300	450	561
151	216	313	471	564

Compound	Compound	Compound	Compound	Compound
572	604b	609	624a	673
592	604c	613	659	
597	607	616	660	
604a	608	623a	672	

Table G

Compound	Compound	Compound	Compound	Compound
116a	161	230	407	427
117a	178	242	408	430
118a	180	295	412	439
135	186	368	420	441
144	201	382	422	446

EXAMPLE D
RSV Assay

[1441] The RSV subgenomic replicon 395 HeLa and APC126 were licensed from Apath (Brooklyn, NY) and were originally developed by Dr. Mark Mceples 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% CO_2 atmosphere.

[1442] Determination of 50% inhibitory concentration (EC_{50}), 90% inhibitory concentration (EC_{90}) and 50% cytotoxic concentration (CC_{50}) 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% CO_2 atmosphere. In each assay, positive control that was previously characterized in the RSV replicon assay was included.

[1443] 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. EC_{50}, 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.

[1444] 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 μL) was added to each well and incubated at room temperature for 8 minutes. Luminescence was recorded using a Perkin Elmer multilabel counter Victor3V. The CC_{50}, 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.

[1445] Table H includes compounds with an EC_{50} value that is less than 1 μM. Table I includes compounds with an EC_{50} value that is equal to or higher than 1 μM and less than 50 μM. Other tested compounds disclosed herein had an EC_{50} value of 50 μM or greater.

Table H

Compound	Compound	Compound	Compound	Compound
106	224	317	366	434
115	226	318	369	436
116	228	319	370	437
116b	232	320	371	442
117	237	321	372	443
117b	239	322	373	444
118	240	323	376	445
118b	241	324	379	447
119	243	325	380	448
120	244	326	383	449
120b	245	327	384	452
122	246	328	385	453
122a	248	330	386	454
123	249	331	387	455
124	250	333	388	456
125	255	334	389	459
126	260	335	390	460
130	271	336	391	462
140	272	338	392	466
141	273	339	393	467
143	275	341	394	470
147	281	342	395	483
166	282	343	396	485
176	283	344	397	486
184	284	345	398	487
189	289	346	400	488
191	292	347	403	489
192	298	348	405	490
193	302	349	406	491
194	303	354	409	493
195	304	355	411	494
198	306	356	413	496
200	307	357	415	497
202	308	358	418	498
204	309	359	419	498d
205	310	360	421	499
208	311	361	423	500
209	312	362	424	501
211	314	363	425	502
218	315	364	428	503
223	316	365	431	504

Compound	Compound	Compound	Compound	Compound
505	533	563	596	637
506	534	564	598	638
507	535	567	600	640
508	536	569	601	641
509	538	571	602	642
510	539	572	603	643
511	540	574	604d	644
514	542	575	605d	645
515	543	576	611	646
516	545	577	612	647
519	546	578	614	650
520	547	579	615	651
521	548	580	621	653
523	550	581	622	659
524	551	583	623b	663
525	552	584	624b	664
526	554	585	626	665
527	555	586	627	667
528	556	588	630	672
529	558	589	633b	675
530	560	590	634	
531	561	594	635	
532	562	595	636	

Table I

Compound	Compound	Compound	Compound
127	168	332	438
128	220	375	461
163	313	378	

EXAMPLE 15
Combination Studies

RSV with Renilla Reporter

[1446] RSV expressing Renilla luciferase (A2-RL-line19F) was 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).

[1447] Host cell HEp-2 was purchased from ATCC (Cat. #CCL-23) and cells were cultured in DMEM/Ham's F-12 50/50 1× containing L-glutamine and 15 mM HEPES (Mediatech, Cat. #10-092-CM). The medium was 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 were maintained at 37 °C in a humidified 5% CO_2 atmosphere.

Drug Treatment and Viral Dosing

[1448] To determine the effect of a combination of compounds, the following procedure was followed. On the first day, 20,000 HEp-2 cells were plated per well in a 96-well plate. On the following day, test articles were 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, was serially diluted (1:3) to 9 distinct concentrations "horizontally" in a 96-well plate, and Compound (B), or a pharmaceutically acceptable salt thereof, was serially diluted (1:3) to 7 distinct concentrations "vertically" in 96-well plate. The serially diluted 200x test articles were then diluted 1:10 into cell culture media to generate 20x test articles. A 5 µL aliquot of the 20x test articles was added in a checkerboard fashion to the cells with 90 µL existing media. Space was 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 was added to the plate and further incubated for 2 days at 37 °C in a 5% CO_2.

Determination of Anti-RSV Activity

[1449] 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.

Cell Viability Assay

[1450] 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 adenosine triphosphate (ATP) present, which signals the presence of metabolically active cells. Assay plates were set up in the same format the anti-RSV assay, except that no virus was added to the cell viability assay. A 100-µL aliquot of CellTiter-Glo

reagent was added to each well and incubated at room temperature for 8 minutes. Luminescence was recorded using a Perkin Elmer multilabel counter Victor3V.

Data Analysis

[1451] Each experiment was performed at N=5 for both anti-RSV activity and cell viability. Mean percent inhibition of the replicon values from the 5 experiments was generated and for anti-RSV activity, it was analyzed using two drug interaction analysis models, Isobologram Analysis and/or Prichard's Model.

Isobologram Analysis

[1452] The effects of drug-drug combinations were evaluated by the Loewe additivity model in which the experimental data were 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 were 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, was 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)

[1453] MacSynergy II software was 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*• *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*• *faB* then we have Bliss synergy; if *faAB* < *faA* + *faB* - *faA*• *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 was used for data analysis.

[1454] 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. For the combination of **574** and BMS-433771 (a fusion protein inhibitor) had a synergy volume of 24.9 $\mu M^2\%$ (additive/minor synergism).

EXAMPLE F
Parainfluenza virus-3 (PIV-3) Plaque Assay

[1455] MA-104 cells are grown in 24-well plates to a confluency of 90% in the presence of minimal essential medium (MEM) supplemented with 10% fetal bovine serum and antibiotics (C-EMEM). The cells are then washed twice with non-complete minimal essential medium (NC-EMEM). Test articles are dissolved in DMSO to a stock concentration of 10 mM.

[1456] An aliquot of 0.5 mL of the test article at various concentrations are then inoculated in triplicate wells and are incubated for 60 mins at 37 °C with 5% CO_2 for the diffusion of test article into MA-104 cells. After the incubation period, a stock of human PIV type 3 are thawed and diluted with NC-EMEM to achieve a viral concentration of 10^4 pfu/mL. An aliquot of 0.1 mL are then inoculated into all the wells except for the negative and test article toxicity control wells. Upon infection, the plates are incubated for 72 h at 37 °C at 5% CO_2. After incubation, the plates are examined under microscopy to record cytotoxicity. The supernatants are collected for viral quantification using a standard plaque assay using MA-104 cells as the indicator cells.

[1457] To perform the plaques assay, MA-104 cells are grown to confluence in 24-well plates. The cells are washed with serum-free medium prior to inoculation of duplicate wells with serial 10-fold dilutions of supernatant sample. After 1 h incubation at 37 °C, the samples are aspirated and 1.0 mL of methyl cellulose overlay media are added to each well. After 6 days of culture, the cells are fixed and stained with 0.06% crystal violet in 1% glutaraldehyde and viral plaques are enumerated. The data are analyzed with Prism software with EC_{50} defined as drug concentration that reduced the viral load 50% from the viral control (VC).

EXAMPLE G
Human metapneumovirus (hMPV) $TCID_{50}$ Assay

[1458] LLC-MK2 cells are grown in 24-well plates to a confluency of 90% in the presence of minimal essential medium (MEM) supplemented with 10% fetal bovine serum and antibiotics (C-EMEM). The cells are then washed twice with non-complete minimal essential medium (NC-EMEM). Test articles are dissolved in DMSO to a stock concentration of 10 mM.

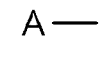
[1459] An aliquot of 0.5 mL of the test article at various concentrations are then inoculated in triplicate wells and are incubated for 60 mins at 37 °C with 5% CO_2 for the diffusion of test article into LLC-MK2 cells. After the incubation period, a stock of human metapneumovirus are thawed and diluted with NC-EMEM to achieve a viral concentration of 10^4 pfu/mL. An aliquot of 0.1 mL are then inoculated into all the wells except for the negative and test article toxicity control wells. Upon infection, the plates are incubated for 7 days at 37 °C at 5% CO_2. After incubation, the plates are examined under microscopy to record cytotoxicity. The supernatants are collected for viral quantification using a standard $TCID_{50}$ assay using LLC-MK2 cells as the indicator cells. The data are analyzed with Prism software with EC_{50} defined as drug concentration that reduced the viral load 50% from the viral control (VC).

[1460] 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.

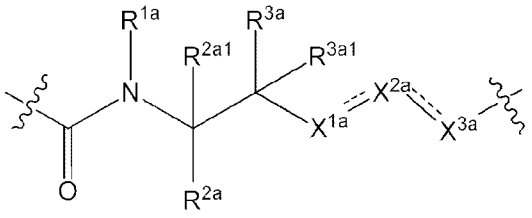
WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:

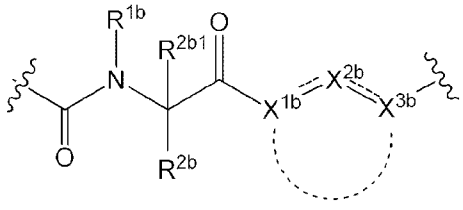


(I)

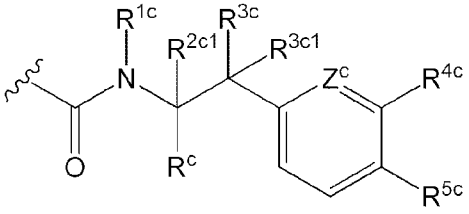
wherein: L is selected from the group consisting of:



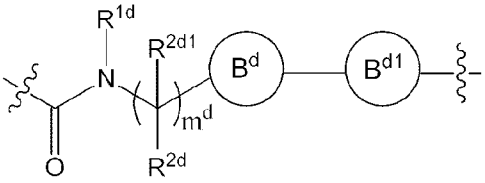
(Ia),



(Ib),



(Ic) and



(Id);

A is selected from the group consisting of an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-2} alkyl), an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

Y 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;

R^{1a}, R^{1b}, R^{1c} and R^{1d} are each independently hydrogen or an unsubstituted C_{1-4} alkyl;

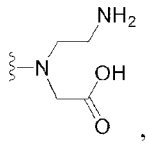
R^{2a}, R^{2a1}, R^{2b}, R^{2b1}, R^{2c}, R^{2c1}, R^{2d} and R^{2d1} are each independently selected from the group consisting of hydrogen, an optionally substituted C_{1-4} alkyl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heterocyclyl(C_{1-6} alkyl), an alkoxyalkyl, an aminoalkyl, a hydroxyalkyl and hydroxy; or

R^{2a1} is hydrogen, and R^{1a} and R^{2a} is joined together with the atoms to which they are attached to form an optionally substituted 5 membered heterocyclyl or an optionally substituted 6 membered heterocyclyl, R^{2b1} is hydrogen, and R^{1b} and R^{2b} is joined together with the atoms to which they are attached to form an optionally substituted 5 membered heterocyclyl or an optionally substituted 6 membered heterocyclyl;

-------- between X^{1a} and X^{2a} represents a single or double bond between X^{1a} and X^{2a}; -------- between X^{2a} and X^{3a} represents a single or double bond between X^{2a} and X^{3a}; provided that -------- between X^{1a} and X^{2a} and -------- between X^{2a} and X^{3a} cannot be both double bonds and at least one of -------- is a double bond;

when -------- between X^{1a} and X^{2a} represents a double bond and -------- between X^{2a} and X^{3a} is a single bond, then X^{1a} is N or CR^{4a1}, X^{2a} is N or CR^{5a} and X^{3a} is NR^{6a1}, C(=O) or $CR^{6a2}R^{6a3}$; and when -------- between X^{1a} and X^{2a} represents a single bond and -------- between X^{2a} and X^{3a} is a double bond, then X^{1a} is NR^{4a} or $CR^{4a2}R^{4a3}$, X^{2a} is N or CR^{5a} and X^{3a} is N or CR^{6a}; or

X^{1a}, X^{2a} and X^{3a} are each independently C, N, O or C(=O), and form a ring or ring system selected from an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl by joining X^{1a} and X^{3a} together; with the proviso that the valencies of X^{1a}, X^{2a} and X^{3a} can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl, and X^{1a}, X^{2a} and X^{3a} are uncharged;

R^{3a} and R^{3a1} are each independently selected from the group consisting of hydrogen, hydroxy, halogen, amino, an optionally substituted C_{1-4} alkyl, an optionally substituted C_{2-4} alkenyl, an optionally substituted C_{2-4} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{1-4} alkoxy, -O-carboxy, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, CHF_2, CF_3 and 

, provided that R^{3a} and R^{3a1} cannot be both hydrogen; or R^{3a} and R^{3a1} together form =N-OR^a; or R^{3a} and R^{3a1} together with the atom to which they are attached can be joined to form an optionally substituted 3

membered ring, an optionally substituted 4 membered ring, an optionally substituted 5 membered ring or an optionally substituted 6 membered ring;

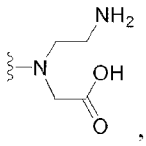
R^{4a}, R^{4a1}, R^{4a2} and R^{4a3} are each independently hydrogen or an unsubstituted C_{1-4} alkyl;

R^{5a} and R^{5a1} are each independently be hydrogen or an unsubstituted C_{1-4} alkyl;

R^{6a} and R^{6a1} are each independently hydrogen, an optionally substituted C_{1-4} alkyl or an optionally substituted alkoxyalkyl;

R^{6a2} and R^{6a3} are each independently hydrogen or an unsubstituted C_{1-4} alkyl;

X^{1b}, X^{2b} and X^{3b} are each independently C, N, O or C(=O), and form indicates a bi-cyclic ring selected from an optionally substituted bi-cyclic heteroaryl and an optionally substituted bi-cyclic heterocyclyl by joining X^{1b} and X^{3b} together, wherein -------- between X^{1b} and X^{2b} represents a single or double bond between X^{1b} and X^{2b}; -------- between X^{2b} and X^{3b} represents a single or double bond between X^{2b} and X^{3b}; and provided that at least one of X^{1b}, X^{2b} and X^{3b} comprises a nitrogen atom and both -------- cannot be double bonds; with the proviso that the valencies of X^{1b}, X^{2b} and X^{3b} can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl; and X^{1b}, X^{2b} and X^{3b} are uncharged;

R^{3c} and R^{3c1} are each independently selected from the group consisting of hydrogen, hydroxy, halogen, amino, an optionally substituted C_{1-4} alkyl, an optionally substituted C_{2-4} alkenyl, an optionally substituted C_{2-4} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{1-4} alkoxy, -O-carboxy, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, CHF_2, CF_3 and  , provided that R^{3c} and R^{3c1} cannot be both hydrogen; or R^{3c} and R^{3c1} together form =N-OR^c; or R^{3c} and R^{3c1} together with the atom to which they are attached can be joined to form an optionally substituted 3 membered ring, an optionally substituted 4 membered ring, an optionally substituted 5 membered ring or an optionally substituted 6 membered ring;

R^a and R^c are each independently hydrogen or an unsubstituted C_{1-4} alkyl;

R^{4c} and R^{5c} are taken together to form an unsubstituted aryl, an unsubstituted heteroaryl or an optionally substituted heterocyclyl;

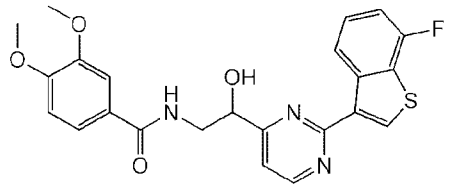
Z^c is N or CH;

m^d is 0 or 1; and

ring B^d is an optionally substituted C_5 cycloalkyl;

ring B^{d1} is an optionally substituted pyridinyl; and

provided that when L is Formula (IIc), then Y is absent; and

provided that the compound is not 

.

2. The compound of Claim 1, wherein L is Formula (Ia).

3. The compound of Claim 2, wherein X^{1a} is CR^{4a1} or $CR^{4a2}R^{4a3}$, X^{2a} is N, and X^{3a} is CR^{6a} or $CR^{6a2}R^{6a3}$.

4. The compound of Claim 2, wherein -------- between X^{1a} and X^{2a} is a single bond, -------- between X^{2a} and X^{3a} is a double bond, X^{1a} is $CR^{4a2}R^{4a3}$, X^{2a} is N, and X^{3b} is CR^{6a}.

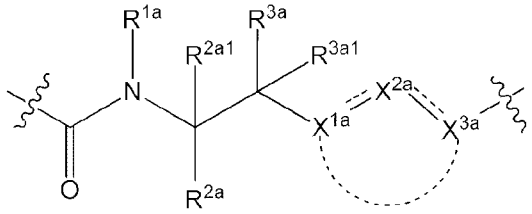
5. The compound of Claim 2, wherein -------- between X^{1a} and X^{2a} is a double bond, -------- between X^{2a} and X^{3a} is a single bond, X^{1a} is CR^{4a1}, X^{2b} is N, and X^{3b} is $CR^{6a2}R^{6a3}$.

6. The compound of Claim 2, wherein -X^{1a}------X^{2a}------X^{3a}- is -CH_2-N=CH- or -CH=N-CH_2-.

7. The compound of Claim 2, wherein -X^{1a}------X^{2a}------X^{3a}- is -N=N-CH_2-, -N=CH-CH_2- or -N=CH-NH-.

8. The compound of Claim 2, wherein -X^{1a}------X^{2a}------X^{3a}- is -CH_2-CH=N-, -NH-CH=NH- or -NH-N=CH-.

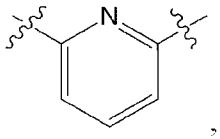
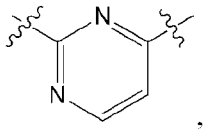
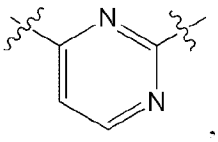
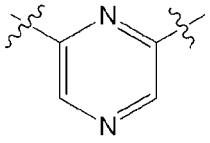
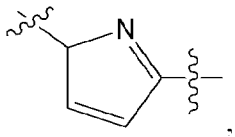
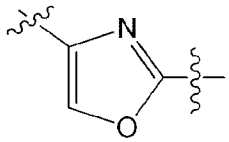
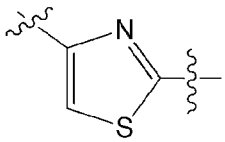
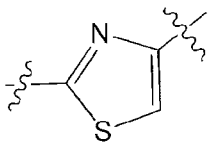
9. The compound of Claim 1, wherein L is Formula (Ia1):

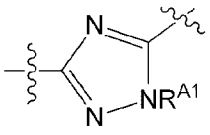
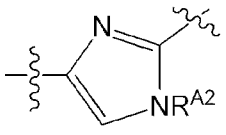
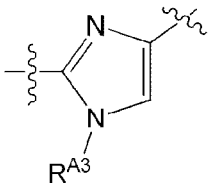
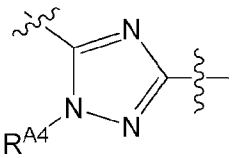
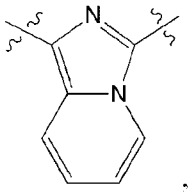
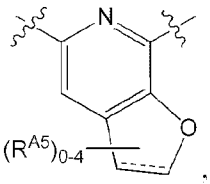
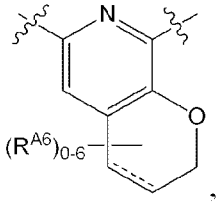
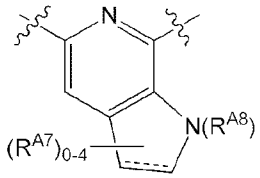
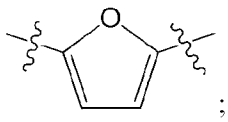


10. The compound of Claim 9, wherein X^{1a}, X^{2a} and X^{3a} is a ring or ring system is an optionally substituted aryl.

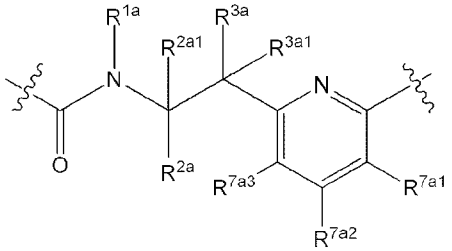
11. The compound of Claim 9, wherein X^{1a}, X^{2a} and X^{3a} is a ring or ring system is an optionally substituted mono-cyclic heteroaryl or an optionally substituted bi-cyclic heteroaryl.

12. The compound of Claim 9, wherein X^{1a}, X^{2a} and X^{3a} is a ring or ring system is an optionally substituted mono-cyclic heterocyclyl or an optionally substituted bi-cyclic heterocyclyl.

13. The compound of Claim 9, wherein X^{1a}, X^{2a} and X^{3a} is a ring or ring system 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  , an optionally substituted  , an optionally substituted  an optionally substituted  , an optionally substituted  , an optionally substituted  , an optionally substituted  and an optionally substituted  ; wherein R^{A1}, R^{A2}, R^{A3} and R^{A4} is each independently hydrogen or an unsubstituted C_{1-6} alkyl; each ------ is independently absent or a bond; each R^{A5}, each R^{A6}, each R^{A7} is an unsubstituted C_{1-6} alkyl, halogen, hydroxy, amino, mono-substituted amino, di-substituted amino or –NH-S(=O)C_{1-4} alkyl; and R^{A8} is hydrogen or an unsubstituted C_{1-6} alkyl.

14. The compound of Claim 1, wherein L is Formula (Ia2):



wherein R^{7a1}, R^{7a2} and R^{7a3} are each independently selected from the group consisting of hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted C_{3-6} cycloalkyl,

an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C_{1-8} alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C_{1-8} alkyl), haloalkyl, an optionally substituted O-amido and an optionally substituted C-carboxy.

15. The compound of Claim 14, wherein R^{7a1} is a C_{1-4} alkoxy, and R^{7a2} and R^{7a3} are both hydrogen.

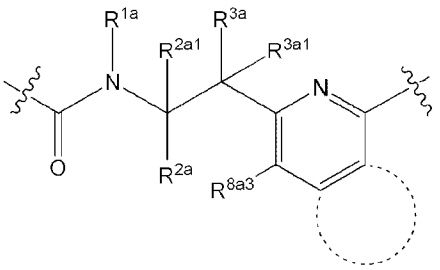
16. The compound of Claim 14, wherein R^{7a1} is a hydrogen, R^{7a2} is an optionally substituted C_{1-4} alkyl, and R^{7a3} is hydrogen

17. The compound of Claim 16, wherein the substituted C_{1-4} alkyl of R^{7a2} is substituted with a substituent selected from the group consisting of halo, hydroxy, C_{1-4} alkoxy, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted C-carboxy, amino, an optionally substituted mono-substituted amino, an optionally substituted di-substituted amino, an optionally substituted C-amido, an optionally substituted N-amido, an optionally substituted N-carbamyl, an optionally substituted N-sulfonamido, an optionally substituted urea, an optionally substituted amidine and an optionally substituted acetylurea.

18. The compound of Claim 14, wherein R^{7a1} is a hydrogen, R^{7a2} is an optionally substituted heterocyclyl, and R^{7a3} is hydrogen

19. The compound of Claim 14, wherein R^{7a1} is a mono-substituted amino, and R^{7a2} and R^{7a3} are both hydrogen.

20. The compound of Claim 1, wherein L is Formula (Ia3):



wherein the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted cycloalkyl an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; and R^{8a3} is selected from the group consisting of hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl,

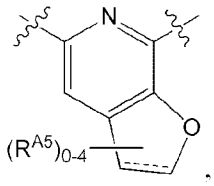
an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C_{1-8} alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C_{1-8} alkyl), haloalkyl and an optionally substituted C-carboxy.

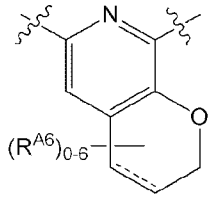
21. The compound of Claim 20, wherein the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted 5-membered cycloalkyl or an optionally substituted 6-membered cycloalkyl.

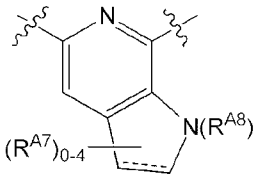
22. The compound of Claim 20, wherein the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted aryl.

23. The compound of Claim 20, wherein the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted 5-membered heteroaryl or an optionally substituted 6-membered heteroaryl.

24. The compound of Claim 20, wherein the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted 5-membered heterocyclyl or an optionally substituted 6-membered heterocyclyl.

25. The compound of Claim 20, wherein the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted 

, an optionally substituted 

or an optionally substituted 

; wherein each ------ is independently absent or a bond; each R^{A5}, each R^{A6}, each R^{A7} is halogen, an unsubstituted C_{1-6} alkyl, hydroxy, amino, an optionally substituted mono-substituted amino, an optionally substituted di-substituted amino, $-(CH_2)_{1-4}OH$, $-(CH_2)_{1-4}NH_2$ or N-sulfinamido (for example, $-NH-S(=O)C_{1-4}$ alkyl), or two R^{A5}, two R^{A6} or two R^{A7}

are taken together to form an optionally substituted 5- membered ring to an optionally substituted 6-membered ring; and R^{A8} is hydrogen or an unsubstituted C_{1-6} alkyl.

26. The compound of any one of Claims 2-25, wherein R^{1a} can be hydrogen.

27. The compound of any one of Claims 2-25, wherein R^{1a} can be an unsubstituted C_{1-4} alkyl.

28. The compound of any one of Claims 2-27, wherein R^{2a} and R^{2a1} are both hydrogen.

29. The compound of any one of Claims 2-27, wherein R^{2a} is hydrogen and R^{2a1} is an optionally substituted C_{1-4} alkyl.

30. The compound of any one of Claims 2-27, wherein R^{2a} is hydrogen and R^{2a1} is an optionally substituted aryl(C_{1-6} alkyl) or an optionally substituted heterocyclyl(C_{1-6} alkyl).

31. The compound of any one of Claims 2-27, wherein R^{2a} is hydrogen and R^{2a1} is an alkoxyalkyl, an aminoalkyl, a hydroxyalkyl or hydroxy.

32. The compound of any one of Claims 2-27, wherein R^{2a1} is hydrogen, and R^{1a} and R^{2a} are joined together with the atoms to which they are attached to form an optionally substituted 5 membered heterocyclyl or an optionally substituted 6 membered heterocyclyl.

33. The compound of any one of Claims 2-27, wherein R^{2a} and R^{2a1} are both an optionally substituted C_{1-4} alkyl.

34. The compound of any one of Claims 2-33, wherein R^{3a} is hydrogen, and R^{3a1} is selected from the group consisting of amino, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{3-6} cycloalkyl, an unsubstituted C_{1-4} alkoxy, hydroxy, halogen and an unsubstituted heteroaryl.

35. The compound of any one of Claims 2-33, wherein R^{3a} is hydrogen, and R^{3a1} is hydroxy.

36. The compound of any one of Claims 2-33, wherein R^{3a} is hydroxy, and R^{3a1} is selected from the group consisting of amino, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{3-6} cycloalkyl, an unsubstituted C_{1-4} alkoxy, hydroxy, halogen, -O-carboxy, an unsubstituted heteroaryl and an optionally substituted heterocyclyl.

37. The compound of any one of Claims 2-33, wherein R^{3a} is hydroxy, and R^{3a1} is an unsubstituted C_{1-4} alkyl.

38. The compound of any one of Claims 2-33, wherein R^{3a} is hydroxy, and R^{3a1} is an unsubstituted C_{2-4} alkynyl.

39. The compound of any one of Claims 2-33, wherein R^{3a} is hydroxy, and R^{3a1} is CF_3.

40. The compound of any one of Claims 2-33, wherein R^{3a} is hydroxy, and R^{3a1} is CHF_2.

41. The compound of any one of Claims 2-33, wherein R^{3a} is halogen, and R^{3a1} is CF_3.

42. The compound of any one of Claims 2-33, wherein R^{3a} is halogen, and R^{3a1} is CHF_2.

43. The compound of any one of Claims 2-33, wherein R^{3a} is hydroxy, and R^{3a1} is an unsubstituted C_{3-6} cycloalkyl.

44. The compound of any one of Claims 2-33, wherein R^{3a} is halogen, and R^{3a1} is an unsubstituted C_{3-6} cycloalkyl.

45. The compound of any one of Claims 2-33, wherein R^{3a} and R^{3a1} are both halogen.

46. The compound of any one of Claims 2-33, wherein R^{3a} is hydrogen, and R^{3a1} is unsubstituted C_{1-4} alkyl.

47. The compound of any one of Claims 2-33, wherein R^{3a} is an unsubstituted C_{1-4} alkoxy, and R^{3a1} is an unsubstituted C_{1-4} alkyl.

48. The compound of any one of Claims 2-33, wherein R^{3a} and R^{3a1} are both an unsubstituted C_{1-4} alkyl.

49. The compound of any one of Claims 2-33, wherein one of R^{3a} and R^{3a1} is a substituted C_{1-4} alkyl substituted with a substituent selected from the group consisting of halogen, hydroxy, amino, mono-substituted amino, di-substituted amino, -N-amido, an optionally substituted mono-cyclic heteroaryl and an optionally substituted mono-cyclic heterocyclyl; and the other of R^{3a} and R^{3a1} is hydroxy.

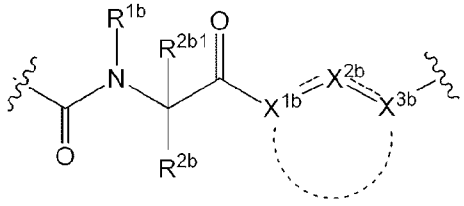
50. The compound of any one of Claims 2-33, wherein one of R^{3a} and R^{3a1} is an optionally substituted mono-cyclic heteroaryl or an optionally substituted mono-cyclic heterocyclyl; and the other of R^{3a} and R^{3a1} is hydroxy.

51. The compound of Claim 50, wherein one of R^{3a} and R^{3a1} is selected from the group consisting of an optionally substituted imidazole, an optionally substituted pyrazole, an optionally substituted pyrrolidine, an optionally substituted piperidine, an optionally substituted piperazine, an optionally substituted morpholine, an optionally substituted triazole, an optionally substituted piperazinone and an optionally substituted azetidine; and the other of R^{3a} and R^{3a1} is hydroxy.

52. The compound of any one of Claims 2-33, wherein R^{3a} and R^{3a1} together form $N=OR^{a}$.

53. The compound of any one of Claims 2-33, wherein R^{3a} and R^{3a1} are join together with the atom to which they are attached to form an optionally substituted 3 to 6 membered ring.

54. The compound of Claim 1, wherein L is Formula (Ib):



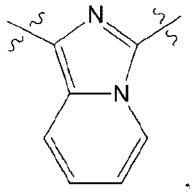
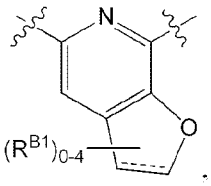
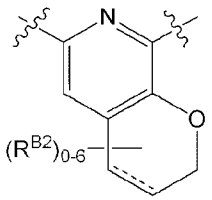
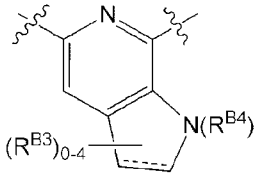
55. The compound of Claim 54, wherein the bi-cyclic ring is an optionally substituted 9-membered bi-cyclic heteroaryl or an optionally substituted 10-membered bi-cyclic heteroaryl.

56. The compound of Claim 54, wherein the bi-cyclic ring is an optionally substituted 9-membered bi-cyclic heterocyclyl or an optionally substituted 10-membered bi-cyclic heterocyclyl.

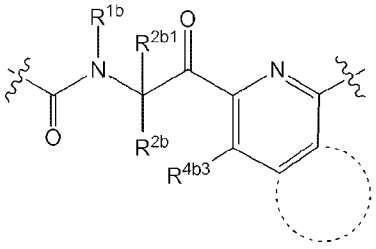
57. The compound of any one of Claims 54-56, wherein X^{1b} is C, X^{2b} is N and X^{3b} is C.

58. The compound of any one of Claims 54-56, wherein X^{1b} is N, X^{2b} is N and X^{3b} is C.

59. The compound of any one of Claims 54-56, wherein X^{1b} is N or C, X^{2b} is C(=O) or O and X^{3b} is N or C.

60. The compound of Claim 54, wherein the bi-cyclic ring is an optionally substituted  , an optionally substituted  , an optionally substituted  and an optionally substituted  ; wherein each ----- is independently absent or a bond; each R^{B1}, each R^{B2} and each R^{B3} is an unsubstituted C_{1-6} alkyl, halogen, hydroxy, amino, mono-substituted amino, di-substituted amino or –NH-S(=O)C_{1-4} alkyl; and R^{B4} is hydrogen or an unsubstituted C_{1-6} alkyl.

61. The compound of Claim 1, wherein L is Formula (Ib1):



wherein: the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted cycloalkenyl an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; and R^{4b3} is selected from the group consisting of hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C_{1-8} alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C_{1-8} alkyl), haloalkyl and an optionally substituted C-carboxy.

62. The compound of Claim 61, wherein the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted 5-membered cycloalkenyl or an optionally substituted 6-membered cycloalkenyl.

63. The compound of Claim 61, wherein the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted aryl.

64. The compound of Claim 61, wherein the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted 5-membered heteroaryl or an optionally substituted 6-membered heteroaryl.

65. The compound of Claim 61, wherein the dashed semi-circle along with the two carbon atoms to which it is connected form an optionally substituted 5-membered heterocyclyl or an optionally substituted 6-membered heterocyclyl.

66. The compound of any one of Claims 54-65, wherein R^{1b} is hydrogen.

67. The compound of any one of Claims 54-65, wherein R^{1b} is unsubstituted C_{1-4} alkyl.

68. The compound of any one of Claims 54-67, wherein R^{2b} and R^{2b1} are both hydrogen.

69. The compound of any one of Claims 54-67, wherein R^{2b} is hydrogen and R^{2b1} is an optionally substituted C_{1-4} alkyl.

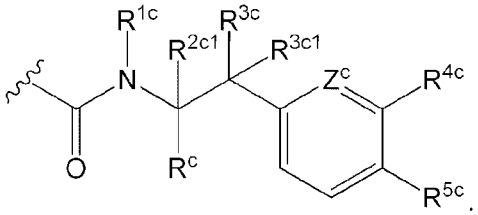
70. The compound of any one of Claims 54-67, wherein R^{2b} is hydrogen and R^{2b1} is an optionally substituted aryl(C_{1-6} alkyl) or an optionally substituted heterocyclyl(C_{1-6} alkyl).

71. The compound of any one of Claims 54-67, wherein R^{2b} is hydrogen and R^{2b1} is an alkoxyalkyl, an aminoalkyl, a hydroxyalkyl or hydroxy.

72. The compound of any one of Claims 54-67, wherein R^{2b1} is hydrogen, and R^{1b} and R^{2b} are joined together with the atoms to which they are attached to form an optionally substituted 5 membered heterocyclyl or an optionally substituted 6 membered heterocyclyl.

73. The compound of any one of Claims 54-67, wherein R^{2a} and R^{2a1} are both an optionally substituted C_{1-4} alkyl.

74. The compound of Claim 1, wherein L is Formula (Ic):



75. The compound of Claim 74, wherein R^{1c} is hydrogen.

76. The compound of Claim 74, wherein R^{1c} is an unsubstituted C_{1-4} alkyl.

77. The compound of any one of Claims 74-76, wherein R^{2c} and R^{2c1} are both hydrogen.

78. The compound of any one of Claims 74-76, wherein R^{2c} is hydrogen and R^{2c1} is an optionally substituted C_{1-4} alkyl.

79. The compound of any one of Claims 74-76, wherein R^{2c} is hydrogen and R^{2c1} is an optionally substituted aryl(C_{1-6} alkyl) or an optionally substituted heterocyclyl(C_{1-6} alkyl).

80. The compound of any one of Claims 74-76, wherein R^{2c} is hydrogen and R^{2c1} is an alkoxyalkyl, an aminoalkyl, a hydroxyalkyl or hydroxy.

81. The compound of any one of Claims 74-76, wherein R^{2c} and R^{2c1} are both an optionally substituted C_{1-4} alkyl.

82. The compound of any one of Claims 74-81, wherein R^{3c} is hydrogen, and R^{3c1} is selected from the group consisting of amino, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{3-6} cycloalkyl, an unsubstituted C_{1-4} alkoxy, hydroxy, halogen and an unsubstituted heteroaryl.

83. The compound of any one of Claims 74-81, wherein R^{3c} is hydrogen, and R^{3c1} is hydroxy.

84. The compound of any one of Claims 74-81, wherein R^{3c} is hydroxy, and R^{3c1} is selected from the group consisting of amino, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{3-6} cycloalkyl, an unsubstituted C_{1-4} alkoxy, hydroxy, halogen and an unsubstituted heteroaryl.

85. The compound of any one of Claims 74-81, wherein R^{3c} is hydroxy, and R^{3c1} is an unsubstituted C_{1-4} alkyl.

86. The compound of any one of Claims 74-81, wherein R^{3c} and R^{3c1} are both halogen.

87. The compound of any one of Claims 74-81, wherein R^{3c} is hydrogen, and R^{3c1} is unsubstituted C_{1-4} alkyl.

88. The compound of any one of Claims 74-81, wherein R^{3c} and R^{3c1} together form $N=OR^{c}$.

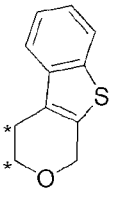
89. The compound of any one of Claims 74-81, wherein R^{3c} and R^{3c1} join together with the atom to which they are attached to form an optionally substituted 3 to 6 membered ring.

90. The compound of any one of Claims 74-89, wherein Z^{c} is N.

91. The compound of any one of Claims 74-89, wherein Z^{c} is CH.

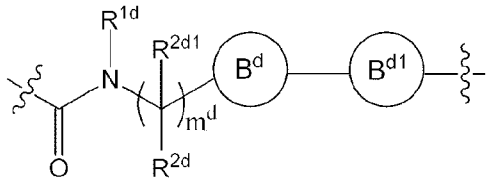
92. The compound of any one of Claims 74-91, wherein R^{4c} and R^{5c} are taken together to form an unsubstituted aryl or an unsubstituted heteroaryl.

93. The compound of any one of Claims 74-91, wherein R^{4c} and R^{5c} are taken together to form an optionally substituted heterocyclyl.

94. The compound of Claim 93, wherein the optionally substituted heterocyclyl is an optionally substituted, 

wherein * each indicate a point of attachment to the piperdinyl ring.

95. The compound of Claim 1, wherein L is Formula (Id):



96. The compound of Claim 95, wherein m^{d} is 0 or 1.

97. The compound of Claim 95, wherein ring B^{d} is an optionally substituted C_5 cycloalkyl.

98. The compound of any one of Claims 95-97, wherein R^{1d} is hydrogen.

99. The compound of any one of Claims 95-97, wherein R^{1d} is unsubstituted C_{1-4} alkyl.

100. The compound of any one of Claims 95-99, wherein R^{2d} and R^{2d1} are both hydrogen.

101. The compound of any one of Claims 95-99, wherein R^{2d} is hydrogen and R^{2d1} is an optionally substituted C_{1-4} alkyl.

102. The compound of any one of Claims 95-99, wherein R^{2d} is hydrogen and R^{2d1} is an optionally substituted aryl(C_{1-6} alkyl) or an optionally substituted heterocyclyl(C_{1-6} alkyl).

103. The compound of any one of Claims 95-99, wherein R^{2d} is hydrogen and R^{2d1} is an alkoxyalkyl, an aminoalkyl, a hydroxyalkyl or hydroxy.

104. The compound of any one of Claims 95-99, wherein R^{2c} and R^{2c1} are both an optionally substituted C_{1-4} alkyl.

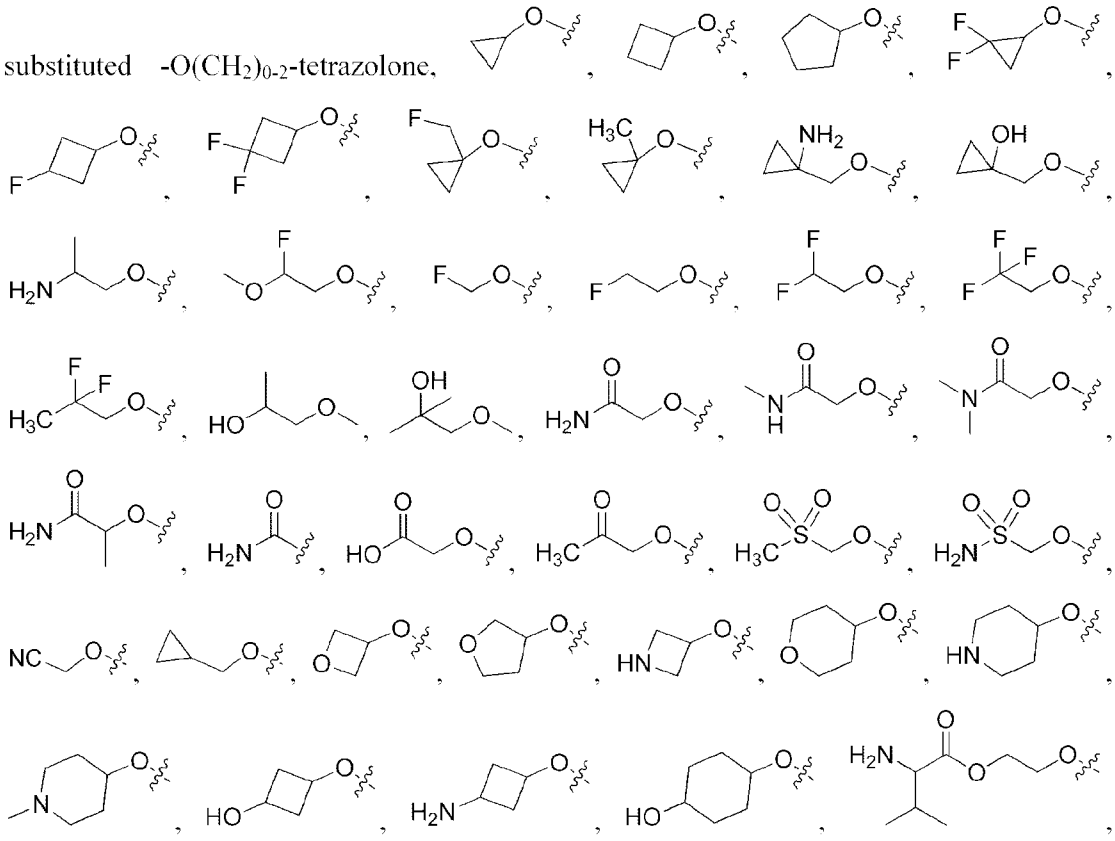
105. The compound of any one of Claims 1-104, wherein A is an optionally substituted aryl.

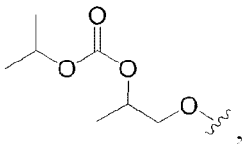
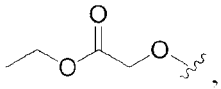
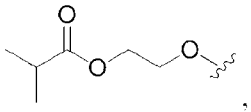
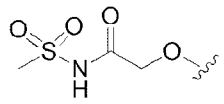
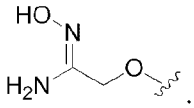
106. The compound of Claim 105, wherein A is an optionally substituted phenyl.

107. The compound of Claim 106, wherein A is a phenyl substituted with one or more substituents selected from the group consisting of: 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, -O-amido, sulfenyl, alkyoxyalkyl, an optionally substituted aryl, an optionally substituted mono-cyclic heteroaryl, an optionally substituted mono-cyclic heterocyclyl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted monocyclic heteroaryl(C_{1-4} alkyl), an optionally substituted monocyclic heterocyclyl(C_{1-4} alkyl), hydroxyalkyl and aminoalkyl.

108. The compound of Claim 106, 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, $-(CH_2)_{1-4}$-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,



 ,  ,  ,  and  .

109. The compound of any one of Claims 106-108, wherein A is a di-substituted phenyl.

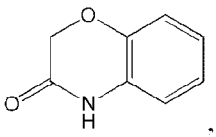
110. The compound of any one of Claims 1-104, wherein A is an optionally substituted cycloalkyl or an optionally substituted cycloalkenyl.

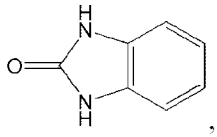
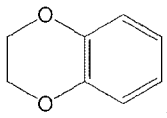
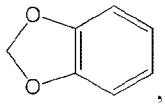
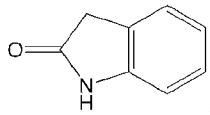
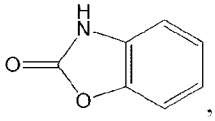
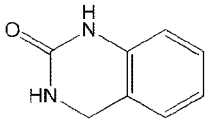
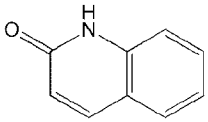
111. The compound of any one of Claims 1-104, wherein A is an optionally substituted aryl(C_{1-2} alkyl).

112. The compound of any one of Claims 1-104, wherein A is an optionally substituted heteroaryl.

113. The compound of Claim 112, wherein the optionally substituted heteroaryl is selected from the group consisting of: an optionally substituted imidazole, 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 quinolone, an optionally substituted imidazole, an optionally substituted oxazole, an optionally substituted isoxazole, an optionally substituted benzoimidazole, an optionally substituted benzooxazole, an optionally substituted benzothiazole and an optionally substituted imidazo[1,2-a]pyrimidine.

114. The compound of any one of Claims 1-104, wherein A is an optionally substituted heterocyclyl.

115. The compound of Claim 114, 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  , optionally substituted  and an optionally substituted  .

116. The compound of any one of Claims 1-73 or 95-115, wherein Y is an optionally substituted aryl.

117. The compound of Claim 116, wherein Y is a mono-substituted phenyl.

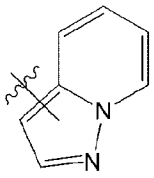
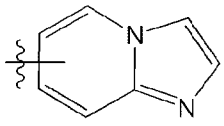
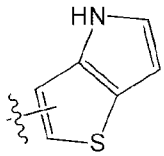
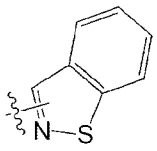
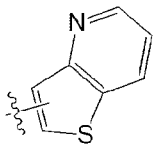
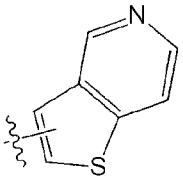
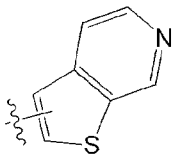
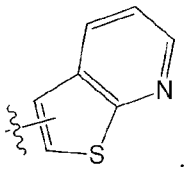
118. The compound of Claim 117, wherein Y is a di-substituted phenyl.

119. The compound of any one of Claims 1-73 or 95-115, wherein Y is an optionally substituted mono-cyclic heteroaryl.

120. The compound of Claim 119, wherein the optionally substituted mono-cyclic heteroaryl is selected from the group consisting of: 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, an optionally substituted isoxazole and an optionally substituted thiazole.

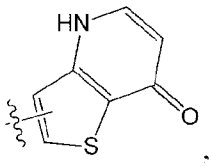
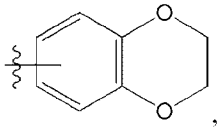
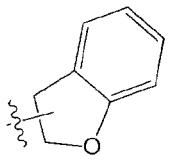
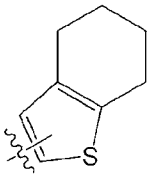
121. The compound of any one of Claims 1-73 or 95-115, wherein Y is an optionally substituted bi-cyclic heteroaryl.

122. The compound of Claim 121, wherein the optionally substituted bi-cyclic heteroaryl is selected from the group consisting of: an optionally substituted benzothiophene, an optionally substituted benzofuran, an optionally substituted indole, an optionally substituted quinoline, an optionally substituted isoquinoline, an optionally substituted benzooxazole, 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, an optionally substituted 2H-indazole, an optionally substituted  , an optionally substituted  , an optionally substituted  , an optionally substituted  , an optionally substituted  , an optionally substituted  , an optionally substituted  and an optionally substituted  .

123. The compound of any one of Claims 1-73 or 95-115, wherein Y is an optionally substituted heterocyclyl.

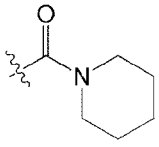
124. The compound of Claim 123, wherein the optionally substituted heterocyclyl is selected from the group consisting of: an optionally substituted pyridinone, an optionally

substituted  , an optionally substituted  , an optionally substituted  and an optionally substituted  .

125. The compound of any one of Claims 1-73 or 95-115, wherein Y is an optionally substituted cycloalkyl.

126. The compound of any one of Claims 1-73 or 95-115, wherein Y is an optionally substituted cycloalkenyl.

127. The compound of any one of Claims 1-73, 93-116 or 119-126, wherein Y is unsubstituted.

128. The compound of any one of Claims 1-73 or 95-126, 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  .

129. The compound of any one of Claims 1-73, 95-115 or 128, wherein Y is an optionally substituted benzothiophene.

130. The compound of any one of Claims 1-73, 95-115 or 128, wherein Y is an optionally substituted benzofuran or an optionally substituted indole.

131. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of: 1, 13-1, 100, 101, 102, 103, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 116a, 116b, 117, 117a, 117b, 118, 118a, 118b, 119, 120, 120a,

120b, 121, 122, 122a, 122b, 123, 124, 125, 126, 127, 128, 129, 131, 132, 133, 134, 138, 139, 142, 143, 144, 145, 146, 147, 148, 151, 152, 153, 154, 155, 158, 159, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 218, 219, 221, 223, 224, 225, 226, 227, 228, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 306, 307, 308, 309, 310, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498a, 498b, 498c, 498d, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604a, 604b, 604c, 604d, 605a, 605b, 605c, 605d, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623a, 623b, 624a, 624b, 625, 626, 627, 628, 629, 630, 631, 632, 633a, 633b, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668,

669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 680, 681 and 682, or a pharmaceutically acceptable salt of the foregoing.

132. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of: 149, 150, 156, 157, 160, 217, 220, 222, 229, 287, 302, 303, 304, 305, 311, 401, 473 and 474, or a pharmaceutically acceptable salt of the foregoing.

133. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of: 130, 135, 140 and 141, or a pharmaceutically acceptable salt of the foregoing.

134. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of: 104 and 161, or a pharmaceutically acceptable salt of the foregoing.

135. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of: 136 and 137, or a pharmaceutically acceptable salt of the foregoing.

136. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-135, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient, or combination thereof.

137. Use of an effective amount of a compound of any one of Claims 1-135, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 136 in the preparation of a medicament for ameliorating or treating a paramyxovirus infection.

138. Use of an effective amount of a compound of any one of Claims 1-135, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 136 in the preparation of a medicament for inhibiting replication of a paramyxovirus.

139. Use of an effective amount of a compound of any one of Claims 1-135, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 136 in the preparation of a medicament for contacting a cell infected with a paramyxovirus.

140. The use of any one of Claims 137-139, wherein the paramyxovirus infection is a human respiratory syncytial virus infection.

141. Use of an effective amount of a compound of any one of Claims 1-135, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 136 in

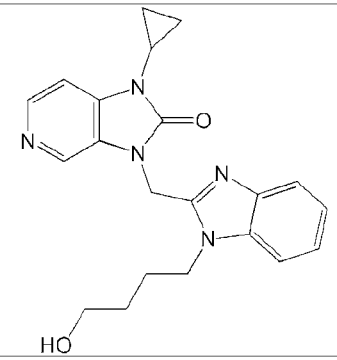
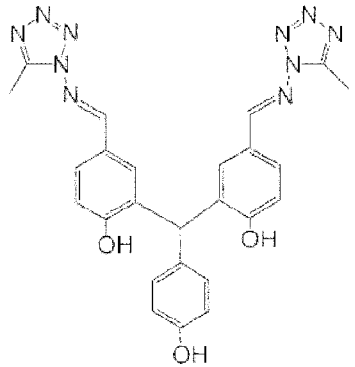
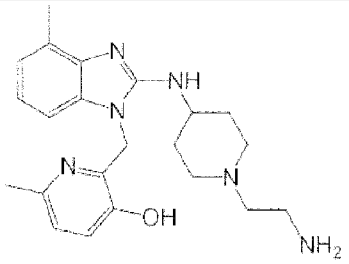
the preparation of a medicament for ameliorating or treating a paramyxovirus infection in combination with one or more agents comprising administering or contacting a cell with an effective amount of the compound of any one of Claims 1-135, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of Claim 136.

142. The use of Claim 141, wherein the paramyxovirus infection is a human respiratory syncytial virus infection; and wherein the one or more agents is 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.

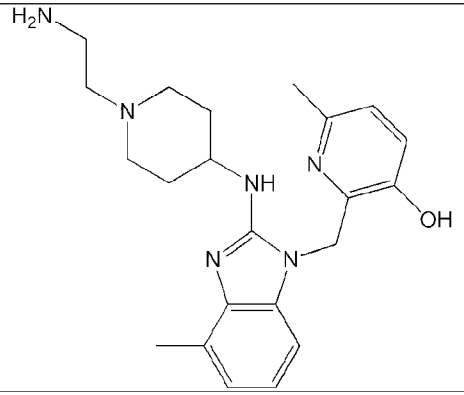
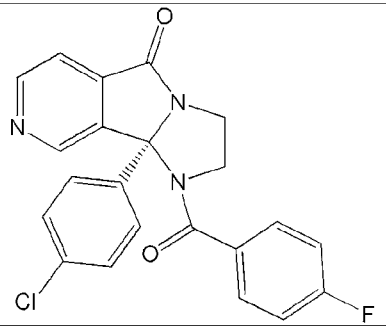
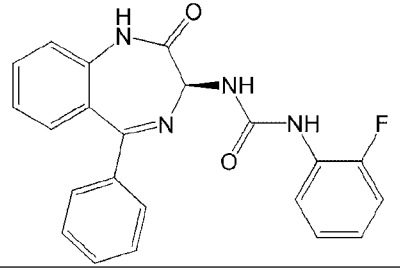
143. The use of Claim 142, wherein the one or more agents is selected from the group consist of RSV-IGIV, palivizumab, motavizumab, 1-cyclopropyl-3-[[1-(4-hydroxybutyl)benzimidazol-2-yl]methyl]imidazo[4,5-c]pyridin-2-one (BMS-433771), 4,4"-bis-{4,6-bis-[3-(bis-carbamoylmethyl-sulfamoyl)-phenylamino]-(1,3,5)triazin-2-ylamino}-biphenyl-2,2"-disulfonic-acid (RFI-641), 4,4'-Bis[4,6-di[3-aminophenyl-N,N-bis(2-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-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), 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.

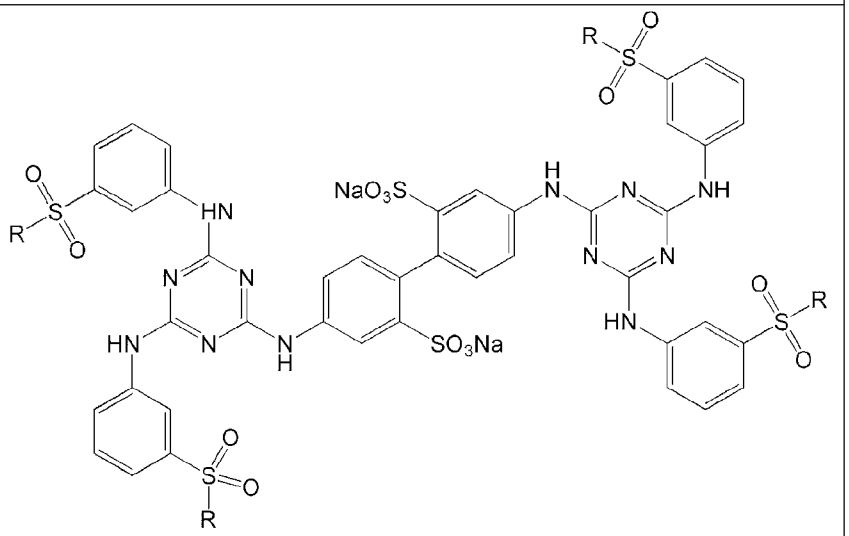
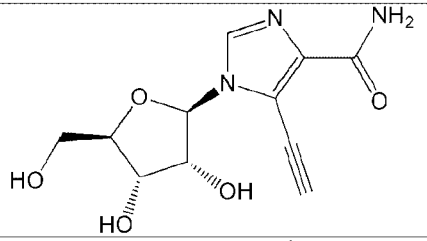
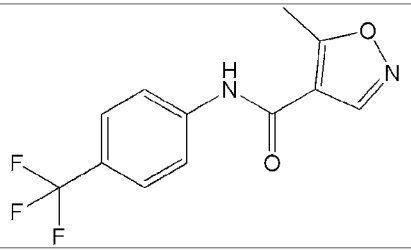
Figure 1

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-piperidinyl]amino]-4-methyl-1H-benzimidazol-1-yl]-6-methyl-3-pyridinol	

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	

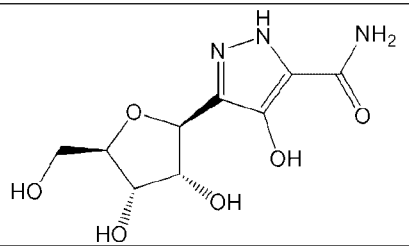
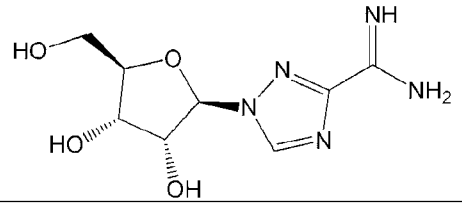
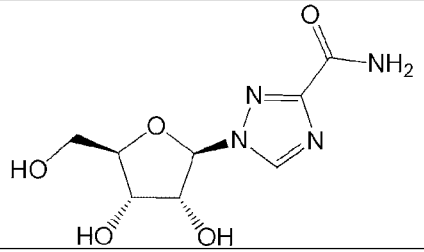
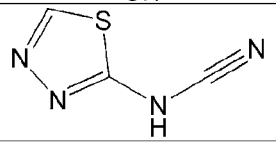
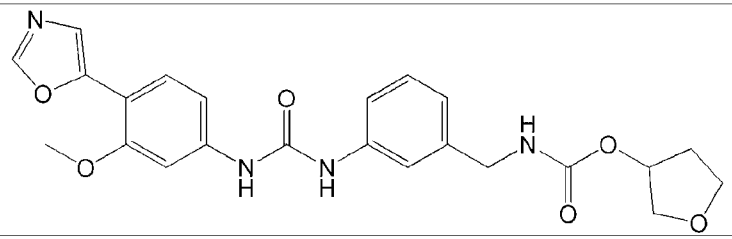
Name or CAS No.	IUPAC Name	Structure
R170591	2-((2-((1-(2-aminoethyl)piperidin-4-yl)amino)-4-methyl-1H-benzo[d]imidazol-1-yl)methyl)-6-methylpyridin-3-ol	
BTA9981	(R)-9b-(4-chlorophenyl)-1-(4-fluorobenzoyl)-2,3-dihydro-1H-imidazo[1',2':1,2]pyrrolo[3,4-c]pyridin-5(9bH)-one (BTA9981)	
RSV-604	(S)-1-(2-fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)urea	

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	

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	
EICAR	5-ethynyl-1-beta-D-ribofuranosylimidazole-4-carboxamide	
leflumomide	5-methyl-N-[4-(trifluoromethyl) phenyl]-isoxazole-4-carboxamide	

Name or CAS No.	IUPAC Name	Structure
JMN3-003	N-(2-chloro-4-methylphenyl)-2-((1-(4-methoxyphenyl)-1H-benzo[d]imidazol-2-yl)thio)propanamide	
MBX300	[2,2-bis(docosyloxy-oxymethyl)propyl-5-acetaoamido-3,5-dideoxy-4,7,8,9-tetra-O-(sodium-oxysulfonyl)-D-glycero-D-galacto-2-nonulopyranosid]onate	
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	

Name or CAS No.	IUPAC Name	Structure
	N-cyclopropyl-5-(4-(2-(pyrrolidin-1-yl)benzamido)benzoyl)-5,6,7,10-tetrahydrobenzo[b]cyclopenta[d]azepine-9-carboxamide	
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	

Name or CAS No.	IUPAC Name	Structure
pyrazofurin	4-hydroxy-3-beta-D-ribofuranosylpyrazole-5-carboxamide	
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-(3-methoxy-4-(oxazol-5-yl)phenyl)ureido)benzylcarbamate	

Name or CAS No.	IUPAC Name	Structure
Mycophenolic acid	(4E)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-2-benzofuran-5-yl)-4-methylhex-4-enoic acid	
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	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/051642

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)

CAPLUS and REGISTRY: Substructure search based on formula (I) of claim 1; keywords: *VIRA*, *VIRUS*, *INFECT*

GOOGLE, AUSPAT, ESP@CENET: Applicant and Inventor Search: ALIOS BIOPHARMA, WANG GUANGYI, BEIGELMAN, L., TRUONG, A., NAPOLITINO, C., ANDREOTTI D., HE, HAIYING, STEIN, K. with keywords, viral, antiviral, virus, infect, paramyxovirus in various combinations.

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	

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 2014	24 November 2014

Name and mailing address of the ISA/AU

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(ISO 9001 Quality Certified Service)
Telephone No. 0262832718

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2014/051642**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/087379 A2 (AMURA THERAPEUTICS LIMITED) 16 July 2009 page 20 compounds at lines 8-9, 11-12, 14-15, 16-18; page 23, lines 11-13, 16-17, 19-21, 22-24; page 26, lines 17-18, 21-22, 24-25, 26-28; page 29, lines 20-22, 24-25, 26-28; page 30, lines 1-3; page 38, lines 11-12, 14-15, 16-17, 20-22; page 41, lines 13-15, 16-17, 20-22, 24-26; page 44, lines 15-16, 18-19, 21-22, 24-26; page 47, lines 21-22, 24-26	1, 54, 56, 66, 69, 105-108, 125, 127 and 136
X	WO 2010/150281 A2 (PANACEA BIOTEC LTD.) 29 December 2010 page 28, compound 26	1, 54, 66, 68, 112-113, 116-117, 128 and 136
X	WO 2013/010380 A1 (MERCK SHARP & DOHME CORP. ET. AL.) 24 January 2013 page 219, Example 131	1-2, 9, 11, 26, 28, 34, 46, 114, 116-117, 128 and 136
X	PERNI, R. B. ET. AL. "Inhibitors of hepatitis C virus NS3-4A protease 2. Warhead SAR and optimization", Bioorg. & Med. Chem. Letters, 2004, 14, 1441-1446 page 1443, Scheme 1, compound 7d	1-2, 9, 11, 26, 29, 34-35, 114, 116 and 127
X	WO 2003/029245 A1 (BRISTOL-MYERS SQUIBB COMPANY ET. AL.) 10 April 2003 page 128, Table 6, Example 119	1, 54, 56, 66, 68, 112-113, 116-117, 128 and 136
X	WO 2003/024955 A2 (SUNESIS PHARMACEUTICALS, INC.) 27 March 2003 page 104, Scheme 36, compound 130	1-2, 9, 11, 26, 29, 34-35, 112-113, 116, 118 and 128
X	WO 2013/059119 A1 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN) 25 April 2013 page 19, compound 3g, page 20, compounds 3i, 3j; page 21, compounds 9, 10, 12; page 22, compound 15	1, 74-76, 78-79, 82-83, 91, 93, 110-111 and 136
X	WO 2013/064518 A1 (SYNGENTA PARTICIPATIONS AG) 10 May 2013 page 31, compound P. 100	1-2, 9, 11, 13, 26, 28, 53, 105-108, 125, 127 and 136
X	WO 1999/061437 A1 (SMITHKLINE BEECHAM CORPORATION) 02 December 1999 claim 15, second compound and claim 16	1-2, 9, 11, 13, 27-28, 48, 105-106, 116-117, 119-120, 127-128 and 136
P,X	WO 2014/031784 A1 (ALIOS BIOPHARMA, INC.) 27 February 2014 claims 1-156, Abstract, Examples	1-143

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/051642

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: **131-135**

because they relate to subject matter not required to be searched by this Authority, namely:

the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
See Supplemental Box

2. [ ] Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

Supplemental Box

Continuation of **Box II**

The said claims do not comply with Rule 6.2(a) because they rely on references to the description and/or drawings.

INTERNATIONAL SEARCH REPORT	International application No. PCT/US2014/051642

Supplemental Box – IPC Marks

C07D 207/267 (2006.01)

C07D 213/40 (2006.01)

C07D 233/58 (2006.01)

C07D 239/34 (2006.01)

C07D 277/28 (2006.01)

C07D 401/04 (2006.01)

C07D 401/06 (2006.01)

C07D 401/12 (2006.01)

C07D 405/12 (2006.01)

C07D 409/04 (2006.01)

C07D 409/14 (2006.01)

C07D 413/04 (2006.01)

C07D 413/12 (2006.01)

C07D 417/04 (2006.01)

C07D 417/06 (2006.01)

C07D 417/12 (2006.01)

C07D 471/04 (2006.01)

C07D 487/04 (2006.01)

C07D 491/048 (2006.01)

C07D 491/052 (2006.01)

C07D 491/20 (2006.01)

C07D 495/14 (2006.01)

A61K 31/33 (2006.01)

A61P 31/14 (2006.01)

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2014/051642**

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 2009/087379 A2	16 July 2009	EP 2240491 A2	20 Oct 2010
		EP 2719700 A1	16 Apr 2014
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		JP 5587790 B2	10 Sep 2014
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		AU 2010264027 A1	19 Jan 2012
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		RU 2012102094 A	10 Aug 2013
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2014/051642**

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.

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		GE P20063767 B	10 Mar 2006
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		HR P20040311 A2	28 Feb 2005
		HU 0402338 A2	28 Feb 2005
		IS 7197 A	24 Mar 2004
		JP 2005510476 A	21 Apr 2005
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		KR 20040041649 A	17 May 2004
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		NO 20041339 A	24 May 2004
		NZ 531870 A	26 Aug 2005
		PE 08452003 A1	23 Oct 2003
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2014/051642**

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 2003/024955 A2	27 March 2003	US 2003114447 A1	19 Jun 2003
		US 6878743 B2	12 Apr 2005
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		EP 2773622 A1	10 Sep 2014
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		PL 344330 A1	22 Oct 2001
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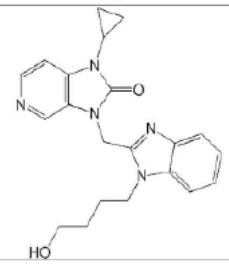
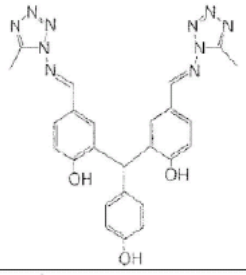
End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

摘要

本文公开了新型抗病毒化合物和包含一种或多种抗病毒化合物的药物组合物，以及合成所述化合物或药物组合物的方法。本文也公开了用一种或多种小分子化合物缓解和/或治疗副粘病毒感染的方法。副粘病毒感染的实例包括由人呼吸道合胞体病毒(RSV)引起的感染。

名称或CAS编号	IUPAC名称	结构
BMS-433771	1-环丙基-3-[[1-(4-羟丁基)苯并咪唑-2-基]甲基]咪唑并[4,5-c]吡啶-2-酮	
VP-14637 (MDT-637)	5,5′-双[1-(((5-氨基-1H-四唑基)亚氨基)甲基)] 2,2′,4″-次甲基三酚	
JNJ-2408068	2-[[2-[[1-(2-氨基乙基)-4-哌啶基]氨基]-4-甲基-1H-苯并咪唑-1-基]-6-甲基-3-吡啶醇